REVIEW

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Obesity-Related Digestive Diseases and Their Pathophysiology

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Obesity is a growing medical and public health problem worldwide. Many digestive diseases are related to obesity. In this article, the current state of our knowledge of obesity-related digestive diseases, their pathogenesis, and the medical and metabolic consequences of weight reduction are discussed. Obesity-related digestive diseases include gastroesophageal reflux disease, Barrett's esophagus, esophageal cancer, colon polyp and cancer, nonalcoholic fatty liver disease, hepatitis C-related disease, hepatocellular carcinoma, gallstone, cholangiocarcinoma, and pancreatic cancer. Although obesity-related esophageal diseases are associated with altered mechanical and humoral factors, other obesity-related digestive diseases seem to be associated with obesity-induced altered circulating levels of adipocytokines and insulin resistance. The relationship between functional gastrointestinal disease and obesity has been debated. This review provides a comprehensive evaluation of the obesity-related digestive diseases, including pathophysiology, obesity-related risk, and medical and metabolic effects of weight reduction in obese subjects. **(Gut Liver 2017;11:323-334)**

Key Words: Obesity; Gastrointestinal disease; Cytokines

INTRODUCTION

The prevalence of global obesity among both women and men increased from 1980 to 2008 (Fig. 1).[1] With a new appreciation for obesity as a disease and well-being in mind, the concerns of obesity and obesity-related disease have been rapidly increased. The health implications by obesity include a wide spectrum of benign digestive diseases such as gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), erosive esophagitis, nonalcoholic fatty liver disease (NAFLD), gallstones, and pancreatitis and digestive organ cancers such as cholangiocarcinoma, hepatocellular carcinoma (HCC), pancreatic cancer, colorectal cancer (CRC), and esophageal cancer (Fig. 2).[2-5] Obesity and related comorbid conditions may also increase risk for common adverse treatment effects in cancer patient.[6]

Both mechanical effect and humoral factors by obesity seem to effect on development of esophageal diseases, whereas pathophysiology of other digestive disorders seems to be related with obesity induced proinflammatory and inflammatory cytokines. The relationship of functional gastrointestinal disease with obesity has debate.

This review provides gastroenterologists with a comprehensive evaluation of the obesity-related digestive diseases, including pathophysiology of carcinogenesis, obesity-related risk of each disease, and medical effect of weight reduction.

PATHOPHYSIOLOGY OF CARCINOGENESIS BY OBESITY

Excessive weight and adiposity induce increase of free fatty acid, leptin, plasminogen activator inhibitor 1 (PAI-1), tumor necrosis factor α (TNF-α), and resistin and decrease of adiponectin. This results in insulin resistance and increased insulin-like growth factor-binding protein 1 (IGFBP1) and IGFBP2. Consequently this increased insulin like growth factor 1 (IGF-1) bioavailability and inhibit apoptosis and increase cell proliferation on target cells.

1. Insulin and IGFs

Obesity is strongly related with insulin resistance, in which insulin and IGF-1 are elevated in obese persons. Increased circulating insulin/IGF1 and upregulation of insulin/IGF receptor signaling pathways are known to be related with the formation of many kinds of cancer.[7] Insulin induced proliferation of colon cancer cells *in vitro*,[8] while IGF-1 inhibits apoptosis, leading to the development of cancer.[9] Higher plasma IGF-1 and lower IGFBP-3 were associated with increased risk of colorectal cancer in a prospective cohort in both men and women.[10,11] High serum

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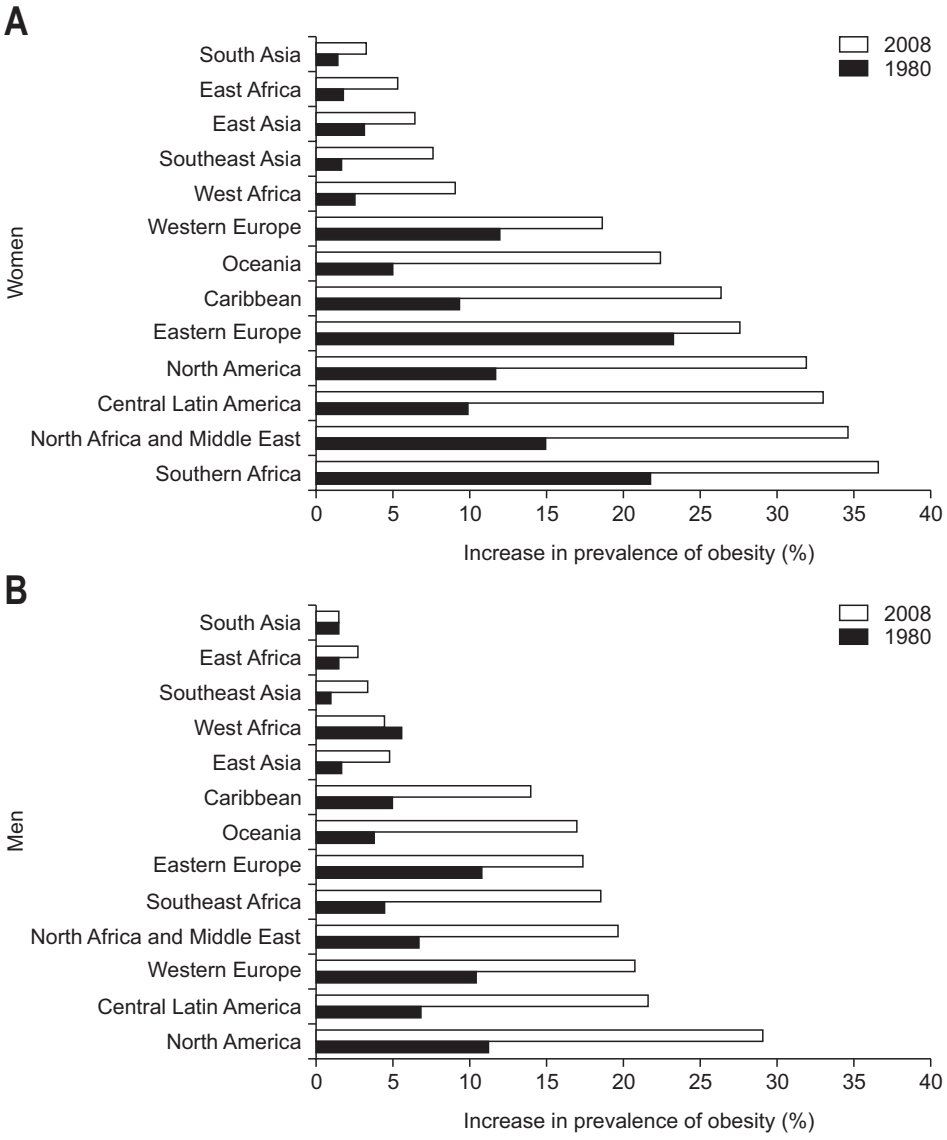

Fig. 1. Estimates of obesity prevalence in women (A) and men (B). Among women, obesity prevalence has increased in all regions. The greatest magnitudes of increase (>20%) were observed in central Latin America, North America, North Africa, and the Middle East. For men, obesity has increased in all regions except South Asia. The greatest magnitude of increase was observed in North America, with an increase of >18%. Adapted from Malik VS, *et al*. Nat Rev Endocrinol 2013;9:13-27, with permission from Nature Publishing Group.[1]

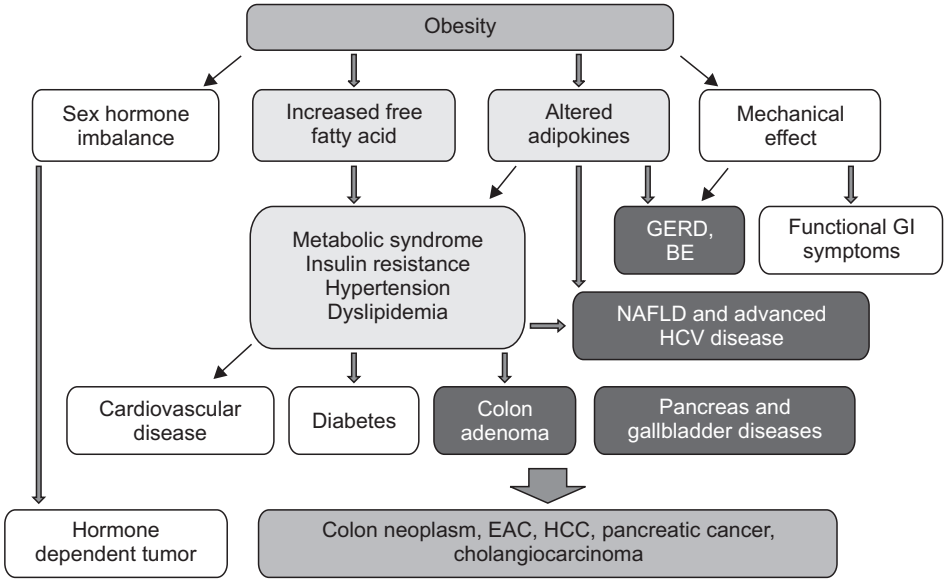

Fig. 2. Medical effect of obesity on digestive diseases. Obesity increases free fatty acids and alters adipocytokines. This metabolic alteration induces metabolic syndrome, including insulin resistance, dyslipidemia, and hypertension. Metabolic alteration and metabolic syndrome contribute to benign and malignant digestive disease. Mechanical effect of obesity may contribute to esophageal disease and several gastrointestinal symptoms.
GERD, gastroesophageal reflux disease; BE, Barrett's esophagus; GI, gastrointestinal; NAFLD, nonalcoholic fatty liver disease; HCV, hepatitis C virus; EAC, esophageal adenocarcinoma; HCC, hepatocellular carcinoma.

C-peptide, a marker for insulin production, increased colorectal cancer risk.[12] Insulin increased IGF-1 that binds to IGF-1 receptor and insulin receptor. After IGF-1 binds IGF-1 receptor, it activates phosphoinositide 3-kinase (PI3K) and Akt/protein kinase B and indirectly activates mammalian target of rapamycin complex 1 (mTORC1). In addition, insulin receptor bind growth factor receptor-bound protein 2 (GRBP2) and activates Ras/Raf/extracellular signal-regulated kinase (ERK) pathway that induces cell proliferation.

A previous study suggested that metformin, oral antihyperglycemic agent, may reduce the risk of cancer.[13] One of suggested anticancer mechanisms of metformin is the inhibition of the mTORC1.[14] The mTOR signaling network plays a pivotal role in metabolism and proliferation of cancer cell.[15] The reduction of circulating insulin and IGF-1 by metformin may be associated with anticancer action.[16]

2. Adipokines

Adipokines are cytokines released from adipose tissue. Adipokines play roles in metabolic control (leptin, adiponectin, resistin, visfatin, retinol binding protein 4, apetin, vaspin, omentin, chemerin, acylation stimulating protein, and agouti signaling protein), inflammation (resistin, TNF, IL-6, IL-1, IL-10, IL-1 receptor antagonist, CCL2, CCL5, CXCL8, CXCL10, macrophage migration inhibitory factor, hepcidin, adipsin, and serum amyloid protein A), and tissue repair (angiotensin, renin, PAI-1, nerve growth factor, vascular endothelial growth factor, transforming growth factor β, hepatocyte growth factor, human epidermal growth factor, insulin like growth factor 1, and tissue factor).[17,18]

Adipocyte-conditioned media can enhance tumorigenesis in cancer cells.[19] These tumorigenic effects of adipocyte seem to be mediated by adipokines such as adiponectin, leptin, TNF, IL-6, IL-8, IL-10, and IL-1 receptor agonists.[20]

1) Leptin

Leptin is an adipocyte-derived hormone that suppresses appetite and increase energy expenditure in hypothalamus and controls body weight.[21] Leptin regulates neuroendocrine axis and inflammatory responses.[22] Amount of body fat is directly correlated circulating leptin and serum leptin increase in obese individuals and drop during weight loss.[23] Leptin has six different leptin receptors: Ob-R, OB-Rb, OB-Rc, Ob-Rd, Ob-Re, and Ob-Rf.[24] OB-Rb mRNA encodes long form of leptin receptor (LEPR-B) and is expressed primarily in the hypothalamus but is also expressed in immune systems. After leptin binds to receptor (LEPR-B), conformational change of receptor activates Jak2 and auto-phosphrylates itself. This serves as a docking site for SHP2 (protein tyrosine phosphatase), STAT5, and STAT3. When SHP2, STAT5, and STAT3 bind to phosphorylated LEPR-B, they are activated by Jak2-mediated phosphorylation and they regulate energy homeostasis and body weight.

Several clinical studies suggested the tumorigenic effect of leptin. Higher plasma leptin levels are associated with esophageal adenocarcinoma (EAC),[25] colon cancer,[26] and endometrial cancer.[27] Increased serum leptin is associated with the recurrence of stage I/II HCC after curative treatment.[28] *In vitro* studies confirmed the regulation effect of leptin on tumorigenesis. Leptin enhances cell proliferation and angiogenesis in esophageal cancer cells,[29] colon cancer cells,[30] HCC cells,[31] and cholangiocarcinoma cells.[32]

2) Adiponectin

Adiponectin consists of four different molecular isoforms (i.e., trimer, hexamer, high molecular weight, and globular).[33] The biological effects of the isoforms are mainly mediated through two classical adiponectin receptor subtypes: AdipoR1 and AdipoR2.[34] The circulating level of adiponectin, secreted from visceral fat adipocytes, has inverse correlation with body mass index (BMI) and is usually higher in women than in men.[35,36] Adiponectin is known as an insulin sensitizer and has antiangiogenic and anti-inflammatory activities. *In vitro* studies have suggested adiponectin involvement in various cancer cell types.[37] Adiponectin inhibits cell proliferation and induces apoptosis both *in vitro* and *in vivo* through different molecular pathways.[38] First, adiponectin inhibited colon cancer cell proliferation via AdipoR1- and AdipoR2-mediated AMP-activated protein kinase (AMPK) activation.[39] AMPK interferes with cellular growth signaling through mTOR, thus inhibiting carcinogenesis. Adiponectin activates AMPK in several cell lines promoting growth arrest and apoptosis via increased p53 and p21 expression. Second, tumor suppressor effects of adiponectin are also mediated via AKT and ERK signaling pathways in pancreatic beta cells and lung epithelial cells.[40,41] Growth factors activate PI3K which results in the phosphorylation of AKT that promotes cellular growth and proliferation. Adiponectin has the molecular potential to antagonize the oncogenic actions of leptin by blocking downstream effector molecules in hepatocellular carcinogenesis.[42]

Several clinical studies have suggested that adiponectin has antitumor effects. The expression of adiponectin receptors was reported to be significantly higher in areas occupied by colorectal tumors.[43] Plasma adiponectin levels are inversely related with gastric cancer and metastasis.[44,45] Lower tissue expression of adiponectin in HCC is associated with poor prognosis.[46] In a prospective study using the Nurses' Health Study and the Health Professionals Follow-up Study among 616 incident colorectal cancer cases and 1,205 controls, plasma adiponectin was significantly associated with reduced risk of colorectal cancer among men.[47]

3) Resistin

Resistin, 12 kDa protein, is referred to as FIZZ3 and is a 108 amino acid prepeptid.[48] It is produced by peripheral blood mononuclear cells, macrophages, bone marrow, pancreatic cells,

adipocytes, spleen, and muscles.[49] Resistin induces IL-1, IL-6, IL-8, IL-12, TNF, and Toll-like receptor 2 through the nuclear factor-κB pathway.[50] Circulating resistin level was higher in patients with colon cancer compared with control subjects.[51] High resistin is risk of breast cancer in pre- and post-menopausal females[52] and promotes growth and aggressiveness of tumor cells through STAT3 activation in breast cancer.[53]

4) Plasminogen activator inhibitor-1

PAI-1 is a protein that is encoded by the SERPINE1 gene. PAI-1 is mainly produced by the endothelium and is also secreted by adipose tissue. PAI-1 inhibits the activity of matrix metalloproteinases (MMPs), which play a crucial role in invasion and migration of malignant cells. PAI-1 modulates cell migration by regulating extracellular matrix (ECM) proteolysis.[54] PAI-1 inhibits plasmin production and sequentially inhibits MMP activation and induce ECM proteolysis and cell migration.[54] First, PAI-1 modulates migration through cell surface receptors such as low density lipoprotein receptor-related protein 1 (LRP1) and protease urokinase-type plasminogen activator/urokinase-type plasminogen activator receptor (uPA/uPAR). PAI-1 binding to uPA/uPAR can also trigger the detachment of cell surface integrins from their ECM ligands and subsequent internalization in an LRP1-uPA/uPAR-dependent manner. Second, PAI-1 regulates cell adhesion through interactions with vitronectin.[54]

Overexpression PAI-1 has been found in esophageal and colorectal cancer.[55] Recently PAI-1 has been suggested as potential cancer therapeutic target.[56]

3. Immuomodulation

Obesity is associated with low-grade inflammation. Chronic inflammation associated with obesity modulates immune cell function.[57] Epithelial γδ T cell function is the guardians of the epithelial barrier and mediate repair.[58] Dysfunction in their function, and subsequently the deterioration of the epithelium can result in undesired consequences for the host. Obese patients are more prone to nonhealing injuries, infection, and disease. Adipocytes can modulate CD4(+) T-cell function through the release of lipids.[59] Free fatty acids were the most prominent modulators of T-cell proliferation. T-cell co-stimulation protects obesity-induced adipose inflammation and insulin resistance.[60]

The amount of adipocytokines produced by adipose tissue is strongly influenced by the immune cells present in adipose tissue.[61] Adipose tissue macrophage numbers increase in obese persons and participate in inflammatory pathways that are activated in adipose tissues.[62] The immune system plays a key role in antitumor activity and also can promote tumor development and progression under certain circumstances. The density of tumor-associated macrophages seems to be correlated with increased angiogenesis, tumor invasion, and poor prognosis.[63]

ESOPHAGEAL DISEASE

1. Gastroesophageal reflux disease

Obesity is a well-known risk factor for GERDs in both Asian and Western.[64,65] Large epidemiological studies have demonstrated that obesity is an important risk factor of GERD.[64-66] Jacobson *et al*.[65] showed that subjects that reported at least weekly symptoms had a near linear increase in the adjusted OR for reflux symptoms for each BMI group. A large study using 8,571 Korean men, who underwent comprehensive screening and endoscopy, demonstrated that high BMI increased the risk of reflux esophagitis with dose-dependent pattern.[64] Furthermore, weight gain (increase of BMI >1) increased the risk of new development of reflux esophagitis.[64] In a small study, which 453 hospital employees responded GERD symptom questionnaires and 196 subjects underwent endoscopy, obesity was associated with reflux symptoms and esophagitis.[67]

Abdominal visceral adiposity, rather than BMI, appears to be more closely associated with reflux esophagitis.[3,68] A large cross-sectional study using 5,329 comprehensive screening individuals demonstrated that odds ratio (OR) for erosive esophagitis correlated with obesity measured by BMI, waist circumference, and abdominal visceral adipose tissue volume ($p<0.001$ for each factor).[3] The multivariate OR for erosive esophagitis was 1.97 for a visceral adipose tissue volume of 500 to 999 cm^3, 2.27 for 1,000 to 1,499 cm^3, and 2.94 for ≥1,500 cm^3, compared with participants who had visceral adipose tissue volumes less than 500 cm^3.[3] When all three obesity indexes were analyzed simultaneously, abdominal visceral adipose tissue volume, but not BMI or waist circumference, was associated with erosive esophagitis.[3]

Pathophysiological mechanism in obesity include lower esophageal sphincter abnormalities, increased risk of hiatal hernia, and increased intragastric pressure. Additionally, alterations in the secretion of adiponectin and leptin from adipocytes is a proposed link between obesity and Barrett's esophagus and EAC.

The data for weight reduction as a treatment for GERD is less robust, but weight reduction appears to be an association with fewer GERD symptoms. In lean person, diet-induced weight reduction correlated with improvement in reflux symptoms.[69] However, even modest weight reduction of 2 to 3 kg caused a remarkable improvement in GERD symptoms, suggesting that changes in diet rather than body weight may have been responsible for improvement of GERD symptom. In obese persons who had symptoms of GERD, diet-induced weight reduction did not improve symptoms or 24-hour esophageal pH values.[70] But weight reduction is related with improvement of erosive esophagitis in a large cohort study.[64] In contrast, the gastric bypass surgery consistently has shown to decrease GERD symptoms.[71-73]

2. Barrett's esophagus and esophageal cancer

GERD and obesity are strong risk factors of EAC and BE. A

landmark population-based case-control study showed that the risk of EAC was 8-fold greater in patients with recurrent GERD symptoms compared with those without GERD symptoms.[74] It is known that GERD can lead to erosive esophagitis, progressing to a metaplastic, specialized intestinal epithelium (Barrett's esophagus).[75] BE progresses to EAC in a small portion, approximately 0.12% to 0.60% per year.[76-78] A meta-analysis of population-based studies demonstrated that weekly GERD symptoms increase EAC risk by approximately 5-fold.[79] Patients with long-standing symptoms, nocturnal symptoms, or more frequent symptoms are at higher risk. However, the severity of symptoms is not associated with an increased risk of EAC.

Obesity is a definite risk factor for EAC. A BMI of 30 to 34.9 kg/m^2 is associated with a 2.4-fold increase in risk of EAC compared with a BMI of less than 25 kg/m^2.[80] Abdominal obesity is associated with BE and EAC (OR, 2.51).[81] A recent Mendelian randomized study using 999 patients with EAC, 2,061 patients with BE, and 2,169 population controls demonstrated that EAC and BE risk increased by 16% (OR, 1.16) and 12% (OR, 1.12) per 1 kg/m^2 increase in BMI.[82]

Obesity increased intraabdominal pressure and promoted formation of hiatal hernia, which is a strong risk factor of GERD.[83,84] Abdominal obesity is associated with BE and EAC after adjusting for GERD.[80] In addition to mechanical effect, abdominal obesity changed circulating levels of inflammatory cytokines that are associated with BE and EAC.[85] Metabolic syndrome are associated with BE and EAC.[86,87] IGF-1 pathway is strongly associated with EAC. Circulating IGFBP3 are inversely associated with BE.[88] A polymorphism in IGF-I gene is associated with BE,[89] and a polymorphism in IGF-I receptor modifies the effect of obesity on the risk of BE and EAC.[90] The IGF pathway is also involved in the risk of progression from BE to EAC.[91] Circulating levels of leptin also had an association with BE and progression of BE to EAC.[25,79,85,92,93] Decreased circulating level of adiponectin also seems to be associated with BE and progression to EAC in some, but not all, studies.[85,92,94,95] Complex metabolic effects of obesity seem to have synergistic effects with GERD on the risk of BE and EAC.[96,97]

COLORECTAL ADENOMA AND CANCER

Obesity is an important risk factor for colorectal adenoma and cancer. Previous studies showed a positive association between obesity measured by BMI and colorectal cancer,[98,99] recent studies suggested that abdominal obesity and metabolic syndrome were stronger predictors of colorectal adenoma than BMI, a marker of general obesity.[100,101] Visceral adipose tissue (VAT) is associated with insulin resistance and higher circulating levels of IGF-I, which may induce carcinogenesis by increased cell proliferation and reduced apoptosis.[102] Several studies demonstrated that direct measurement of VAT using computed tomography is a better predictor of insulin resistance or hypertension than waist circumference or BMI.[103,104] Small studies were inconsistent about the association between VAT and colorectal neoplasia.[105-107] However, a large cross sectional study using 3,922 screening persons demonstrated colorectal adenoma had a positive association with VAT and high waist circumference when they were considered separately but only VAT contributed to colorectal adenoma when both were considered simultaneously.[4] Obesity measured by BMI seems to impose a greater risk of colorectal cancer for men than for women.[98,108,109] In a large study, colorectal adenoma had a dose-response correlation with VAT in both sexes, whereas it was related with metabolic syndrome, BMI, and waist circumference in men but not in women.[4] Women seem to accumulate less VAT with weight gain than men.[3,110]

Large prospective cohort studies have demonstrated that obesity increases the risk of colorectal cancer by 1.5-fold compared to normal weight persons.[111] However, a recent Western study showed no association between BMI and CRC.[112] In sex-specific meta-analysis, the incidence of colorectal cancer was higher with obesity, with relative risk (RR) varying from 1.37 to 1.95 for CRC in men, whereas the association between obesity and CRC was weaker in women.[113-115] The incidence of CRC was higher in women with obesity in two of the three studies (RR, 1.15).[114-116] A pooled analysis using 300,000 Japanese subjects reported a significant association between BMI and CRC (HR [per 1 kg/m^2 increase in BMI], 1.03 and 1.02 for men and women, respectively).[117] Two studies showed a significant increase in colon cancer in men but not women (HR [per 5 kg/m^2 increase in BMI], 1.12 and 1.25).[118,119] A recent Western study showed no association between BMI and CRC.[112] In summary, BMI appears to increase the risk of CRC in men, but less in women. This gender difference may be explained by a protective effect of estrogen attributable to apoptosis induction and cell proliferation inhibition[120] or differences in adipose tissue distribution, as the more pronounced visceral adiposity in men than in women.[121]

LIVER DISEASE

1. Nonalcoholic fatty liver disease

NAFLD is the most frequent chronic liver disease and its prevalence is 14% to 30% of the general population. Obesity is the most important risk factor for NAFLD. The prevalence of NAFLD is 4.6-fold in the obese population and up to 74% of obese individuals have fatty liver.[122] Among morbidly obese patients undergoing bariatric surgery for weight loss, 84% to 96% have NAFLD and 2% to 12% have severe fibrosis or cirrhosis.[123-125] NAFLD is also strongly associated with insulin resistance and metabolic syndrome.[126,127] Among individuals with NAFLD, about 90% have features of metabolic syndrome.[128]

The development of NAFLD is known to be through a "two hit" process.[129,130] The first "hit" includes accumulation of fat in hepatocytes, which is associated with insulin resistance, and

fatty acid metabolism dysregulation that leads to steatosis. The second "hit" causes hepatocyte inflammation and necrosis, which can lead to cirrhosis and fibrosis.[129,130]

2. Advanced hepatitis C-related disease

The presence of hepatic steatosis, along with obesity and diabetes mellitus, seems to increase the risk of HCC in chronic HCV. Hepatic steatosis is one of established histopathologic features of chronic HCV with a prevalence from 31% to 72%.[131-134] A Japanese cohort study demonstrated that hepatic steatosis increases the risk for the development of HCC in chronic HCV (RR, 2.81) and BMI directly correlated with steatohepatitis.[135] In a Japanese cohort study consisted of 1,431 patients with chronic HCV following for up to 10 years, obesity is an independent risk factor for HCC development in chronic HCV.[136] The risk of HCC in chronic HCV increased in overweight patients (HR, 1.86) and obese patients (HR, 3.10) as compared to underweight patients.[136] Another Japanese cohort study demonstrated that diabetes mellitus, based on a positive 75 g oral glucose tolerance test, increased the risk of HCC development in chronic HCV.[137] NAFLD and its associated risk factors such as obesity and diabetes increase the risk of HCC development in chronic HCV.[138]

3. Cirrhosis and HCC

Several epidemiologic studies have suggested the possible link between diabetes mellitus and HCC.[139,140] Many patients with diabetes have NAFLD, a risk factor for HCC. It seems that NAFLD causes HCC via cirrhosis, even if the exact pathogenesis is unclear. One study showed that features of nonalcoholic steatohepatitis (NASH) are more frequently observed in HCC arising in cryptogenic cirrhosis than in HCC patients of viral or alcoholic etiology.[141] HCC may be a late complication of NASH-induced cirrhosis. NAFLD, the predominant manifestation of metabolic syndrome in the liver can progress to cirrhosis and HCC.[142] Metformin decreases HCC risk in a dose-dependent manner in both population-based and *in vitro* studies.[143]

PANCREATO-BILIARY DISEASE

1. Gallstone and biliary cancer

Obesity is well known risk factor of cholesterol gallstone and exposes patients to increased risk of gallstone-related complications and cholecystectomy. Clinical and epidemiological studies have suggested that obesity is positively related with the risk of gallbladder cancer. Obesity may modulate lipid and endogenous hormones metabolism, affect gallbladder motility, increase the risk of gallstones, and also increased the risk of gallbladder cancer.[144]

Several epidemiologic studies suggested an association between diabetes mellitus and cholangiocarcinoma. A meta-analysis using 15 studies demonstrated that patients with diabetes had a higher risk of cholangiocarcinoma comparing to individuals without diabetes.[145] Another meta-analysis using nine articles (four case-control and five cohort studies) showed that patients with diabetes had an increased risk of extrahepatic cholangiocarcinoma (OR, 1.61 for case-control studies; RR, 1.61 for cohort studies).[146]

2. Pancreatic cancer

Several epidemiologic studies have suggested relationship of pancreatic cancer with high body mass and lack of physical activity.[147-149] High BMI (BMI of ≥30 kg/m^2) was associated with an increased risk of pancreatic cancer compared with normal (BMI of <23 kg/m^2). Moderate physical activity had an inverse relationship with pancreatic cancer comparing to the highest and lowest categories. Furthermore, high BMI is associated with decreased survival in patients with pancreatic cancer.[149,150] Overweight or obese individuals develop pancreatic cancer at a younger age than persons with a normal weight.[149]

GASTRIC CANCER

The association between obesity and gastric cancer has not been well studied. A meta-analysis from 10 studies with 9,492 gastric cancer and 3,097,794 total population demonstrated that obesity (BMI>25) was associated with an increased risk of gastric cancer (OR, 1.22).[151] In stratified analysis, obesity (BMI>25) was associated with an increased risk of cardia gastric cancer (OR, 1.55) and gastric cancer among non-Asians (OR, 1.24) but had no association with noncardia gastric cancer and Asian gastric cancers.

Another meta-analysis from 24 prospective studies with 41,791 cases demonstrated that both overweight (BMI, 25 to 30) and obesity (BMI≥30) were not associated with risk of total gastric cancer.[152] However, BMI was positively associated with the risk of gastric cardia cancer but not with gastric noncardia cancer. These results indicate that obesity is related with cardiac cancer but not with noncardiac cancer.

FUNCTIONAL GASTROINTESTINAL DISEASE

Meta-analysis of 21 studies comprising data from 77,538 individuals demonstrated obesity increased the risk of upper abdominal pain (OR, 2.65), gastroesophageal reflux (OR, 1.89), diarrhea (OR, 1.45), chest pain/heartburn (OR, 1.74), vomiting (OR, 1.76), retching (OR, 1.33), and incomplete evacuation (OR, 1.32), whereas all abdominal pain, lower abdominal pain, bloating, constipation/hard stools, fecal incontinence, nausea and anal blockage had no association with obesity.[153]

For Australian adults, the prevalence of 26 gastrointestinal symptoms was determined by a validated postal questionnaire which was sent to 5,000 randomly selected residents.[154] The response rate was 60%. The prevalence of obesity (BMI≥30 kg/m^2) and overweight was 25.1% and 36.1%, respectively. The

adjustment for socioeconomic characteristics and eating behaviors had a positive association with abdominal pain (OR, 1.34), esophageal symptoms (OR, 1.35), and diarrhea (OR, 1.86), whereas dysmotility symptoms and constipation had no association with obesity.[154] Of 3,927 invited subjects, 1,731 (44.1%) responded to the questionnaire to assess the occurrence of functional bowel (FB) symptoms in Northern Norway.[155] In a multivariate regression model, obesity increased the risk of FB (OR, 1.61).[155]

Upper abdominal pain may be related to postprandial stomach distention or delayed gastric emptying. Diarrhea may be related to increased food intake leading to increased osmotic loads and poor stool consistency.

METABOLIC AND MEDICAL EFFECT OF WEIGHT REDUCTION

Weight reduction improved metabolic syndrome and insulin resistance and subsequently may reduce the risk of obesity-related benign diseases.[156,157] Many observational studies have shown that people who have a lower weight gain during adulthood have a lower risk of colon cancer, breast cancer, and endometrial cancer. Because most studies about whether weight reduction prevents cancer were from cohort and case-control studies, these observational studies can be difficult to interpret. Nevertheless, weight reduction has been recommended for cancer prevention in world-wide.

Obesity also may contribute to poor prognosis and low survival in obesity-related cancer patients. Weight reduction by bariatric surgery appear to reduce obesity-related benign disease and cancers in extreme obese perosons.[158-160] Also bariatric surgery in extreme obese patients reduced all-cause and cause-specific mortality.[161] The high effect of Bariatric surgery on obesity-related medical condition may be below; whereas most lifestyle modification result in weight reduction of less than 10 percent, bariatric surgery combined with lifestyle changes result in weight reduction of 30 percent.

In one observational study of 1,053 patients with stage III colorectal cancer, neither BMI nor weight change was significantly associated with an increased risk of cancer recurrence and death in patients with colon cancer.[162] In one cohort study of 25,291 colon cancer patients who received treatment in adjuvant chemotherapy trials, obesity and underweight status were associated independently with inferior outcomes.[163] Recent meta-analysis using eight studies showed that obesity is associated with poorer overall and breast cancer survival in pre- and post-menopausal breast cancer.[164]

Several studies about medical weight reduction strategies showed successful weight reduction in cancer patients. A telephone-based lifestyle interventions led to significant weight loss that was still evident at 24 months, without adverse effects on quality of life, hospitalizations, or medical events.[165] In a multicenter study using 692 overweight and obese women with breast cancer, a behavioral weight loss intervention can lead to clinically meaningful weight loss.[166] But it should be further evaluated whether these intentional medical weight reduction has potential benefit on cancer recurrence and survival or not. Nevertheless, intentional weight reduction has been recommended as one of the important life style modification in obesity-related cancers.

CONCLUSIONS

Overweight and obesity, particularly abdominal visceral obesity, increased the risk of a wide spectrum of benign digestive diseases such as GERD, BE, erosive esophagitis, NAFLD, gallstones, and pancreatitis and digestive organ cancers such as cholangiocarcinoma, HCC, pancreatic cancer, colorectal cancer, and esophageal cancer.

Both mechanical and humoral factors caused by obesity seem to be involved in the development of esophageal diseases, whereas pathophysiology of other digestive disorders seems to be related with obesity induced proinflammatory and inflammatory cytokines. Excessive weight and adiposity induce increase of free fatty acid, TNF-α, and resistin and decrease of adiponectin. This results in insulin resistance and altered IGF-1 pathway and inhibits apoptosis and increase cell proliferation on target cells.

Therefore weight reduction can improve the insulin resistance and subsequently seems to reduce the incidence of obesity-related cancer and mortality.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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