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Gastroenterol Clin N Am
34 (2005) xi–xiii

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Preface

Obesity

David A. Johnson, MD, FACP, FACG
Guest Editor

Obesity has become a major health problem in most industrialized nations. In the United States, obesity may be responsible for more than 300,000 deaths per year. Additionally, obesity has costs from medical expenses and lost productivity that are estimated to exceed $100 billion per year. Obesity has particular relevance for gastroenterologists because of the associated causality of gastrointestinal (GI) disorders such as cholelithiasis, pancreatitis, liver disease and GI cancer (in particular colon). Additionally, gastroenterologists often evaluate and treat the GI-related anatomic and metabolic complications following surgery for obesity. In the very near future, it is anticipated that gastroenterologists additionally may play a viable role as therapeutic endoscopic therapies continue to evolve.

Pender and Poires define the epidemiology of obesity. Approximately 100 million adults meet the criteria for obesity, and this number continues to rise. Although the number of obese adults has doubled from the 1980s, the number of morbidly obese adults has quadrupled. Their article sets the perspective that all physicians, irrespective of specialty, are dealing with a high percentage of patients that meets the definition of obese.

The metabolic consequences of diabetes are extremely prevalent but also potentially reversible by effective intervention strategies. Drs. Richardson and Vinik evaluate the metabolic consequences of obesity and highlight which of these are amenable to correction with weight reduction achieved by gastric bypass.

There is an alarming array of metabolic complications that may develop following surgical treatment of obesity. Drs. Jalagani and Vinik provide

0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.011

a summary of these conditions that may present as GI consequences. Prevention, diagnosis, and treatment of these disorders are necessary parts of lifelong care of patients after bariatric surgery.

Obesity has been linked as causal for symptomatic gastroesophageal reflux disease (GERD) in many patients. Although patients with GERD typically are told to lose weight, the data to support this have not been evidence-based. Drs. Katz, Uribe, and Shah review the available literature on the implications for causality of obesity and the response to weight reduction interventions.

It is recognized that one of the very prevalent GI complications of obesity is liver disease. In fact, autopsy series demonstrate that obesity is associated with a sixfold increase in the relative risk for cirrhosis. Obesity often is accompanied by the metabolic syndrome, a chronic inflammatory condition that promotes insulin resistance and hepatic lipid accumulation (fatty liver). Dr. Diehl presents a review of the disease association and the implications for treatment.

The complications of diabetes extend beyond the metabolic complications. There is growing recognition of the potential carcinogenic consequences of excessive endogenous insulin production associated with type II diabetes. Dr. El-Serag discusses the consequences of this condition as it relates in particular to the esophageal and colon cancer potential risks.

Diet intervention has been a mainstay of therapy for obesity treatment. Over the years, may of these fad-type diets have been shown to have little benefit. Recently, there has been a great deal of interest in the best and most scientifically founded dietary interventions. Dr. Balart presents an overview of the latest popular dietary strategies. Whether these diets will be fads... or famous is the focus of his discussion.

The pharmacologic approach to therapy for obesity, albeit a potentially viable option as opposed to surgery, has not been shown in the past to be effective in inducing or sustaining weight loss. Dr. Kaplan provides an overview of past, present, and future medical and pharmacologic therapies. In the subsequent article, he also provides guidance as to improved recognition for the symptoms related to bariatric surgery and how to deal with these often problematic and occasionally debilitating complaints.

Surgical intervention for obesity can be classified into two broad categories: those that that cause gastric restriction or maldigestion and malabsorption. Drs. DeMaria and Jamal review the past surgical intervention strategies and focus on the safety and effectiveness issues of current best surgical practice.

The idea of endoscopic treatment of obesity was introduced in the early 1980s with the Garren balloon. Although this approach was associated with a sizeable complication rate that ultimately led to the product being withdrawn from the market, interest has remained concerning the prospect of developing space-occupying intragastric devices to facilitate weight loss. Additionally, given recent advances in endoscopic placations and suturing,

these approaches are emerging as potentially viable strategies. Drs. Rajan and Gostout provide insight into the potential horizon role of endoscopy as therapeutic intervention.

There is an increasing awareness of the GI consequences of bariatric surgery that require endoscopic intervention. Drs. Huang and Farraye provide an overview of the role of endoscopy in the diagnosis and management of GI complications of bariatric surgery. Given the increasing prevalence of obesity and the increasing number of surgeries for this indication, it is key that gastroenterologists understand not only the endoscopic appearances, but also appropriate intervention strategies.

There clearly is an epidemic of obesity. Given the prevalence of this condition, any physician providing clinical care will be involved in the care of obese patients. Gastroenterologists will play an active role in the evaluation and treatment of these patients. Thereby, it is essential to fully understand the scope of the problem and the opportunities for intervention. On behalf of the authors of each of these articles, I would issue our collective hope that this monograph provides you an expanded insight and enhances the care plan you can provide to this patient population. If those goals are achieved, then the intent of the authors is sanctified.

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Epidemiology of Obesity in the United States

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A description of art history would not be complete without a description of Paleolithic art. *The Venus of Willendorf,* 24,000–22,000 BC (Fig. 1) is one of the earliest examples of art that is in existence today. Residing at the Naturhistorisches Museum in Vienna, the *Venus* is carved out of limestone and stands 11.1 cm tall. Modern man's imagination would probably create an image similar to movie star Daryl Hannah in *Clan of the Cave Bear*. The *Venus'* creator however, sculpted an obese figure whose thighs are pressed together to the level of the knees. She reminds clinicians today of a figure in the examination room of the nation's obesity clinics.

Although it is doubtful that this sculpture represents the typical woman of the Paleolithic era, she does prove that there have been obese people since the dawn of man. So what is all the current discussion concerning obesity about? Why is mankind suddenly so concerned with something that has been around since *The Venus of Willendorf*?

In the United States, approximately 300,000 annual deaths are attributed to obesity [1]. Severe obesity is associated with a twofold increase in mortality [2]. In comparing the life expectancy of the obese with that of the nonobese, one finds a significant number of years of life lost (YLL). Severe obesity can result in a 22% reduction of life expectancy. There is a significant difference in estimated YLL between the different races and between genders. Generally, younger obese adults had more YLL compared with older obese adults. Black men younger than 40 had the maximum YLL at 20 years [3].

Cost

The estimated burden of obesity is based on the prevalence of the diseases and estimated proportion of the diseases attributed to obesity [4]. As such,

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doi:10.1016/j.gtc.2004.12.010

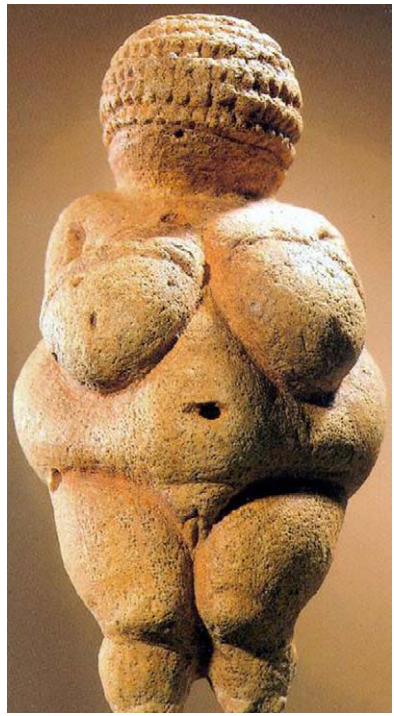

Fig. 1. Venus of Willendorf (c. 24,000–22,000 BC) (Courtesy of Naturhistorisches Museum in Vienna, Austria).

the combined indirect and direct cost of obesity has been estimated at $117 billion [5]. This cost of obesity-related disease consumes upwards of 6% of United States health care dollars, second only to tobacco-related costs [6]. In most European countries, the percentage of national health care cost is generally one third of the United States costs [5].

Prevalence

There are several methods for classifying an individual as being overweight. The standard (which is not perfect) takes the patient's weight in kilograms and divides this by height in meters squared. The resulting number or body mass index (BMI) can be used to classify how overweight a person is relative to others. The Metropolitan Life Insurance Company tables have the BMI cutoff for obese as 27.8 or more in men and 27.3 in women. This BMI generally reflects a 20% increase in the individual's ideal body weight (IBW) [7]. A BMI of 40 generally corresponds to 100 pounds over IBW, categorizing the patient as morbidly obese (Table 1).

The 1991 National Institutes of Health Consensus Conference on the surgery of obesity underscored the importance of this threshold with its

Table 1
Weight categories according to the National Center for Chronic Disease Prevention and Health Promotion (Centers for Disease Control and Prevention)

Body mass index	Weight status
Below 18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
30.0 and above	Obese

declaration that diets, exercise, behavioral modification, and drugs are not effective in the morbidly obese [8]. Several of the recent surveys documenting obesity trends have noted that there is a tendency toward over-reporting height and under-reporting weight in the surveys that gather their information over the telephone. This bias in the reporting can underestimate the increase in the most overweight groups.

There have been several recent surveys from which the BMIs of Americans within the last few years can be compared with those of the past decades. From 1999 to 2000 as part of the National Health and Nutrition Examination Survey (NHANES), a cross-sectional, stratified, multistage probability survey of 4115 adult men and women in the United States was undertaken. Since 1960, these surveys have been used to determine obesity trends in America. NHANES III is a statistically represented national probability sample of the United States. Part of this comprehensive health examination of the noninstitutionalized, civilian population involved height and weight measurements [9].

Data from NHANES III showed the prevalence of obesity had increased by 8% over the period of 1988 to 1994 [9]. Obesity in the United States had been relatively stable during the period of 1960 to 1980. NHANES III data has estimated the overall prevalence of obesity in the United States to be 22% [10] (Fig. 2).

The Behavioral Risk Factor Surveillance System (BRFSS) is a telephone survey conducted by the Centers for Disease Control and Prevention questioning a cross-section of noninstitutionalized civilian adults. The questionnaire primarily asks about behaviors that increase the risk of the top 10 causes of death in the United States [11]. From 1986 to 2000, data were collected, and from this, obesity trends have been examined. Even with the self-reporting bias, there has been a quadrupling in the prevalence of individuals with a BMI of 40 or greater during the 14-year data period, and the prevalence of the superobese (BMI greater than 50) increased by a factor of five. The prevalence of obesity (BMI greater than 30) increased by a factor of two [12].

The BRFSS estimated prevalence is almost 50% of that estimated by the NHANES III data. This discrepancy is the result of under-reporting of weight and over-reporting of height in the self-reporting data collection survey of

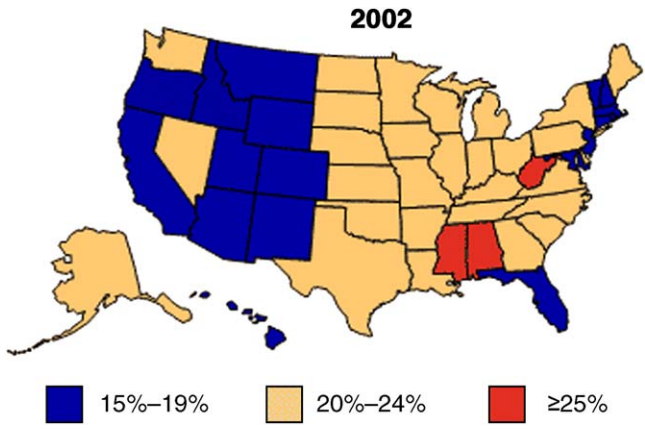

Fig. 2. Obesity prevalence, 2002. (*From* the National Center for Chronic Disease Prevention and Health Promotion.)

BRFSS. The NHANES data are based on measured weight and height. Nonetheless, both surveys have revealed an alarming trend in obesity.

Race

This increase is seen in every region, race, gender, and educational level across the United States [9]. From 1960 to 1980, the prevalence of obesity increased by 3% in white women, 6% in white men, and 7% in black women. In black men, however, the prevalence of obesity increased by 28% [13]. The more recent data of the NHANES III found no significant difference between racial/ethnic groups in the prevalence of obesity in men. About 50% of non-Hispanic black women age 40 years and older, however, were found to be obese. Also, 80% of non-Hispanic black women had a BMI of greater than 25, compared with the general population prevalence of 64% [9].

Age

The age of onset of obesity can determine the relative risk of obesity-related mortality. A study 300,000 subjects in the American Cancer Society's Cancer Prevention Study I confirmed that greater body weight is associated with a higher relative risk of death. This relative risk associated with greater BMI declines with age. Younger adult subjects who have a BMI greater than 25 have a higher relative risk of death from any cause and from cardiovascular disease than older individuals with a similar BMI [14].

Recently, there has been great attention paid to the obesity trend in children and adolescents. Examination of the NHANES data found that the prevalence of obesity has increased in some age and sex groups of preschool children. Comparing 4- and 5-year-old girls who were overweight in 1971 through 1974 with those who were overweight in 1988 through 1994

demonstrated an increase from 5% to 10%. Comparing these same periods for children between the ages of 2 months to 5 years found the prevalence to be higher for girls than boys. There was no change in the prevalence of overweight in the 1- to 3-year olds during these periods. Examination of race during these periods revealed that the prevalence of overweight among children is higher in Mexican American populations than in non-Hispanic blacks and non-Hispanic whites [15].

The prevalence of overweight in children, defined as a BMI of greater than the 95th percentile for age and sex was examined by the National Longitudinal Survey of Youth. This cohort of 8270 children collected data on children aged 4 to 12 years. It found that prevalence increased significantly among white ($P = 0.03$), Mexican American ($P < 0.001$), and African American ($P < 0.001$) children. The prevalence of overweight in children increased to 21.8% among Mexican American children, 21.5% among non-Hispanic black children, and 12.3% among non-Hispanic white children by 1998. Compared with 1986, overweight children in 1998 were heavier ($P < 0.001$). Also, demographic differences in the prevalence of childhood overweight by 1998 could be seen, as overweight increased fastest among minorities and southerners [16]. Examination of the NHANES data from 1999 to 2000 for adolescents revealed the prevalence of overweight among 12- through 19-year olds as 15.5%. This is compared with a prevalence of 10.5% from 1988 to 1994 (NHANES III) [17].

Etiology

The etiology of obesity is both simple and complex. Until recently, the accepted dogma was that obesity occurs when the intake of calories exceeds expenditure. It is now apparent however, that genetic, environmental, and psychologic factors play major roles in this equation. Some individuals are more efficient in their use of food than others. Others are less efficient in storage, energy expenditure, and mobilization of fat stores.

Genetic factors are apparent in the much higher prevalence of obesity in children of the morbidly obese and in variations among ethnic groups such as the Pima Indians. Environmental factors are more difficult to define, but the evidence points to the recent changes in American lifestyle, including less exercise, increased consumption of soft drinks, large portions, and the ready availability of inexpensive foods. Psychologic factors include binge eating. In addition, medical factors such as hypothyroidism, Cushing's disease, pregnancy, trauma, and the use of some steroids or tranquilizers frequently are followed by an increase in weight.

Summary

The challenges of the epidemic are not limited to concerns about bulk and weight. The disabilities caused by obesity are physiologic and

psychosocial. The increased waist to hip girth is associated with increased risk of cardiovascular disease, hyperlipidemia, hypertension, and diabetes [18]. Obesity also has been related directly to increased risk of sleep apnea, cancer [19], gallbladder disease, musculoskeletal disorders [20], severe pancreatitis [21], bacterial panniculitis [22], diverticulitis [23], infertility [24], urinary incontinence [25], and idiopathic intracranial hypertension [26]. The psychosocial factors and quality of life in the obese population also have been documented. Although there is some debate, the obese have been found to be twice as likely to suffer from anxiety, impaired social interaction, and depression when compared with the nonobese population [27,28].

Although advances in obesity surgery have resulted in long-term, lasting treatment of this disease and some of its comorbidities (ie, diabetes, hypertension, sleep apnea), There is a pressing need to develop a comprehensive medical and nutrition plan to reduce the prevalence of this newly identified disease state. Some draw parallels to tobacco and the morbidity and mortality associated with its use. Perhaps there are similarities in these two epidemics. Both start with education of the population as to the morbidities and mortality associated with the disease. As with tobacco, this education is especially important for youth. Without a plan of education to promote nutrition and increased physical activity, and continued research into the causes of obesity, the prevalence of obesity will continue to rise in the United States.

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Metabolic Implications of Obesity: Before and After Gastric Bypass

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The United States and worldwide prevalence of obesity is accelerating and has doubled in the last 20 years [1]. The latest National Health and Nutrition Examination Survey shows that over 60% of adult Americans are obese or overweight, and half of these people are obese (Fig. 1).

The rapid increase in obesity and overweight in the United States and elsewhere has generated a secondary epidemic of metabolic syndrome insulin resistance, (dysmetabolic syndrome) [2–11], with all its attendant cardiovascular risk factors.

This is especially true for type 2 diabetes mellitus (T2DM) [4], which is associated most directly with body weight (Fig. 2) [6–12], but also with hypertension, dyslipidemia, and microalbuminuria [2–5]. In a national sample of adults, a 1 kg increase in measured weight increased the risk of diabetes by 4.5% [10]. Even in the top half of the normal, healthy weight range (body mass index [BMI] 22.0 to 24.9), women in the Nurses' Health Study and men in the Health Professionals Follow-up Study doubled their risk of developing diabetes [13].

Metabolic syndrome most recently has been defined as the constellation of insulin resistance (manifested by fasting glucose over 110 mg or a diagnosis of T2DM), visceral adiposity (resulting in abdominal obesity and increased waist circumference), high blood pressure, and dyslipidemia (hypertriglyceridemia or low high-density lipoprotein [HDL] cholesterol) [14] (Fig. 3). Metabolic syndrome also is associated with nontraditional risk factors, which include microalbuminuria [15], endothelial and neurovascular dysfunction [16], and a proinflammatory/prothrombotic state including

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doi:10.1016/j.gtc.2004.12.009

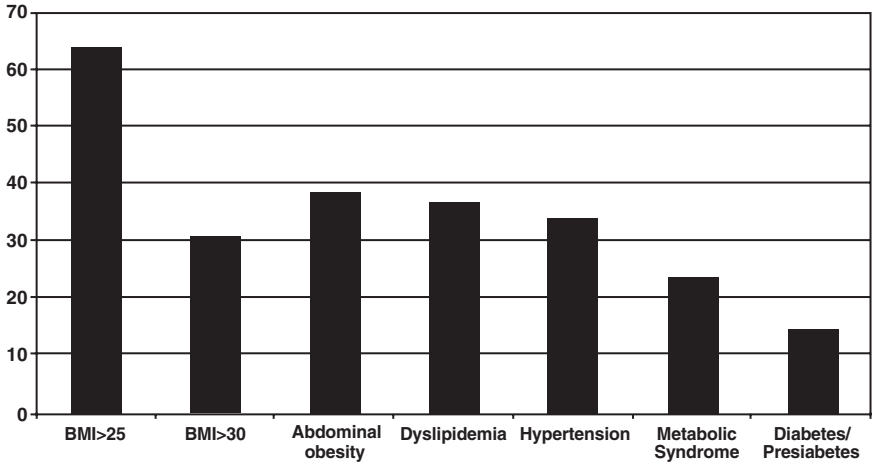

Fig. 1. Percentage of the adult population (*Data from* National Health and Nutrition Examination Survey).

elevated C-reactive protein, tumor necrosis factor α (TNF-α), interleukin (IL)-6, fibrinogen, plasminogen activating inhihitor-1 (PAI-1) [2] (Fig. 4). First associated by Reaven [17] as a syndrome whose components were related by insulin resistance, the cluster of risk factors that define metabolic syndrome increase cardiovascular disease morbidity by two- to threefold [2,13,17–19]. Twenty-four percent of all United States adults have metabolic syndrome, while 40% of adults over 50 years of age are afflicted [2–5]. By age 65, every second American will have it [4].

Additional metabolic abnormalities associated with obesity (and metabolic syndrome) include polycystic ovaries syndrome (PCOS, the

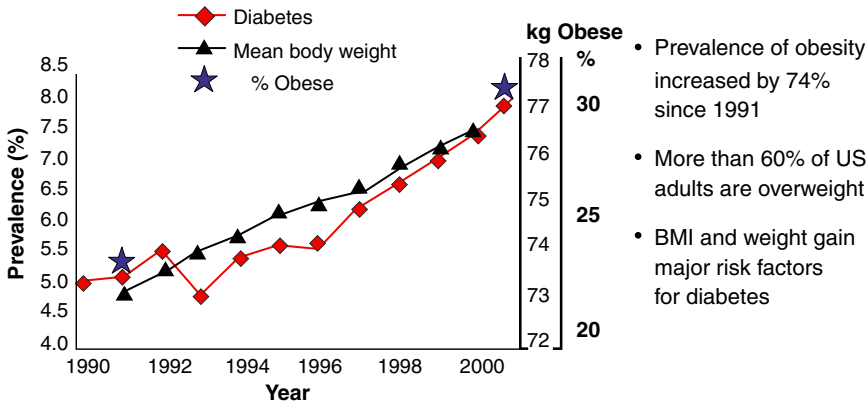

Fig. 2. Prevalence of obesity and diabetes (1990–2000). (*From* Ford ES, Mokdad AH, Giles WH, et al. Obes Res 2003;11:1223–31; with permission.)

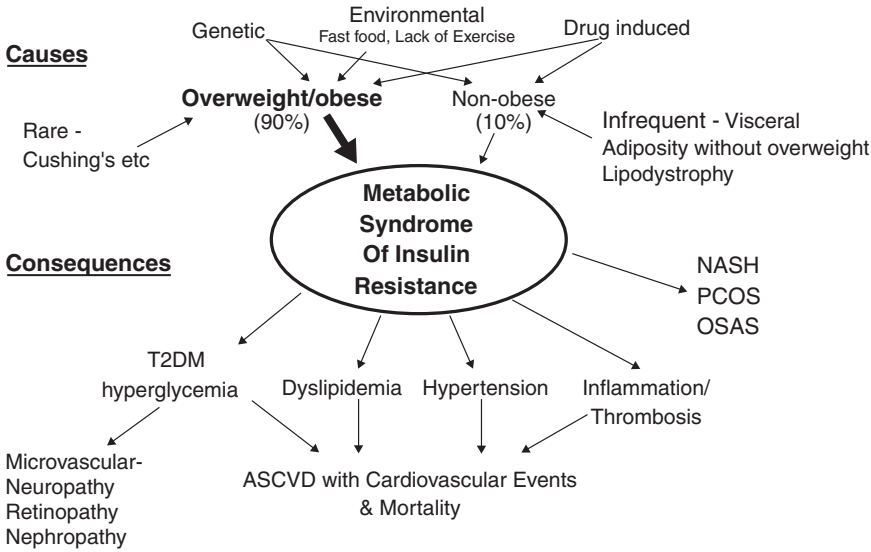

Fig. 3. Metabolic syndrome.

most common chronic disorder in women) [20] and nonalcoholic steatohepatitis (NASH), which is arguably the most common cause of chronic liver disease in the United States, Europe, and Japan [20,21]. PCOS affects approximately 4% to 10% of women. It is associated with hyperandrogenism, hirsutism, anovulation, infertility, and increased cardiovascular and cancer risk. NASH occurs in 2% to 4% of the population [2] with its precursor, nonalcoholic fatty liver disease (NAFLD, or hepatic steatosis) occurring in 16% to 23%. PCOS and NASH are rising with the obesity tide.

Nonmetabolic but equally distressing chronic conditions engendered or aggravated by obesity include osteoarthritis of the spine, hips, knees and feet; hypoventilation and sleep apnea (which have been associated with atrial fibrillation and cor pulmonale); and obesity-induced hypogonadism in males. Sleep apnea and sleep disturbance also have been associated with insulin resistance, and treatment of sleep apnea may result in improvements in insulin-mediated glucose disposal [22].

Causes of the obesity epidemic

The long-present but ill-supported notion that corpulence might be categorized best as a disease state rather than evidence of a sinful nature, moral turpitude, or failure of will power began to advance with the discovery in 1994 of leptin, the absence of which produces extreme obesity in affected rodents and (rarely) humans [23–25].

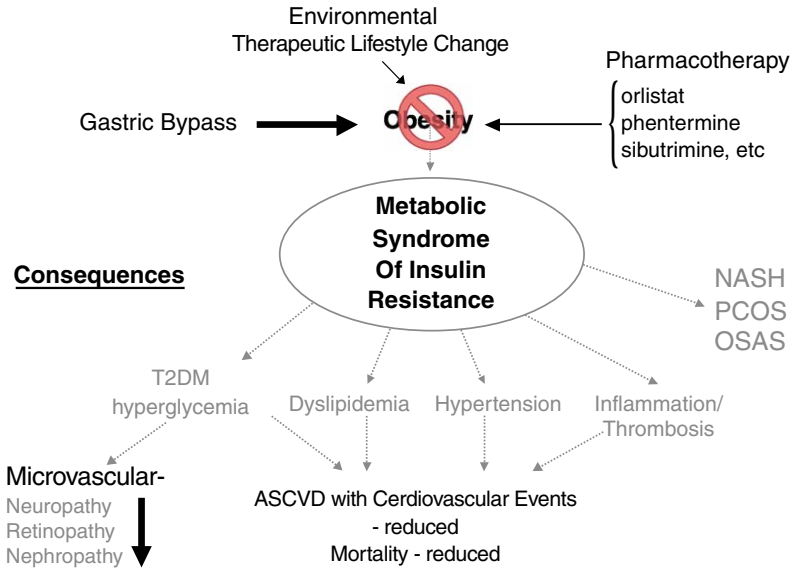

Fig. 4. Metabolic syndrome: causes and consequences.

The centrally mediated component that defends body fat mass after weight loss long has been known from observation of human weight regain in controlled trials of diet, exercise, and pharmacologic weight loss, and from animal experiments. Overweight and obese individuals' efforts to lose weight are stymied by their own physiology. Systems that regulate body weight defend body fat stores by compensatory changes in appetite and energy expenditure that counter any weight loss [26]. Thus, there is strong and increasing evidence that obesity as a disease has a major biologic underpinning, and it should be treated as any other chronic health disorder, using an increasingly aggressive treatment plan as the severity of the disease (increasing obesity) indicates. Treatment should start with therapeutic lifestyle change, escalating through mono- and poly-pharmacologic therapies, and ending in surgical intervention when required by failure of previous efforts or by the magnitude of the obesity, which is beyond the capabilities of the early-line treatments to manage. Similarly, agencies charged with paying for medical costs should be required to include coverage for this disease state, as for hypertension, diabetes, and other illnesses [27].

Although up to 75% of the population is capable of developing excess adipose tissue if provided with plenty of tasty food and no reason to exercise, there are recent environmental factors present in civilization that have created just these conditions. Larger portion size, carbonated beverages, higher fat and fructose sweetener content, lower fiber intake (ie, more refined, processed foods) have been implicated [28,29]. Increasing television or video

game watching and declining exercise during leisure time have been legitimate targets in the search for alterations in the environment [30].

Pathophysiology of metabolic syndrome and its relation to obesity

The fat cell is not a passive depot for storing calories, but an endocrine organ that signals the brain, liver, muscle, islet, and vascular endothelial cells. It modulates their action and metabolism, alters coagulation, actively participates in the hypothalamic-pituitary-adrenal axis, and affects eating behavior and energy expenditure. Leptin proved to be critical to maintaining body weight by means of central and peripheral actions on eating behavior and activity (energy expenditure) and by increasing muscle glucose uptake and fatty acid oxidation [31]. Thus leptin has a positive (dampening) effect on the development of insulin resistance.

Other cytokines produced by the fat cell include IL-6 and TNF-α, which aggravate insulin resistance by reducing muscle glucose uptake. Additionally, by increasing plasma-free fatty acids, TNF impairs insulin signaling. This effect is mediated by activation of serine kinases that phosphorylate insulin receptor substrates-1 and -2. These reduce the ability of serine kinases to mediate insulin action. Although both TNF-α and IL-6 correlate with obesity, impaired glucose tolerance, and insulin resistance, it is IL-6 that is related most to visceral fat stores. IL-6 also increases C-reactive protein (CRP) [32]. Adipose tissue also has receptors for over 12 peptides (eg, insulin, glucagon, growth hormone, and angiotensin II), steroids (glucocorticoid, vitamin D, androgen, estrogen, and progesterone), thyroid hormones, the catecholamine receptors (α1 and 2; β1, 2, and 3), plus the cytokines (leptin, IL-6 and TNF-α), which are produced there. Adipose tissue is modulated by all of these.

All of the adipocyte signaling factors increase in response to fat cell hypertrophy. In contrast, plasma concentrations of the hormone adiponectin, expressed more in subcutaneous as opposed to visceral fat, is related inversely to obesity and insulin resistance, and improves insulin sensitivity when given to obese animals or when levels are elevated by weight loss, thiazolidinedione, or metformin administration [33]. Adiponectin affects liver and muscle, enhancing insulin sensitivity by reducing hepatic glucose output and influx of free fatty acids (FFAs), and increasing fatty acid oxidation and glucose use. Adiponectin also inhibits monocyte adhesion to and increases nitric oxide production in endothelial cells, protecting the vascular wall. Thus, adiponectin is unique among the adipocyte-derived factors because it increases with depletion of fat cell triglyceride store and counters the development of diabetes and suppresses inflammation and atherogenenesis.

Hormones and enzymes (and their substrates) related to the renin-angiotensin-aldosterone axis that are responsible for vascular tone and sodium retention by means of aldosterone secretion (eg, angiotensin II,

angiotensin converting enzyme, and angiotensinogen) also are produced by and correlate with the mass of adipose tissue and provide a connecting link between obesity and hypertension [34].

An additional endocrine role of fat is its generation and metabolism of gonadal and adrenal steroids [32]. Adipose tissue produces many of the enzymes that convert steroid hormones from one class to another (eg, androgens to estrogens by aromatase) but also from active to inactive (or inactive to active) forms within the same class. The outstanding example in this category is 11-β hydroxy steroid dehydrogenase 1, which interconverts cortisone, a poor agonist of glucocorticoid and mineralocorticoid receptors to cortisol, which is a potent agonist of both. As the mass of adipose tissue increases, the relative contribution of these enzymes to whole body steroid metabolism becomes quite significant, with adipose tissue contributing up to 100% of circulating estrogen in postmenopausal women and resulting in suppression of the hypothalamic-pituitary-testicular axis in obese men, rendering them hypogonadal [35–39].

Furthermore, there is evidence that cortisol, produced locally in visceral fat, is implicated in the differentiation of adipocytes from precursors, and may promote the regional adiposity characteristic of metabolic syndrome along with its components and companion syndromes, including diabetes, hypertension, dyslipidemia, hypertension, cardiovascular disease, and polycystic ovarian syndrome [40,41].

A recent evaluation of the offspring of patients with type 2 diabetes also suggests that those at risk for obesity and insulin resistance may have inherited a defect in mitochondrial oxidative phosphorylation, resulting in impaired intramyocellular fatty acid metabolism. This provides further support for the view of obesity and the propensity for it to be biologic.

Not all obese persons have metabolic syndrome. In fact, various studies report that as many as 20% of obese individuals are insulin sensitive when formally studied, and epidemiologic studies defining metabolic syndrome have an even higher proportion [4,42–44].

Likewise, there are nonobese patients who meet the other criteria for metabolic syndrome and have increased cardiovascular risk. In both cases, the key differentiating factor seems to be the ratio of subcutaneous fat to visceral fat [44].

Summary of pathophysiology

The pathophysiologic underpinning of metabolic syndrome, which accompanies abdominal obesity, is the hypertrophied fat cell and the attendant increased secretion of multiple factors that accompany the triglyceride-engorged adipocyte [32]. As these cells become filled with fat, they release increasing amounts of cytokines (except the protective adiponectin, whose secretion is related inversely to the size of the adipocytes). Other than adiponectin and possibly leptin, all of these have deleterious effects on glucose

and lipid metabolism, increase insulin resistance, and produce inflammation in the liver and vascular system. The increasing release of FFAs from enlarged fat cells increases the delivery of fatty acids to the liver, muscle, and other tissues. Increased FFA reduces glucose use by all these tissues by mechanisms that only now are being elucidated. [45,46]. One of the consequences of this increased delivery of fatty acids is storage of fat in nonadipose tissues, including muscle, the liver, and the pancreas. The latter may play a role developing insulin deficiency and overt diabetes mellitus.

Evaluation of obesity

Obesity implies increased amounts of body fat, but weight alone can be misleading because of variations in body muscle. Indirect measures of fat mass using underwater weighing, electrical impedance, dual energy X-ray absorptiometry scanning, or fat imaging using CT or MRI are cumbersome and expensive. Instead, most practitioners and even research protocols substitute BMI as a reasonable indicator of obesity. BMI is calculated as kg/m^2. Although it, like the body weight, does not address the degree of adiposity directly (only a 0.7 correlation with body fat; therefore not a precise measure), it provides a reasonable approximation of the degree of obesity. Another key parameter is the waist circumference, which estimates the degree of central adiposity and reflects the metabolically active visceral adipose burden. Both the World Health Organization and the National Cholesterol Education Program include a form of this measure in their respective definitions (see Fig. 3).

Treatment

There are two separate goals worth achieving in people with metabolic syndrome and obesity: reduction of cardiovascular risk to the same as those without these risk factors, and reduction of weight to avoid the direct effects on respiration, joints, income, and psychosocial well being. The former can be achieved by nonweight loss methods to correct dyslipidemia, hypertension, and hyperglycemia. This, however, produces onerous and financially burdensome pill (or insulin)-taking: two to three or more each of antidiabetic, lipid-lowering, and hypotensive agents [47,48]. Thus, a method of meeting metabolic and nonmetabolic goals by means of weight loss, although so far mostly elusive, would be worthwhile, if only to reduce the numbers and expense of drugs required to meet targets for blood pressure, glucose, and lipids.

Lifestyle

Trials of lifestyle intervention, including nutritional and behavior counseling, prescribed exercise, and meal replacement interventions, have been successful, but weight loss generally has been modest (2 to 7 kg more

than control groups) and not sustained (greater than 66% weight regain within 24 months of the end of the active intervention phase of the trials [49–51]), except for the Diabetes Prevention Program [49], where the intensive lifestyle arm members regained only 43% of their lost weight over 4 years.

Herbal

Some randomized trial data are available in the scientific literature about the use of herbal therapies for weight loss. Most deal with ephedrine and caffeine or closely related substances derived from plants. This combination, used pharmaceutically, has a long track record of modest success but now is banned because of concerns about the cardiovascular safety of ephedrine alkaloids [52–55].

Pharmacologic

Several meta-analyses suggest that antiobesity agents are effective and can produce a modest improvement in some of the key cardiovascular risk factors (diabetes, hypertension, and dyslipidemia) [50,51]. Only two weight-loss drugs, orlistat, a lipase inhibitor, and sibutramine, a combined serotonin and norepinephrine reuptake inhibitor, are approved for long-term use. Sibutramine has been removed from the market in Italy and is under investigation elsewhere because of concerns with cardiovascular effects (hypertension and arrhythmias). Although more effective than most behavioral interventions in terms of weight loss, the mean decrease is still dissatisfying (2.7 kg more weight loss on orlistat, 4.6 kg on sibutramine, compared with the control groups, which were essentially on behavioral intervention therapies [51,56,57]). Orlistat treatment had a minor positive effect on other components of metabolic syndrome [51,57]. Waist circumference decreased 0.7 to 3.4 cm, total, low-density lipoprotein cholesterol declined by about 0.3 mmol/L and triglycerides by 0.05 mmol/L. Systolic blood pressure was reduced on average by 1.8 mmHg, and fasting blood sugar was reduced by 1.3 mmol/L. HbgA1C declined by 0.2%. Sibutramine had no positive metabolic effect on any glucose or lipid parameter besides a 0.13 mmol/L increase in HDL, and overall had a negative impact on blood pressure (increase in both systolic and diastolic blood pressure by 1.8 mmHg [56]. Metformin has been used for weight loss, but it is relatively impotent (3% weight loss after 1 year, 2% after 4 years [49]) as a weight loss drug, as opposed to its more evident effects on glucose and insulin concentrations and menstrual cyclicity in PCOS. The α-glucosidase inhibitor (starch blocker) acarbose also has been shown to reduce the frequency of conversion of prediabetes to diabetes [58] Older catecholaminergic agents, such as phentermine, mazindol, and diethylpropion, are not approved for long-term use.

Bariatric surgery

In stark contrast to the average 4% to 8% drop in body weight found with lifestyle change or pharmaceuticals, the effect of bariatric surgery, whether vertical gastric banding (VBG), laparoscopic adjustable gastric banding, or (laparoscopic) Roux-en Y gastric bypass (RYGBP), is spectacular, with typical weight losses of 25 (gastric banding) to 60 kg, or up to 50% of initial body weight (RYGBP). In addition to lower initial weight loss, weight tends to return over time with VBG; most United States surgeons thus prefer RYGBP [59,60].

Benefits of weight loss on metabolic syndrome risk factors, diabetes complications, and mortality

There is abundant evidence that, just as excess adiposity increases the risk of diabetes, hypertension, dyslipidemia, and mortality, so intentional weight loss reduces these risks. Weight loss after gastric bypass, maintained for up to 8 years, reduces blood pressure, improves abnormal lipid levels, and reduces the risk of diabetes by approximately 75%. Postgastric bypass and non-surgically induced weight loss lowers mortality rate (hazard rate ratio) by 24% (0.76; 95% confidence interval, 0.60 to 0.97) [61–64]. It seems that the metabolic and endocrine consequences of obesity are at least in part, reversible.

Large controlled intervention trials in Finland [65] and the United States [47] have proven that weight loss caused by lifestyle intervention (and less successfully, metformin) can reduce the risk of developing type 2 diabetes, reduce blood pressure and triglycerides, and increase HDL cholesterol in high-risk individuals with well-categorized metabolic syndrome. This was accomplished by losing about 4.5% and 7.5% of body weight. Conversion rates from impaired glucose tolerance to diabetes were reduced by 58% (34% by metformin). Fasting and 2-hour postglucose load blood glucose and insulin, triglycerides and total cholesterol, systolic and diastolic blood pressure, and waist circumference were reduced (most parameters below or near 0.05% significance), and HDL cholesterol increased slightly (and nonsignificantly).

Unfortunately, only about 40% of the subjects in the intensive lifestyle treatment groups could meet the lifestyle goals, and benefits diminished over 4 years. These results were, of course, in interested subjects who had volunteered, and then received much better dietary counseling and exercise supervision than available to most people. These results are somewhat depressing, because the standard recommendation for overweight or obese patients with diabetes, hypertension, or other portions of metabolic syndrome is to lose 5% to 10% of their body weight by maintaining a daily 700 calorie deficit and exercising 1 hour per day 6 to 7 days per week. The track record for managing established type 2 diabetes is even worse.

HgbA1C levels and BMI are rising nationwide in spite of multiple new therapies, with a smaller percentage achieving the American Diabetes Association HgbA1C goal of 7% [66].

Results of bariatric surgery: metabolic syndrome and components

Bariatric surgery has emerged as an important therapy for metabolic syndrome for patients starting with BMIs over 35 [67–70]. At 1 year follow-up, metabolic syndrome resolved in 89% of women subjected to laproscopic gastric bypass [71]. Patients with prediabetes uniformly are rendered euglycemic [72]. Sixty percent to 80% of patients with type 2 diabetes resolve their requirement for insulin, and 90% less oral hypoglycemic therapy is required. Additionally, 100% of patients achieve an average HgbA1C of 6%, in contrast to only 58% in the lifestyle interventions (which were in less obese people). These trials are not directly comparable, however, as a critical difference is that the Diabetes Prevention Program and Finnich Diabetes Prevention Study were randomized; in addition the follow-up period for the surgical studies is shorter (2 versus 4 years [72–76]. Hypertension resolves or improves at 1 to 2 years in 80% to 90% of diabetic patients subjected to LRYGPB [72], although with time, it tends to become reestablished [76].

Dyslipidemia

As expected from epidemiologic and interventional trials of weight loss for dyslipidemia, RYGBP resulted in the resolution of hypercholesterolemia in 37% and amelioration in 41% of 107 patients, along with a reduction of myocellular lipid content, which correlates highly with insulin resistance, whereas adiponectin concentrations, which are a marker for insulin sensitivity, rose [77–79].

The inflammatory markers IL-6, TNF-α, CRP, leptin, the procoagulant PAI-1, and angiotensinogen all fall after RYGBP [80,81].

Nonalcoholic fatty liver disease

Unfortunately, while much liver biopsy data have been generated that confirm the high prevalence of hepatic steatosis and steatohepatitis, with unsuspected fibrosis found in up to 10% of patients, the hepatic outcome of bariatric surgery is unknown, although even the presence of cirrhosis seems not to worsen the immediate outcome [82–84]. The jejunoileal bypass was associated with worsening of previous liver injury, which led to its becoming outmoded [85].

Polycystic ovaries syndrome

No prospective trials of surgically induced weight loss have been performed in women with PCOS. The expectation is that bariatric surgery would be

helpful in reinitiating ovulatory menstrual cycles based on (fairly ineffective) attempts to reduce weight using lifestyle change, meal replacement, and metformin [85–88]. The possibility of interference with reproduction by the surgery itself (eg, tubal adhesions) appears not to be of great concern [89].

Complications of type 2 diabetes mellitus

The incidence of diabetic sensory neuropathy is reduced by reduction of blood glucose to near normal [47,90]. Cure of type I diabetes by pancreas transplant has similar effects on sensory and autonomic neuropathy [91]. It is therefore not too surprising that at least one group has discerned an improvement in neuropathy in their gastric bypass patients, all of whom were rendered euglycemic. Diabetic neuropathy was present in 25% of patients preoperatively, and symptomatic improvement was reported by 50% of patients after surgery. Thirty-three percent were much improved, and 17% were improved [74]. In the same study, patient-reported erectile dysfunction was present in 11 of 48 males before gastric bypass; two noted improvement after surgery.

Prevention or reversal of established nephropathy and retinopathy has not been addressed in patients whose diabetes has been cured by bariatric surgery. Using the same models of prevention and cure in type I diabetes mellitus as for neuropathy, one can hope that renal disease will stabilize or improve after weight loss surgery [91].

Summary

The components of metabolic syndrome including type 2 diabetes, plus the associated cardiovascular risk markers (elevated blood pressure, dyslipidemia, and serum markers of inflammation and hypercoagulability) are ameliorated or resolve after RYGBP, with improvement in major comorbidities noted in most patients [72–81]. Although not yet subjected to a truly randomized trial, mortality appears to be reduced compared with the rate in control patients in a well-designed cohort-controlled study [92].

Changes in the political and health care financing of obesity

In April 2003, Zerhouni established the Task Force for Obesity Research that has developed a strategic plan (http://obesityresearch.nih.gov/). This acknowledges the public health challenge and has provided an important advocacy role in the national political arena. The National Institutes of Health have asked for a 10% increase in proposed funding for obesity-related research for 2005, which would be $440 million (still low in comparison to other disease states with less impact on mortality (eg, HIV/AIDS research receives $2.97 billion) [93]. Food and Drug Administration commissioner Dr. Mark McClellan announced that ‘‘accelerated approval’’ (‘‘fast-track’’),

normally reserved for agents targeting terminal cancer or AIDS, would be applied to antiobesity drug development [94]. More recently the Centers for Medicare and Medicaid Services renounced language in the Medicare Coverage Issues Manual stating that obesity is not an illness. This begins a new Medicare policy and should begin to remove barriers for coverage of obesity-related interventions, to be based on medical evidence demonstrating improved health in Medicare beneficiaries. The overall view of health care policy makers, in basic research, public health, and health care finance, appears to be undergoing a sea-change in its attitude to obesity. Legislation will be needed to provide economic disincentives for fast food, portion size, and television watching, and incentives will be needed to reward exercise.

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Gastroenterol Clin N Am
34 (2005) 25–33

GASTROENTEROLOGY
CLINICS
OF NORTH AMERICA

Metabolic Complications of Bariatric Surgery: Diagnosis and Management Issues

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The type and severity of metabolic complications resulting from bariatric surgery vary widely and depend on the particular operation performed. All long-term metabolic complications are observed incompletely, because follow-up of patients after bariatric surgery historically has been poor in the long term [1] or has not included complete data on metabolic status [2].

Gastric banding is a purely restrictive procedure that only decreases the stomach's food capacity. This procedure usually has lower amounts of weight loss than Roux en Y gastric bypass (RYGBP) and other surgical approaches; metabolic complications are lower but not absent. B12 deficiency, severe thiamine deficiency, nutrient-related neuropathy, and bone loss have been reported after vertical banded gastroplasty [3–7] despite assertions that no important nutrient deficiencies occur after this type of procedure [8]. Most studies with metabolic information include small numbers of patients. For example, Giusti et al studied 31 patients after the procedure for 12 months and found no major micronutrient deficiencies (B12, folate, iron) despite significant loss of body fat (36.8%) and lean tissue (9.6%) postoperatively [9]. Parathyroid hormone and 25 hydroxy vitamin D levels were not assessed. Longer-term studies of patients after gastric banding, however, do not report precise nutritional and metabolic evaluations [10], and it is possible that patients losing large amounts of weight in a short period of time may have deficiencies.

RYGBP combines gastric restriction with intestinal bypass. A small gastric reservoir is created from the cardia of the stomach, separated and

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0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.008

anastomosed to the proximal jejunum; nutrients bypass the entire duodenum. Limitation in nutrient intake and malabsorption both occur, and weight loss is greater than with gastric banding alone. Most patients have at least one micronutrient deficiency on long-term follow-up [11] and inadequate protein intake over at least the next year [12]. Severe protein–calorie malnutrition requiring hospital stay and even causing death has been reported [13].

Biliopancreatic diversion combines gastric restriction, intestinal bypass, and additional anatomic rearrangement to create malabsorption by limited nutrient exposure to the distal ileum. It often is reserved for the superobese or those who have failed a previous bariatric procedure [8]. Compared with RYGBP, similar nutrient deficiencies have been observed [14,15].

A significant percentage of patients (20% to 30%) may have micronutrient deficiencies even before surgery despite morbid obesity [8,16,17]. Studies of actual nutrient intake after bariatric surgery show inadequate ingestion of iron, calcium, and folate [18]; not all nutrient deficiencies are related to malabsorption. Therefore, patients usually are prescribed supplements. Oral multi-vitamins, iron supplements, and calcium often are advised [19]. Compliance with vitamins can be poor (33% to 64%), and even taking a typical multivitamin routine with 100% of the RDA of iron, folate, and vitamin B12 did not prevent deficiencies in all patients [16,20].

There are two common and several rare metabolic complications of bariatric surgery.

Complications

Anemia

Anemia occurs frequently after RYGBP and can be a persistent and progressive problem. Prospectively evaluated patients had an incidence of 36.8% despite advice to ingest a multi-vitamin daily; 3.5% required transfusions [21]. Iron deficiency is a common contributor, particularly in menstruating females. In addition to lower intake of iron-containing nutrients such as red meat, legumes, poultry, and fish [18], iron absorption is disrupted by decreased stomach acid and no exposure of nutrients to the duodenum and proximal jejunum where iron is absorbed primarily. A randomized study was conducted in menstruating females administered oral iron (320 mg twice daily) versus placebo in addition to a daily standard multi-vitamin. This routine prevented iron deficiency in those who were compliant with the regimen. The same routine corrected it in those placebo patients who developed iron deficiency and later were started on therapy [17]. Although the incidence of anemia is lower in men, it is not absent or insignificant (22%), and it occurs later in men than in women (29 months postoperatively versus 6 months) [20], illustrating the importance of ongoing follow-up. Nutritional anemias may be multi-factorial after gastric bypass

surgery; deficiencies in B12 and folate have been observed in 70% and 40%, respectively [21]. In addition to decreased intake of both nutrients, both B12 and folate absorption are decreased by reduced gastric acid [22]. B12 absorption is decreased further by inadequate intrinsic factor secretion [23] and folate by the lack of nutrient exposure to duodenum where it usually is absorbed. Folate deficiency is prevented with standard-dose daily multivitamins containing 400 μg of folate, although in reproductive age women, higher amounts may be needed to prevent neural tube defects may be needed [20]. B12 deficiency was treated successfully in 95% of patients with 350 μg of crystalline oral vitamin B12 daily [25]. Intramuscular supplements can be used to treat those who do not respond to oral therapy. One regimen is 1000 to 3000 μg of intramuscular B12 beginning 6 months postoperatively and repeated at 6- to 12-month intervals, but this has not been studied prospectively [14]. B12 and folate deficiencies may contribute to anemia and should be treated. The importance of the downstream effects of subclinical deficiency is illustrated by the case of a woman 2 years after gastric bypass with subclinical B12 deficiency. Her exclusively breast-fed 10-month-old infant developed severe B12 deficiency with vomiting, failure to thrive, and megaloblastic anemia [26]. The importance of maintaining adequate B12 and folate levels in reproductive aged women is demonstrated further by cases of severe neural tube defects in pregnancies after gastric bypass [24].

Vitamin D deficiency and bone disease

Vitamin D deficiency is the second major metabolic complication of weight reduction surgery. Even before obese individuals undergo bariatric surgery, they exhibit abnormalities of the parathyroid axis. Obese individuals have higher parathyroid hormone (PTH) levels and 1,25 hydroxy-vitamin D levels but lower 25 hydroxy-vitamin D levels than normal-weight controls. During observation on a metabolic ward with controlled intake of calcium and phosphorus, obese individuals excreted less calcium in the urine [27]. These observations are consistent with mild hyperparathyroidism, but no individual in this study had actual hypercalcemia. Larger surveys [28] of morbidly obese individuals before bariatric surgery confirm and extend these data. In this study, 25% of individuals had PTH levels above the normal range; hypercalcemia was rare (0.5%), and hypocalcemia was occasional (3.5%). Bone mineral density (BMD) before weight loss can be higher than normal [29]. The cause of these weight-related abnormalities is unknown but may represent an adaptation to the large load on the skeleton obese individuals endure. It is useful to recall that even morbidly obese individuals may harbor micronutrient deficiencies, and a few patients with vitamin D deficiency likely were present in the Hamoiu group also [14,28].

During weight loss, bone density decreases [29]. Supplementing calcium by 1 g per day suppressed indices of bone turnover and reduced bone loss

measured by BMD [30,31]. Bone loss after bariatric surgery may be caused by both alteration in mechanical load of the skeleton and hyperparathyroidism from calcium and vitamin D deficiency or by other factors [32]. A spectrum exists: from normal compensatory adjustment to decreased weight bearing as weight loss occurs all the way to severe metabolic bone disease, osteomalacia with spontaneous fractures, and hypocalcemic tetany [33–35].

Osteomalacia often is not recognized by physicians. Osteomalacia causes diffuse bone pain from microfractures and muscle weakness and a proximal myopathy likely from prolonged high parathyroid hormone levels [36,37]. Arthralgias and synovitis also can occur. Plain radiographs show Looser's lines (pseudofractures), and bone scans show widespread uptake in multiple areas that look like diffuse metastatic disease. Elevated levels of PTH and decreased levels of 25 hydroxy-vitamin D (less than 20 pg/mL is truly abnormal, unlike the reference range listed by most assays) [38] occur well before the onset of depressed levels of 1, 25 hydroxy-vitamin D and hypocalcemia. It has been estimated that one half of the osteomalacia in the United States is caused by gastric surgery, and all physicians would do well to assess vitamin D status in patients with prior gastric procedures [39].

After RYGBP, studies reveal vitamin D deficiency and decreased bone mass even when patients are advised to take 1200 mg of calcium and 400 to 800 IU of vitamin D daily [40]. The magnitude of bone density decline varies from 3% to 9% depending on the site examined within the first year. Ott et al examined 26 patients 10 years after surgery compared with controls who achieved weight loss by diet alone. They found lower serum calcium, increased alkaline phosphatase, low 25 hydroxy-vitamin D, and lower bone mass at the hip (severely depressed in 2 out of 26 patients) [41]. Some of the Roux en Y patients had taken vitamin and calcium supplements. Goode et al [42] attempted to intervene by administering a total of 1.2 g calcium per day plus 8 μg of vitamin D per day (the equivalent of 400 IU) to women 3 or more years after RYGBP. This therapy did not change bone mass, PTH, or bone resorptive markers, most likely because the doses were not high enough [42]. The optimal amount of vitamin D and calcium repletion remains unknown.

Jejunoileal bypass operations were performed commonly in the 1970s but have been abandoned in favor of RYGBP and vertical banded gastroplasty. Patients who have undergone this older procedure still may be encountered. Jorgensen et al studied 84 patients 15 to 20 years after surgery and found vitamin D deficiency and secondary hyperparathyroidism in one third to one half of patients [43]. Vage found low vitamin D levels in 45% of patients 25 years after surgery [44]. Parfitt found osteomalacia by bone biopsy in 20% of patients despite vitamin D2 (5000 IU per day) supplementation [45]. Malabsorption and steatorrhea were purposeful and more severe in these patients. Similarly, after biliopancreatic diversion, hypocalcemia and hyperparathyroidism are very common [46].

Bone loss clearly occurs even after vertical banded gastroplasty [47]. Small studies have not shown evidence of hyperparathyroidism or vitamin D deficiency; it is not known whether bone loss represents skeletal adaptation to weight loss.

Rhabdomyolysis

Rhabdomyolysis can occur from unrelieved muscle pressure during bariatric surgery. A prospective study of 66 patients included 50 who underwent laparoscopic gastric banding and 16 who underwent laparoscopic RYGBP. Four patients (25%) of the Roux en Y group had a creatine kinase level greater than 10,000 IU/L (upper limit of normal 210), complained of low back pain, and had dark urine from myoglobinuria. Acute renal failure did not occur. When creatine kinase rose to greater than 5000 IU/L, clinical measures were instituted, including fluid replacement, forced diuresis, and alkalinization of the urine. Twenty-two percent of patients had creatine kinase levels of greater than 5000 IU/L. Risk factors for rhabdomyolysis included body mass index BMI greater than 60 kg/m^2 and long duration of operation. This study illustrates that this condition is more common than previously thought but that prompt treatment can prevent permanent sequelae [48].

Wernicke's encephalopathy

Wernicke's encephalopathy is caused by severe thiamine (vitamin B1) deficiency (beriberi) and classically presents with a clinical triad of ocular changes (nystagmus, ocular nerve palsies), ataxia, and apathetic mental confusion. Injury to the mamillary bodies and structures around the third and fourth ventricle occur and can be imaged on MRI as symmetric areas of increased T2 signal. Eleven cases have been reported after gastric bypass surgery; two occurred after vertical banded gastroplasty [49–54]. Thiamine is absorbed in the small intestine, mostly in the jejunum and ileum. It is a water-soluble vitamin requiring a continuous ongoing supply. Even patients with purely restrictive operative procedures can develop thiamine deficiency if nutrient intake is inadequate. Cases have occurred as soon as 2 weeks and as long as 13 years after surgery. Fatalities have been reported, but early recognition and immediate treatment with 100 mg of thiamine every 8 hours can be successful.

Vitamin A deficiency

Vitamin A deficiency only has been reported after biliopancreatic diversion. Postoperatively, increasing incidence and severity have been noted (69% by 4 years after surgery) [55]. Occasional symptomatic patients have been reported with typical symptoms of night blindness, xeropthalmia, Bitot spots, and anemia [56,57]. Deficiency of vitamin A (a fat-soluble

vitamin) is caused by the malabsorptive aspects of this procedure. Patients have responded to vitamin A supplementation with resolution of symptoms and signs.

Acute postgastric reduction surgery neuropathy

A unique neuropathy is seen following bariatric surgery. It has been termed APGARS (acute postgastric reduction surgery) neuropathy. The most prominent clinical features are progressive vomiting, weakness, and hyporeflexia. Pain; numbness; incontinence; and impairment of vision, hearing, attention, and memory may occur. Objective signs include gaze-evoked nystagmus, severe proximal symmetric lower extremity weakness, and hyporeflexia. Diagnostic studies show axonal sensorimotor polyneuropathy on electromyogram, worst in the quadriceps; nerve biopsies show demyelination without inflammation. Patients have been treated with nutritional measures, vitamins, and minerals with improvement. APGARS may be an overlap syndrome caused by deficiencies of multiple nutrients [6,58].

Immobilization hypercalcemia

Immobilization hypercalcemia is an uncommon metabolic complication of critical illness sometimes seen in patients with spinal cord injuries [59]. An enhancement of osteoclastic activity by unknown mechanisms causes release of a flood of calcium from bones independent of PTH which typically is suppressed. Hypercalciuria and osteoporosis may occur. Two recent patients have been reported by Alborzi and Leibowitz: one after laparoscopic gastric banding and one after Roux en Y. Both had complicated, long ICU stays. Both responded to pamidronate infusions, and hypercalcemia resolved. These authors also reviewed 17 other bariatric surgery patients who required ICU stays and found two additional patients who had unexplained hypercalcemia [60]. Critically ill bariatric surgery patients may be at increased risk for this metabolic disorder, and calcium levels should be followed.

Recommendations

All physicians should know the potential metabolic problems of these patients and help to diagnose, prevent, and treat them for the entire duration of the patient's life. Although interventional studies are not complete, the following recommendations can be made.

In the immediate postoperative period, monitor creatine kinase levels and institute hydration and urinary alkalinization for extremely elevated values. Monitor calcium in those with complicated courses and long periods of immobilization. Pamidronate should be used to treat immobilization hypercalcemia.

During outpatient follow-up, monitor serum iron, hematocrit, 25 hydroxy-vitamin D, parathyroid hormone, and vitamin B12 levels in all patients at 6-month intervals until stable on replacement, then yearly. Provide multivitamins including 400 μg of folate and 350 μg of vitamin B12 for all patients and 320 mg of iron twice daily for all menstruating females. Administer 1500 mg daily of calcium and vitamin D in amounts to keep parathyroid hormone and 25 hydroxy-vitamin D levels in the normal range, starting with 800 to 1000 IU daily. Physicians should recognize that much higher doses of vitamin D may be required. Monitor bone density every 1 to 2 years. For patients who have undergone malabsorptive procedures, monitor vitamin A yearly. If patients have unusually poor oral intake, administer thiamine parenterally.

Metabolic benefits of bariatric surgery greatly exceed complications. The entire list of metabolic complications can be rectified with prevention or early medical intervention. Obesity is increasingly prevalent and surgical intervention more common, even in children; lifelong follow-up is necessary. The care of patients after bariatric surgery is likely to involve many physicians other than surgeons.

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Gastroenterol Clin N Am
34 (2005) 35–43

GASTROENTEROLOGY
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Gastroesophageal Reflux Disease and Obesity

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Gastroesophageal reflux disease (GERD) is one of the most common disorders seen by primary care providers and gastroenterologic specialists in the United States, affecting up to 40% of the population. Its pathogenesis is multi-factorial. Standard textbooks and review articles refer to weight reduction as an important component of treatment and obesity as a risk factor for symptoms of GERD. Conflicting data also suggest that obesity may be a risk factor for the development of Barrett's esophagus and adenocarcinoma of the esophagus. Despite these references, the scientific foundation for a causal relationship between obesity and GERD is at best marginal, and epidemiologic study are results contradictory. This article reviews the available literature and attempts to put into perspective the relationship of these two common entities.

Effect of food on reflux

The pathophysiology of GERD is complex, and as such, the effects of different foods and their association with reflux are difficult to sort out. The most important pathophysiologic abnormality in GERD is a decrease in lower esophageal sphincter pressure, either in the resting state or in association with a transient lower esophageal sphincter relaxation (TLESR). It is, therefore, crucial to control lower esophageal sphincter pressure when examining the effect of different foods and diet in general on the genesis of reflux episodes or symptoms. The frequency of TLESRs, the dominant mechanism for the occurrence of reflux episodes in most normal subjects and

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0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.003 *gastro.theclinics.com*

patients with mild GERD may change the effects of meals in general and of specific foods on reflux symptoms. So, for example, resting lower esophageal sphincter pressure in normal controls is decreased by fat, which also increases the frequency of TLESRs. Meals with a high fat content would be expected to have the effect of increasing postprandial reflux episodes and predisposing to symptoms of GERD. It should be noted, however, that TLESR frequency may be increased simply by distending the gastric fundus, so any meal, regardless of its composition will to some degree promote reflux. In patients with a low resting lower esophageal sphincter pressure, an increase in postprandial reflux will occur regardless of the meal composition or size because of the incompetent barrier. As such, those with an incompetent sphincter may experience symptoms simply by bending over, stooping, or lying down. Further, the speed at which one eats will affect the frequency of postprandial reflux. Meals eaten quickly (less than 5 minutes) will produce more postprandial reflux than meals eaten slowly (over 30 minutes) [1]. In summary, because of variation in basal or resting lower esophageal sphincter pressure and infrequency of TLESRs, the effect of food and meal composition is difficult to decipher.

Lower esophageal sphincter pressures in obesity have been studied infrequently. In the studies that have been done, however, basal pressure in the morbidly obese appears to be similar to those of ideal body weight [2]. Two studies have shown an increase in the presence of a hiatal hernia in patients with obesity and GERD [3,4]. It is possible that these patients have an increase in intra-abdominal pressure, which may increase the cephalad movement of a hiatus hernia and increase the predisposition to reflux events [5]. Gastric volume has been shown to be normal, as has gastric emptying in the obese patient [6]. Gastric acid production is also likely normal [7], although one study showed a higher maximal gastric acid response to gastrin stimulation [8]. An increase in acid sensitivity in obese subjects was seen in one study compared with those of normal body weight [9]. In addition, gastric emptying is delayed after a large meal and in meals of high caloric density, so that a large meal containing a high degree of fat might predispose to TLESRs and a greater risk for reflux.

It is in the background of this complex pathophysiology that experimental observations regarding meals and genesis of GERD must be interpreted. This is illustrated by a study that compared the effect of a 61% by calorie fat meal (high-fat) compared with a 16% by calorie fat meal (low-fat) on acid exposure using pH monitoring. Normal (asymptomatic) subjects who remained upright after a meal had increased esophageal acid exposure after the high-fat compared with the low-fat meal in the second and third hours after completing the meal. In patients with symptomatic reflux, however, the fat content had little influence on postprandial reflux in the upright position [10] (Table 1). Increased esophageal acid exposure was observed in both groups after both high- and low-fat meals when studied postprandially in the recumbent position.

Table 1
Average upright esophageal acid exposure (% time) after high-fat versus low-fat meals in normals and reflux patients*

Normals	Low-fat meals	High-fat meals
First hour	1.8	7.4
Second hour	2.1	8.1
Third hour	0.5	2.9
Reflux patients		
First hour	19.5	25.8
Second hour	22.3	27.2
Third hour	26.1	9.8

* The fat content, by calories, of the low-fat and high-fat meals was 16% and 61% respectively.

Symptoms

There is further controversy as to the association of symptomatic GERD and its relationship to obesity. A large population-based Swedish study failed to show any relationship between body mass index (BMI) and GERD symptoms. In this study, the odds ratio (OR) of having heartburn was similar in those with BMI of 25 kg/m^2, 25 to 29 kg/m^2, and over 30 kg/m^2 [11]. Other large-scale studies have shown that GERD is common in the general population and especially so among the overweight. In one of these studies, a BMI greater than 30 kg/m^2 was associated with an OR of 2.8 of having frequent reflux symptoms [12]. A second cross-sectional, population-based study examining the rate of hospitalization for GERD-related diagnostic codes found that there was a higher hospitalization rate for reflux codes in patients with an elevated BMI (hazard ratio 1.22) compared with normal-weight controls [13]. More recent studies, the first a cross-sectional, population-based study from the United Kingdom done as part of a *Helicobacter* eradication trial, found that the adjusted OR for frequent heartburn and regurgitation in those with BMI greater than 25 kg/m^2 was 1.82 and 1.50 respectively and 2.91 and 2.23 respectively for BMI greater than 30 kg/m^2 (compared with controls with BMI less than 25 kg/m^2). When symptom severity was examined, the OR was not as great in the two overweight groups, but still was 1.19 in both compared with the ideal body weight population [14]. Another population-based, cross-sectional case control study from Sweden (an expansion of the negative study discussed previously) showed that there was a dose–response association between increasing BMI and reflux symptoms for men and women, although it was stronger in women. The OR for the risk of reflux was increased in the severely obese (defined as BMI greater than 35 kg/m^2). The authors found an OR of 3.3 for men and 6.3 for women compared with normal-weight controls. The authors further noted that premenopausal women who were obese were more likely to have reflux symptoms than postmenopausal women. If the postmenopausal woman was on estrogen replacement

therapy, however, the association with GERD was more likely. In addition, there was some suggestion that a reduction in BMI could reduce reflux symptoms [15]. A recent study in which a validated reflux questionnaire was used to identify patients with GERD, 27 of 42 patients (64%) in a bariatric surgery program were found to have abnormal ambulatory 24-hour esophageal acid exposure, compared with only 9 out of 30 (30%) asymptomatic volunteers ($P = 0.04$) [16]. In addition, heartburn, acid regurgitation, dysphagia, and asthma were more prevalent in the bariatric surgery patients than in the general population.

These pH data should be interpreted with caution, however, in light of contrary data from a Swedish study in which 50 consecutive obese patients referred for bariatric surgery were prospectively studied and found to have 24-hour ambulatory pH metry and endoscopy findings no different than the general population [17]. Overall, however, the weight of the epidemiologic evidence would seem to support a connection or an association between GERD and obesity.

Erosive esophagitis

Epidemiologic studies also have attempted to examine the association of obesity and esophageal mucosal disease. A retrospective case control study of patients who were seen at a tertiary referral center, all of whom underwent gastric analysis and endoscopy, found that those with excessive body weight were more likely to have esophagitis than normal-weight patients [4]. A hiatal hernia also was an independent risk factor for esophagitis in this same study. Even when controlling for the presence of a hiatus hernia, BMI remained a risk factor for erosive esophagitis. The presence and severity of erosive esophagitis, using the Los Angeles classification for erosive esophagitis (grades A through D) in patients with *Helicobacter pylori*, negative serology was assessed in four prospective multi-center, randomized, double-blind trials comparing esomeprazole and other proton pump inhibitors, looking for independent risk factors for severity of erosive esophagitis. In this study, obesity (OR, 1.21) was an independent risk factor for the development of grades C and D erosive esophagitis but not the milder grades [18]. This OR is not sufficiently high to recommend a change in practice for the obese patient, but it does suggest a relationship. A study evaluating the incidence of reflux esophagitis in the Chinese found that BMI was higher in patients with erosive esophagitis than in those with endoscopy-negative GERD [19]. The most recent study (the ProGERD study) recruited 6215 patients from 1253 centers in Germany, Austria, and Switzerland. Questionnaires were administered, *H. pylori* status was determined, and endoscopy was performed in all volunteers. Ultimately, 5289 patients were studied for risk factors associated with GERD. Logistic regression analysis identified several independent risk factors for erosive esophagitis, including overweight (BMI greater than 25 kg/m^2).

When severe esophagitis (grades C and D) was considered, BMI of at least 25 to 30 kg/m^2 was associated with an OR of 1.7 (confidence interval [CI], 1.2 to 2.3, $P = 0.0011$). BMI of at least 30 to 40 kg/m^2 had an OR of 1.971 (CI, 1.327 to 2.926, $P = 0.0008$) for severe erosive esophagitis. Overweight was second to age older than 60 years and male gender as having the greatest odds of erosive esophagitis [20]. The difference was small, however. Although other studies fail to show an increase in erosive esophagitis in obese patients with GERD, the balance of the more recent evidence seems to favor a relationship.

Patients with long-standing GERD are at risk for the development of Barrett's esophagus and esophageal adenocarcinoma (a rapidly rising cancer among Caucasian males). It is, therefore, of greatest concern that there has been a well-documented association between BMI and carcinoma of the esophagus and gastric cardia. One study found an adjusted OR of 7.6 for esophageal adenocarcinoma in patients with the highest BMI compared with the lowest and an OR of 16.2 for cancer patients with BMI greater than 30 kg/m^2 compared with those with a BMI less than 22 kg/m^2. In addition, an increase in OR for adenocarcinoma of the cardia (OR, 4.3) was demonstrated among those most obese compared with ideal body weight [21]. This is supported by a second study in which a BMI above the lowest quartile, smoking, and low fruit and vegetable consumption were associated with an increase in esophageal adenocarcinoma and gastric cardia adenocarcinoma [22]. Finally, a systematic review of the literature identified obesity as an independent risk factor for adenocarcinoma of the esophagus (OR, 5.5 to 7.3) [23]. These latter two studies are perhaps the most concerning and distressing link between obesity and its effect on the natural history and severity of GERD.

Weight loss and gastrointestinal reflux disease

To prove that obesity is an independent risk factor for GERD, one would need to show that weight reduction would decrease symptoms or an objective marker of reflux. Despite this, few studies have looked at the effect of weight loss as a treatment for GERD. Most that have looked at this showed no effect. The first used endoscopic outcomes to follow 32 obese patients put on a weight loss regimen and allocated into two groups: one on cimetidine, the other on placebo. No difference in improvement of either symptoms or endoscopic findings was seen after 8 to 12 weeks of treatment, with no benefit believed to have been obtained from weight loss alone [24]. A second study randomized 20 obese patients (average BMI 31.4 kg/m^2, all above 28 kg/m^2) to a very low calorie diet or to a control. Twenty-four-hour pH monitoring, endoscopy, and esophageal manometry were performed at baseline and after 6 months. Subsequently, the control patients were placed on the weight reduction diet, and the same group was studied after an

additional 6 months. There was no reduction in reflux based on pH measurement, symptoms, or endoscopic findings in either group, even in patients who lost weight [25]. The only study showing a positive outcome was a study of 34 patients with a BMI greater than 23. Twenty-seven patients lost a mean of 4 kg found that GERD symptoms improved by 75% from baseline. The authors found a direct correlation between weight loss and symptom score. The major problem with this study is that the inclusion group had an overall lower BMI than the former studies [26]. There are no prospective studies examining the relationship of obesity and the outcome of traditional medical therapy in GERD. Additionally, there are no studies examining whether obesity affects pharmacodynamics or pharmacokinetics of proton pump inhibitors.

Approach to the patient

As there are no definitive studies that address the outcomes of traditional medical therapy in patients with obesity and GERD, the authors approach these patients in a similar fashion to those with reflux disease who are of ideal body weight. They address issues of lifestyle modifications, reminding patients to avoid eating before going to bed, begin medical therapy, usually with a proton pump inhibitor once daily before breakfast for 4 to 8 weeks, and proceed accordingly. In considering alternatives to medical therapy, the most recently approved endoscopic therapies (endoluminal gastric plication, radiofrequency energy ablation, and ethylene vinyl alcohol injection) have not been studied directly in those with a BMI greater than 30 or 35 kg/m^2. Therefore, there is no way of knowing what the outcomes will be in this patient population. At this time, the authors are not offering endoscopic interventions to people who have BMIs greater than 35 kg/m^2 unless they

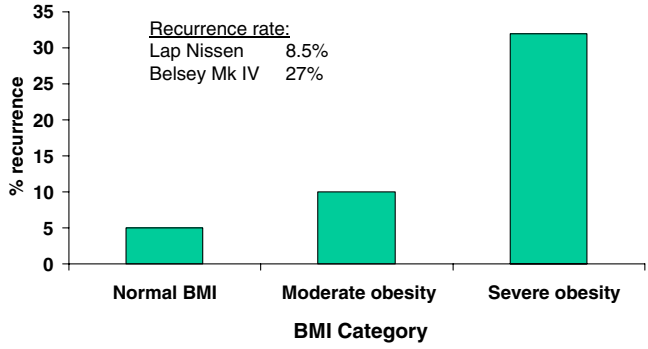

Fig. 1. Bar graph suggesting that there is a higher failure rate for antireflux surgery in obese patients. (*From* Perez AR, Moncure AC, Rattner DW. Obesity adversely affects the outcome of antireflux operations. Surg Endosc 2002;16:986–9; with permission.)

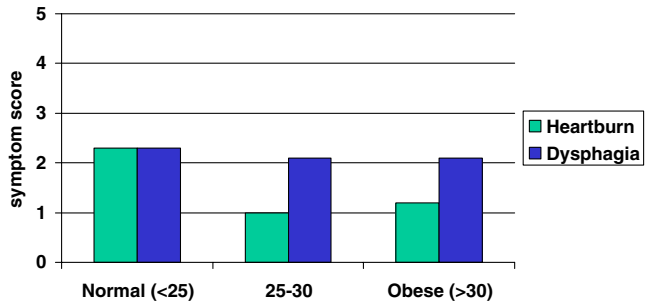

Fig. 2. Bar graph showing no difference in surgical outcome regardless of preoperative weight. (*From* Fraser J, Watson DI, O'Boyle CJ, et al. Obesity and its effect on outcome of laparoscopic Nissen fundoplication. Dis Esophagus 2001;14:50–3; with permission.)

are part of a clinical trial. Antireflux surgery is always an option in patients with GERD, with a symptomatic response to proton pump inhibitors. One study looking at the effect of BMI on antireflux surgery outcomes found a high rate of recurrence (31%) in patients with BMIs greater than 30 kg/m^2 compared with a recurrence rate of 8% in patients with BMIs between 25 and 29.9, and only 4.5% in patients with BMIs less than 25 kg/m^2 [27] (Fig 1). A study by Fraser et al [28] found no difference in symptom scores after antireflux surgery in those of normal body weight compared with obese patients (Fig. 2). These relatively poor outcomes have not been addressed directly in other surgical trials. Other surgical interventions have not been studied systematically in the overweight patient with GERD, although some surgeons have suggested that a gastric bypass with a Roux-en-Y anastomosis may be useful in the patient with GERD and obesity. In general, these patients present a difficult problem for the surgeons, and the systematic study of bariatric surgery and its effect on GERD should prove helpful.

Summary

Logic would suggest that obesity would be a strong risk factor for causing GERD and certainly for exacerbation of GERD. Though the balance of the epidemiologic data support a relationship, true cause and effect cannot be documented. Thus, making the recommendation to lose weight to the GERD patient who is obese is reasonable. Other health reasons, however, supersede GERD as the primary impetus to lose weight.

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Gastroenterol Clin N Am
34 (2005) 45–61

GASTROENTEROLOGY
CLINICS
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Hepatic Complications of Obesity

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Autopsy series demonstrate that obesity is associated with a sixfold increase in the relative risk for cirrhosis [1]. Recent studies in obese people and experimental animals are beginning to clarify why. Obesity often is accompanied by metabolic syndrome, a chronic inflammatory condition that promotes insulin resistance and hepatic lipid accumulation (fatty liver) [2]. As metabolic syndrome and related inflammatory state become more severe, the risk of more serious liver damage (ie, fatty liver hepatitis or steatohepatitis) increases [3]. This is likely to be exacerbated by concomitant exposure to other hepatotoxic agents, including alcohol, certain drugs, or hepatitis viruses. In some individuals, chronic steatohepatitis is accompanied by a fibrogenic response that eventually results in cirrhosis [4]. Like other chronic liver diseases, obesity-related cirrhosis increases the risk for primary hepatocellular carcinoma [5]. This article details data pertinent to the diagnosis, prognosis, and treatment of individuals with obesity-related liver disease and summarizes new information about the mechanisms that drive liver disease progression in obese individuals.

Epidemiology of obesity-related liver disease

Obese individuals can acquire any kind of liver disease that develops in nonobese people. In certain types of liver disease, such as chronic hepatitis C [6–8], toxin-induced liver disease [9], and alcoholic liver disease [10], the obese state seems to increase the severity of liver damage that ensues. For example, the incidence of elevated liver enzymes increases with body mass index (BMI) in factory workers who are exposed to industrial toxins [9]. Obesity increases the risk of fulminant liver failure from halothane and certain other anesthetic agents [11]. Overweight-obesity is also an independent risk factor for hepatic fibrosis in alcoholic liver disease and in

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0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.012 *gastro.theclinics.com*

chronic hepatitis C [6–8,10]. In addition, high BMI decreases the success of interferon-based antiviral therapy [12]. Independent evidence from several medical centers indicates that unrecognized obesity-related liver disease explains most cases of cryptogenic cirrhosis [13–15]. Finally, among individuals with established cirrhosis, overweight-obesity significantly increases mortality, independently of Child's Pugh score and age [15]. Therefore, obesity and liver disease are a potentially deadly combination.

General pathobiology

Why obesity potentiates liver damage is unclear. Diverse mechanisms have been postulated, ranging from the early suggestions that excessive adipose tissue provides a reservoir that permits sustained exposure to fat-soluble toxins [9,16] to more recent evidence that certain factors that are produced by adipose tissue (eg, adipokines) promote hepatic inflammation and fibrosis [17,18]. It is also possible that some obese individuals suffer from multiple, discrete types of liver disease, and that the adverse effects of these conditions are additive. In this regard, it is important to note that obesity is associated strongly with gallstones, which increase the risk of chronic biliary tract disease [19,20].

The correlation between fatty liver disease (FLD) and obesity is particularly strong [21]. Overeating long has been blamed for the accumulation of fat within hepatocytes (ie, hepatic steatosis) in people and animals. Indeed, the cause–effect relationship is so robust that force feeding is employed commercially in the goose pate industry (foie gras). Evidence that the prevalence of FLD increases with BMI in both genders and all races supports a causal role for excessive adiposity in human FLD [22]. Consistent with this concept, liver biopsies demonstrate FLD in over 80% of morbidly obese patients at the time of bariatric surgery [23].

Obesity-related FLD cannot be distinguished from FLD that is caused by habitual consumption of alcoholic beverages [24]. Hence, obesity-associated liver disease has been termed nonalcoholic FLD (NAFLD) [25]. Although common in obese individuals, NAFLD also can occur in people with lipoatrophy (who are excessively lean), people with normal BMIs, and individuals who are taking certain drugs [26]. Emerging evidence suggests that the common mechanistic thread that links NAFLD in all of these conditions is insulin resistance and the associated chronic inflammatory state or metabolic syndrome [27].

Metabolic syndrome is a constellation of frequently associated disorders, including obesity, type 2 diabetes mellitus, dyslipidemia (elevated total cholesterol with low high-density cholesterol, hypertriglyceridemia), and hypertension. Emerging evidence suggests that NAFLD is the hepatic consequence of metabolic syndrome which, in turn, results from various conditions (including excessive adiposity) that lead to a relative overproduction of

proinflammatory mediators [3]. Because NAFLD is the most common type of obesity-related liver disease, the rest of this article will focus on this entity.

Nonalcoholic fatty liver disease

Histologic spectrum and histology-specific pathogenesis

Nonalcoholic fatty liver disease is a heterogeneous entity that ranges from steatosis, on the most clinically benign end of the spectrum, to cirrhosis, at the opposite extreme, where most liver-related morbidity and mortality occur. Steatohepatitis (SH) is an intermediate stage in this spectrum of histopathology [25,28] (Fig. 1).

Fatty liver is characterized by the accumulation of fat within hepatocytes. This lipid is stored predominately as triglyceride and can be deposited within hepatocytes either as a single large lipid droplet (macrovesicular steatosis) or as multiple tiny lipid droplets (microvesicular steatosis). Although inflammatory cell infiltration and dead hepatocytes are not conspicuous in fatty livers, hepatocyte production of potentially noxious reactive oxygen species is increased. Thus, it is likely that more serious liver damage is constrained, because most hepatocytes up-regulate antioxidant defenses and other survival responses that protect them from oxidant stress [29].

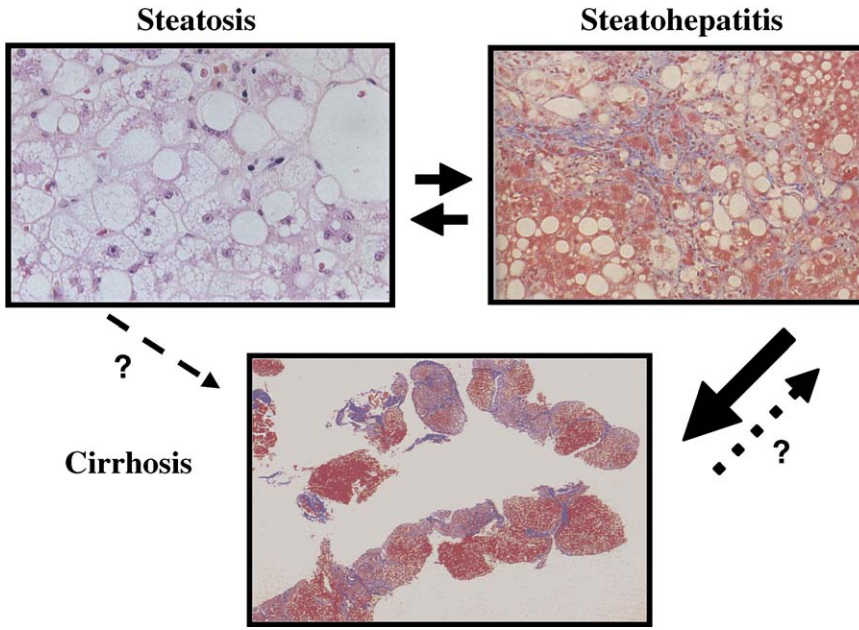

Fig. 1. Histopathologic spectrum of fatty liver disease.

Fatty liver hepatitis SH is diagnosed when histologic features of hepatocyte injury (ballooning and Mallory bodies) and death (apoptotic bodies) become evident. Such injury is typically most evident in acinar zone 3 (the perivenular area) and often is accompanied by an infiltration of acute and chronic inflammatory cells. SH is thought to result when fatty liver adaptations to oxidants become insufficient to prevent progressive damage that accelerates death in relatively large numbers of hepatocytes [30]. A list of factors that have been shown to promote progression from simple steatosis to steatohepatitis in experimental animals is shown in Box 1. It is important to emphasize that SH is defined by histological criteria. The condition can coexist with cirrhosis and cannot be distinguished reliably from simple steatosis by laboratory tests or physical characteristics.

Cirrhosis occurs when the repair response to chronic liver injury distorts normal hepatic lobular architecture with fibrous scar and parenchymal nodules. The accumulation of fibrous tissue along hepatic sinusoids (sinusoidal fibrosis) or around individual hepatocytes (pericellular or chicken wire fibrosis) may occur in fatty livers, but is more common in steatohepatitis. Nevertheless, as in other types of chronic liver injury (eg, chronic hepatitis C), most individuals with steatohepatitis never develop cirrhosis. Those who do often have had liver injury for more than 10 or 20 years [4,15,31]. As fibrosis progresses indolently, fibrous bands bridge portal and central areas of the liver, gradually isolating nodules of hepatic parenchyma. The severity of hepatic fibrosis (F) is sometimes staged according to its extent. F0 = no fibrosis, F1 = fibrosis restricted to portal areas, F2 = fibrosis bridging only occasional portal/central areas, F3 = more extensive fibrous bridging, F4 = extensive fibrosis with definite parenchymal nodularity. Curiously, hepatocyte steatosis often disappears by the time that cirrhosis is evident. As in livers with cirrhosis caused by other types of chronic liver injury, hepatocyte dysplasia and neoplasia (hepatocellular carcinoma) sometimes are identified [5,32].

Box 1. Factors that increase steatohepatitis in experimental animals

High polyunsaturated fat diets
High sucrose diets
Ethanol diets
Choline deficient/methionine restricted diets
Carbonyl iron
Bacterial lipopolysaccharide
Leptin deficiency or resistance

Clinical manifestations and natural history

People with NAFLD may be entirely asymptomatic and have few features of liver disease, even when there is considerable hepatic fibrosis. Vague constitutional complaints, such as malaise and weakness, however, are reported by many patients, and careful physical examination detects hepatomegaly in almost 75% of individuals [33]. When sufficient fibrosis has developed to cause portal hypertension, splenomegaly, spider telangectases, palmar erythema, gynecomastia, ascites, lower extremity edema, portal hypertensive bleeding, or hepatic encephalopathy may occur. Severe non-alcoholic steatohepatitis (NASH) also can lead to jaundice, coagulopathy, or fever.

As with other liver diseases, the overt, clinical manifestations of NAFLD are related closely to the histological severity of the liver disease. Severe steatohepatitis is rare in NAFLD, but it has been reported in some morbidly obese patients following bariatric, jejunoileal bypass surgery. Similar to the severe steatohepatitis that develops in some individuals with alcohol-induced FLD, severe NASH in postjejunoileal bypass patients was characterized by sudden development of tender hepatomegaly, jaundice, and fever. This illness often was associated with a prodrome similar to influenza that included malaise, anorexia, and weakness. Although most patients gradually recovered, either spontaneously or following certain interventions (ie, total parenteral nutrition, antibiotics, or surgical reversal of the bypass), others deteriorated and died from the hepatorenal syndrome and multiple organ failure [34–37]. The long-term fate of individuals who survived severe NASH in the postoperative period has not been characterized well, but at least some of these patients progressed to cirrhosis and experienced subsequent liver-related morbidity and mortality [38]. The rapidly progressive liver disease that occurred in some patients following jejunoileal bypass surgery led to the abandonment of this procedure for weight management. Fortunately, severe NASH does not appear to be a typical outcome of modern bariatric surgery [39]. The explanations for this remain uncertain. Possibilities include better patient selection and revised surgical protocols.

In any case, it is important to emphasize that cirrhosis can also develop in relatively asymptomatic individuals with NAFLD. The chance of developing cirrhosis seems to be much higher in individuals who exhibit features of liver cell injury and inflammation (ie, NASH) than in those with simple steatosis [4,40]. The hepatic fibrosis seems to evolve gradually over 1 to 2 decades, and, thus, histologic progression may go unrecognized until the patient develops an overt manifestation of portal hypertension, such as hypersplenism or ascites [15,32]. Because only a few, small studies have evaluated serial liver biopsies in relatively asymptomatic patients with NAFLD, the true incidence of cirrhosis in this disease is unknown. Studies in patients with alcohol-induced steatohepatitis suggest that 10% to 50%

patients develop advanced fibrosis or cirrhosis within 5 to 10 years [41,42]. Although far fewer NASH patients have been studied, virtually identical rates of progression have been described [4,31]. There is some evidence that host factors, such as age, obesity, and type 2 diabetes, may influence disease progression in NASH. Recent studies from France and the United States demonstrated that age over 45 to 50 years, BMI greater than 30 kg/m^2, and a diagnosis of type 2 diabetes were associated independently with cirrhosis in NASH patients with mildly elevated serum aminotransferase values. In both studies, over two thirds of older obese or diabetic patients had significant hepatic fibrosis that was unsuspected before the liver biopsy was performed [15,43].

The natural history of obese patients with cirrhosis caused by NAFLD is no better than lean individuals who become cirrhotic from other causes, such as chronic hepatitis C. Indeed, at least one recent study suggests that it may be worse [32]. Multiple factors are likely to contribute to the poor prognosis of obese cirrhotic patients. First, because obesity generally is not appreciated to be a risk factor for liver disease, subclinical liver disease often is overlooked until patients present with overt manifestations of portal hypertension or hepatocellular carcinoma.

In well-compensated cirrhotic patients without overt clinical manifestations of advanced liver disease (ie, ascites, jaundice, encephalopathy, or gastrointestinal [GI] bleeding), one or more of these complications develop at a rate of about 25% to 30% per decade [44]. Hence, within 20 years, more than half of cirrhotic patients will have developed some complication of their liver disease. Nevertheless, until liver-related complications occur, death from liver disease is rare. Thus, the 10-year risk of liver-related mortality in patients with well-compensated cirrhosis is less than 10%. Once a cirrhotic patient has suffered a liver-related complication, however, the 5-year risk of liver-related mortality jumps to about 50%. Patients with persistent manifestations of advanced liver disease (eg, diuretic-refractory ascites, chronic encephalopathy, or jaundice) have the highest risk of dying from their liver disease, with 1-year mortality rates approaching 50%. Alcohol abuse accelerates the rate of hepatic decompensation and doubles the risk of liver-related mortality in patients with cirrhosis.

Diagnosis

The diagnosis of NAFLD requires a combination of noninvasive and invasive tests, because there is no single test that is perfectly sensitive or specific for diagnosing this disease. Patients generally are referred to physicians for further evaluation of elevated alanine or aspartate aminotransferases or gamma glutamyl transpeptidase values that are detected incidentally, when blood tests are done for other reasons, such as life insurance evaluations. Sometimes, patients are referred for the evaluation of hepatomegaly or because abdominal ultrasonography demonstrates possible

fatty liver. Occasionally, liver disease is not suspected until an individual presents with a complication of portal hypertension, such as ascites, hypersplenism, GI bleeding, or encephalopathy.

History and physical examination

When taking the history, it is important to get information about possible causes of liver disease and also to assess the severity of symptoms that are related to liver disease. Concerning the first objective, the physician should inquire about factors that increase the risk of viral hepatitis. These include previous blood transfusion, needle stick exposures, multiple sexual partners, illicit drug use, and birth or childhood in areas of the world where hepatitis (A, B, or C) is endemic. Although one, rare hepatitis C genotype (genotype 3) may cause hepatic steatosis [45], most cases of NAFLD are not caused by hepatitis B or C infection. Therefore, a diagnosis of chronic hepatitis B or C generally excludes a diagnosis of NAFLD. In some patients, however, these diseases may coexist, and this increases the severity of the liver damage and the risk of developing cirrhosis. Conversely, NAFLD patients who have never been exposed to hepatitis A, B, or C are not immune to these hepatitis viruses, and thus, are at risk for developing accelerated liver disease if they become infected.

Information about lifetime alcohol consumption also should be obtained. Certain levels of alcohol consumption (ie, more than one drink per day in women or more than two drinks per day in men) increase the risk for alcohol-induced liver damage [22]. Lower levels of alcohol ingestion might potentiate liver damage in obese individuals. Because certain drugs have been associated with NAFLD (Box 2), a history of exposure to any of these agents raises suspicion for that diagnosis.

In addition to obesity, type 2 diabetes and other insulin-resistance syndromes (eg, dyslipidemia or polycystic ovary syndrome), other, rarer, inherited conditions have also been associated with NAFLD (Box 3). Therefore, it is important to ascertain if the patient or family members have had any of these comorbid conditions, because these increase the risk for NAFLD.

In summary, the history and physical examination should include a thorough search for clues of other types of chronic liver diseases, including autoimmune hepatitis (eg, hirsutism or amenorrhea), hemochromatosis (hyperpigmentation, congestive heart failure, arthritis, or impotence), alpha-1 antitrypsin deficiency (neonatal jaundice, emphysema), Wilson's disease (hemolytic anemia or neuropsychiatric symptoms), primary biliary cirrhosis (pruritus, acholic stool, hypothyroidism, CREST syndrome, or osteoporosis), or primary sclerosing cholangitis (inflammatory bowel diseases or symptoms of cholestasis). If any of the latter diagnoses are suspected, then NAFLD becomes less likely as an explanation for the liver enzyme abnormalities, even in an obese individual.

Box 2. Potential causes of severe nonalcoholic steatohepatitis: drugs

Cytotoxic/cytostatic drugs
L-Asparaginase
Azacitidine
Azaserine
Azauridine
Bleomycin
Methotrexate

Antibiotics
Puromycin
Tetracycline

Other drugs
Amiodarone
Coumadin
Dichloroethylene
Ethionine
Ethyl bromide
Estrogens
Flectol H
Glucocorticoids
Hydrazine
Hypoglycin
Orotate
Perhexilene maleate
Safrole
Total parenteral nutrition

To estimate the severity of the underlying liver damage, it is necessary to look for symptoms and signs of liver dysfunction and portal hypertension. These include jaundice, dark urine, acholic stools, or pruritus; GI bleeding; ascites or lower extremity edema; or personality changes, insomnia, decreased memory or ability to concentrate, asterixis, lethargy, confusion, or coma. A history of any of these suggests that cirrhosis might be present and implies that the risk of liver-related morbidity and mortality is increased.

Blood tests

Liver enzymes

Nonalcoholic fatty liver disease often is diagnosed, because relatively asymptomatic individuals are referred for the evaluation of serum alanine

Box 3. Potential causes of severe nonalcoholic steatohepatitis: inherited and acquired metabolic conditions

Inborn errors of metabolism
Abetalipoproteinemia
Congenital generalized lipodystrophy
Familial hepatosteatosis
Galactosemia
Glycogen storage disease
Hereditary fructose intolerance
Homocystinuria
Prader Willi syndrome
Systemic carnitine deficiency
Tyrosinemia
Refsum's syndrome
Schwachman syndrome
Weber Christian syndrome
Wilson's disease

Acquired metabolic disorders
Diabetes mellitus, type 2
Lipodystrophy (drug-induced)
Inflammatory bowel disease
Jejunoileal bypass
Kwashiorkor and marasmus
Obesity

aminotransferase (ALT), aspartate aminotransferase (AST), or gamma glutamyl transpeptidase (GGT) values that are elevated. Generally, the liver enzyme values are increased less than fourfold. Towering aminotransferase values (eg, greater than 10-fold elevations) are very unusual in patients with NAFLD and suggest either an alternative cause of liver injury or the superimposition of drug- or viral-induced liver injury in someone with underlying NAFLD. The liver enzyme values correlate poorly with the severity of the underlying liver disease, and, thus, have no value in predicting which patients have steatosis rather than steatohepatitis, or steatohepatitis alone as opposed to steatohepatitis plus cirrhosis. The AST value tends to be at least twice the ALT value in many patients with alcohol-induced steatohepatitis, whereas this pattern of liver enzyme values generally does not occur until patients with NASH develop cirrhosis. Therefore, the AST/ALT ratio may be helpful in identifying patients in whom alcohol abuse is the etiology of steatohepatitis. GGT elevations are common in alcoholic FLD and NAFLD, and there is some evidence that

increased GGT values are a sensitive marker of insulin resistance. Therefore, GGT elevations are not useful for distinguishing alcoholic FLD from NAFLD. Some patients with NAFLD also have accompanying, minor (generally, 1.5- to twofold) elevations in serum alkaline phosphatase values. Greater increases in alkaline phosphatase values prompt suspicion of associated biliary tract disease or the superimposition of some hepatic infiltrative process, such as a granulomatous infection or a malignancy.

Bilirubin, albumin, prothrombin time, ammonia, platelet count

Bilirubin, albumin, prothrombin time, ammonia, and platelet count tests are more useful than the liver enzymes in estimating liver disease severity, because the first four tests reflect hepatic function. Additionally, low platelet count is a marker of portal hypertension, because thrombocytopenia develops as platelets become sequestered in the spleen during portal hypertension. Increased bilirubin, decreased albumin, prothrombin time prolongation, hyperammonemia, and thrombocytopenia suggest advanced liver disease.

Other blood tests

Hyperglycemia and dyslipidemia (decreased high-density lipoproteins and hypertriglyceridemia) have been associated with NAFLD. Classically, patients with NAFLD test negative for other causes of liver disease. Therefore, autoantibodies and viral markers are negative; the alpha 1 antitrypsin phenotype, transferrin saturation, and ceruloplasmin values are normal. It is not uncommon, however, for one or more of these tests to be abnormal in any given individual with NAFLD. For example, lifestyle factors may increase the risk of infection with hepatitis B or C. Hence, some patients with NAFLD may have chronic viral hepatitis also. Hyperferritinemia and increased transferrin saturation also have been noted in many people with NASH, although most of these do not have the C282Y or H63D mutations in the HFe gene that are thought to cause genetic hemochromatosis.

Imaging studies

Various imaging modalities, including abdominal ultrasonography, computerized axial tomography (CAT) scan, and MRI can be used to detect hepatic steatosis. The various imaging tools differ, however, in their sensitivities and specificities for diagnosing fatty liver. Abdominal ultrasonography is probably the most common imaging test used to screen for hepatic steatosis. A recent study that compared sonogram and liver biopsy results in patients with FLD, however, demonstrated that sonography only had a positive predictive value of 77% and a negative predictive value of 67% [46]. Hence, reliance on ultrasonography to detect fatty liver will

provide incorrect diagnostic information in one out of every three or four people. Standard CAT scan is actually less sensitive than abdominal ultrasonography in detecting fatty liver, although this can be improved when density-calibrated CAT scanning is performed [47]. Abdominal MRI provides the most reliable noninvasive approach for detecting and quantifying hepatic steatosis. The correlation between hepatic fat content as estimated by proton MRI spectroscopy and triglyceride concentration measured by biochemical analysis of liver samples is almost perfect [48]. This test, however, is more expensive and less widely available than ultrasonography or CAT scanning. Moreover, none of these imaging modalities is able to distinguish simple steatosis from steatohepatitis and cannot identify cirrhosis until sufficient hepatic fibrosis has occurred to cause overt portal hypertension, manifested by collateral vessel formation, splenomegaly, or ascites. Therefore, although imaging studies are attractive, because such tests are noninvasive, they have limited sensitivity and specificity for diagnosing and staging FLD. In addition, many are more expensive than standard percutaneous liver biopsy. Hence, imaging tests are not the most cost-effective for diagnosing or staging FLD.

Liver biopsy

Liver biopsy is the gold standard test for confirming the clinical suspicion of NAFLD. This is particularly helpful in atypical patients who have physical findings or blood test results that suggest the presence of more than one type of liver disease (eg, NASH plus hepatitis C or NASH plus iron overload). Biopsy is also the most sensitive means for staging FLD, because histology distinguishes steatohepatitis from steatosis and permits the identification of hepatic fibrosis long before overt sequelae of portal hypertension develop. Thus, liver biopsy provides useful prognostic information that can be used to guide subsequent management recommendations.

Prevention and treatment

Primary prevention

Primary prevention has not been defined for most patients with primary NAFLD (ie, NAFLD that is not secondary to particular drugs). As mentioned earlier, however, a strong association between insulin resistance and NAFLD has been demonstrated, suggesting that insulin resistance may precede NASH [3]. In animal models with fatty livers and in isolated liver cells, treatment with insulin-sensitizing agents such as metformin or thiazolidinediones improves hepatic steatosis and insulin sensitivity [49,50]. If the same effect occurs in people with fatty livers, then these agents or other approaches (ie, diet modification and exercise) that improve insulin

resistance may prevent NASH by removing the fatty liver state that serves as the primary vulnerability factor for NASH.

Secondary prevention

In people who already have developed NAFLD, situations that increase hepatic oxidative stress promote progression from steatosis to steatohepatitis. Therefore, treatments that reduce net oxidant production are predicted to prevent the progression from NAFL to NASH. Such treatments might include discontinuing alcohol consumption and implementing certain dietary modifications, supplemental antioxidants, or treatments that inhibit endogenous factors that promote proinflammatory cytokine production.

Although studies in experimental animals support each of these strategies, there is less evidence that any of them is uniformly beneficial in people. Box 4 summarizes treatments that have been effective in preventing or improving NASH in experimental animals.

Evidence-based treatments

Only a smattering of small clinical trials in patients with NASH has been published [51–62]. Many of these studies were not randomized, controlled trials. Rather, small groups of selected patients were treated for up to 1 year and then reassessed to determine if treatment had improved some pretreatment parameter(s). The efficacy of various pharmacologic interventions has been difficult to judge. Because liver biopsy was not a uniform criteria for enrollment among the various studies, it is not possible to distinguish the patients who may have entered the trials with subclinical cirrhosis from those who had merely steatosis or steatohepatitis when treatments were initiated. Often, study endpoints were aminotransferase values or sonogram results, parameters that are notoriously unreliable measures of the histologic severity of liver injury and fibrosis. In the few studies that compared

Box 4. Treatments for steatohepatitis in experimental animals

Insulin-sensitizing agents
Metformin
Troglitazone
Leptin
Adiponectin

Reduce or inhibit intestinal bacterial endotoxins
Probiotics

Inhibit TNFα activity directly
Antibodies to TNFα

pre- and post-treatment biopsy findings, the duration of therapy may have been insufficient to change a gradually evolving process, such as cirrhosis. Moreover, small sample size plus heterogeneous histology at the onset of therapy might have obscured a small treatment benefit in some subgroup of patients. Consequently, there is not consensus about the efficacy of any pharmacologic agent in preventing disease progression or reversing NASH. A list of the various agents that have been studied as treatments for patients with NAFLD is shown in Box 5.

Because virtually nothing is known about the impact of treatment on the natural history of NAFLD, it is not possible to provide a well-justified treatment algorithm. Nevertheless, given the putative pathogenic mechanisms for NAFLD and the findings of preliminary treatment trials, it is reasonable to suggest dietary modification and exercise. Although many clinicians emphasize the importance of weight loss, studies of prediabetic or obese individuals demonstrate that very minor reductions in body weight (ie, about 10% to 20%) improve insulin sensitivity and hypertension [63–65], suggesting that minor weight loss also may improve NAFLD. Moreover, rapid, extreme weight loss may accelerate the progression of NASH to cirrhosis and also increases the risk of gallstone disease. Therefore, this should be avoided. Vitamin E is another attractive therapeutic agent for NASH, because it is an inexpensive antioxidant that likely is safe if doses of 400 to 600 IU per day are used. Insulin-sensitizing agents such as metformin or a second-generation thiazolidiendione (eg, rosiglitazone or pioglitazone) are indicated in patients with overt type 2 diabetes or polycystic ovary syndrome. Although pilot studies suggest that either type of insulin-sensitizing agent may improve liver enzyme elevations

Box 5. Treatments evaluated in patients with nonalcoholic fatty liver disease

Insulin-sensitizing agents
Metformin
Troglitazone
Rosiglitazone
Pioglitazone

Antioxidants
Vitamin E
Betaine

Lipid-lowering drugs
Gemfibrozil
Atorvastatin
Ursodeoxycholic acid

in NASH patients, large, prospectively randomized, controlled trials have not been done. Additionally, both agents have potential toxicity in patients with liver disease. According to the Physician's Desk Reference, lactic acidosis may complicate metformin therapy. Troglitazone, the parent thiazolidiendione, was removed from the market as a first-line treatment for type 2 diabetes because of idiosyncratic, but severe, hepatotoxicity. Treatment of dyslipidemia is not contraindicated, because there is no evidence that NASH enhances the risk of toxicity from these agents, and a report suggests that atorvastatin might improve liver enzyme abnormalities in NASH. Ursodeoxycholic acid (ursodiol) is safe and well-tolerated by patients with many types of chronic liver disease. Although a small study suggests that ursodiol might have some efficacy in NASH, a recently completed, large prospective trial could not confirm these benefits [62]. The latter study demonstrated that equal numbers of ursodiol-treated and placebo-treated patients improved over the course of follow-up. Proponents of ursodiol argue that both treatment groups benefited from rigorous lifestyle modification in this study, making it impossible to demonstrate the advantages of ursodiol. Given that the drug is expensive and its benefits are unproven, however, this agent might be reserved for patients who are refractory to other less expensive therapies (ie, diet and exercise).

Once patients with NAFLD develop cirrhosis, management is identical to that of patients with cirrhosis from any other cause of liver disease. For example, treatment with beta blockers reduces the incidence of portal hypertensive bleeding in patients with large esophageal or gastric varices. Dietary sodium restriction and diuretics reduce ascites and edema formation; lactulose improves hepatic encephalopathy; and norfloxacin reduces the risk of recurrent spontaneous bacterial peritonitis. Vaccination against hepatitis A and B protects nonimmune cirrhotics from infection with these viruses. Regular screening with abdominal ultrasonography and serum tests for alpha fetoprotein improve the early detection of hepatocellular carcinoma. Ultimately, liver transplantation is useful in improving the survival of patients with decompensated cirrhosis or with small hepatocellular carcinomas that are confined to the liver and who have no other contraindication to general surgery.

Summary

Obesity increases the risk and severity of liver disease. The most common form of liver disease that occurs in obesity is NAFLD. A better understanding of the basic disease mechanisms and natural histories of NAFLD is needed to guide management and treatment of obese patients and others with this disorder. Large, prospective, randomized, controlled treatment trials also are needed. Ideally, such studies will focus on well-defined patient subsets and monitor the impact of therapy on clinically relevant endpoints, such as liver-related morbidity and mortality.

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Gastroenterol Clin N Am
34 (2005) 63–82

GASTROENTEROLOGY
CLINICS
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Obesity and Disease of the Esophagus and Colon

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Obesity is associated with several digestive diseases including gallstones, esophageal disease (gastroesophageal reflux and its complications erosive esophagitis, BE and esophageal adenocarcinoma), colon polyps and cancer, and liver disease (nonalcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma). This article discusses the evidence linking obesity to the different manifestations of gastroesophageal reflux disease (GERD) and colorectal cancer.

Obesity in the United States

Definition of obesity

Obesity is defined as an excessively high amount of body fat or adipose tissue in relation to lean body mass. Body mass index (BMI) has become the accepted measure of obesity. The BMI is correlated more highly with body fat than any other indicator of height and weight [1]. BMI is calculated by dividing the person's weight in kilograms by the square of the height in meters (kg/m^2). The World Health Organization has defined the normal range of BMI to be between 18.5 and 24.9. Grade 1 overweight is 25 to 29.9; grade 2 overweight is 30 to 39.9; and grade 3 overweight is 40 or more. Obesity typically is defined as a BMI of 30 or greater. Morbid obesity often is defined as a BMI above 40. In addition to size of the adipose tissue deposits, however, there also is concern for the distribution of fat throughout the body.

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0889-8553/05/$ - Published by Elsevier Inc.
doi:10.1016/j.gtc.2004.12.006

Epidemiology of obesity in the United States

Results of the National Health and Nutrition Examination Survey 1999 indicate that an estimated 61% of United States adults are either overweight or obese. The prevalence of overweight (BMI 25.0 to 29.9) has increased from 33% of the population in 1980 to 35% of the population in 1999, while obesity (BMI of at least 30.0) has nearly doubled from approximately 15% in 1980 to an estimated 27% in 1999. The percentage of children and adolescents who are defined as overweight has more than doubled since the early 1970s. About 15% of children and adolescents are now overweight. Changes in lifestyle, most notably in diet and physical activity, are the likely culprits of the obesity epidemic [2–4].

Obesity and gastroesophageal reflux disease

Frequent symptoms of GERD affect between 10% and 20% of the adult population in the United States. The prevalence of GERD and its complications, including erosive esophagitis, BE, and esophageal adenocarcinoma, has been increasing in the United States and Western Europe. For example, the incidence of esophageal adenocarcinoma in the United States increased fourfold over the past 20 years [5]. Similar increases have been observed in the United Kingdom, Scandinavian countries, and Australia [6]. The reasons for this rise in GERD and its complications have not been identified clearly.

It has been hypothesized that the rising rates of GERD and its potential complications in western populations might be caused by obesity. The bulk of evidence linking obesity and GERD is epidemiological in nature and it will be reviewed in the following section.

Obesity and gastroesophageal reflux disease symptoms

There have been at least eight cross-sectional studies that examined GERD symptoms using validated questionnaires in randomly selected samples of the general population. These studies were conducted in six countries from North America or Western Europe [7–14]. GERD was defined as at least weekly frequency of symptoms in most studies. Of the eight studies, five showed a significant positive association between obesity and GERD [7–11], and three [12–14] showed no association. Detailed descriptions of these studies are shown in Table 1. Compared with normal BMI, the pooled weighted risks of GERD symptoms among overweight and obese persons were 1.5-fold and twofold, respectively. These estimates are based on seven studies that presented data to allow for calculation of unadjusted odds ratios (ORs).

The adjusted ORs for obesity also are presented in Table 1. Seven studies adjusted for age and sex. Two studies adjusted for race [11,14], three for

Table 1
Characteristics of studies examining obesity and gastroesophageal reflux disease symptoms*

Reference	Country	Study sample and method of data collection	Case definition	Number of cases	Control group	Number of controls	Body mass index	Adjusted odds ratio (95% confidence interval)
Andersen et al, 1991 [12]	Denmark	Random sample of general population was mailed a validated questionnaire.	Participants with GERD symptoms	114	Persons from the study population without GERD symptoms	1207	< 25 25–29 > 30	1.0 1.0 (0.7–1.5) 1.4 (0.8–2.4)
Locke et al, 1999 [8]	United States	Random sample of Olmstead County residents age 25–74 years were mailed a validated questionnaire.	Participants with GERD symptoms stratified by frequency of symptoms	872	Persons from the study population without any GERD symptoms in the past one year	652	< 24 24–27 27–30 > 30	 1.0 1.4 (0.9–2.3) 2.0 (1.2–3.3) 2.8 (1.7–4.5)
Oliveria et al, 1999 [11]	United States	Random sample of persons at least 18 years old identified by random digit dialing had a phone interview using a validated questionnaire.	Participants with heartburn more than once per week	916	Among patients with heartburn, those with heartburn less than once per week	1084	Continuous variable	1.02 (1.01–1.04)
Lagergren et al, 2000 [13]	Sweden	Random sample of the general population had in-person interviews using a validated questionnaire.	Participants with GERD symptoms at least once per week for year or more	135	Persons from the study population with less frequent or absent GERD symptoms	685	< 25 25–30 > 30	 1.0 1.0 (0.6–1.4) 1.1 (0.6–2.0)

(*continued on next page*)

Table 1 (*continued*)

Reference	Country	Study sample and method of data collection	Case definition	Number of cases	Control group	Number of controls	Body mass index	Adjusted odds ratio (95% confidence interval)
Wu et al, 2003 [14]	United States	Population-based sample of randomly selected persons had in-person interviews using a structured questionnaire.	Participants with GERD symptoms at least once per week	258	Patients from the study population with less frequent or absent GERD symptoms	1098	< 23 23–25 25–28 > 28	 1.0 1.1 (0.7–1.6) 1.3 (0.9–2.0) 1.4 (0.9–2.0)
Murray et al, 2003 [9]	United Kingdom	Randomly selected from 10537 persons previously evaluated for effects of *Helicobacter pylori* eradication on dyspepsia were administered self-administered a structured questionnaire.	Participants with GERD symptoms	643	Persons from the study with heartburn less than once per week	4045	< 25 25–30 > 30	Heartburn 1.0 1.8 (1.3–2.5) 2.9 (2.1–4.1)

Nilsson et al, 2003 [10]	Norway	65,363 persons had BMI measured and a self-administered validated questionnaire.	Participants with severe reflux symptoms	3113	Persons from the study cohort with no GERD symptoms in the prior 12 months	39872		Women
							< 25	1.0
							25–30	2.0 (1.7–2.4)
							30–35	3.9 (3.3–4.7)
							> 35	6.3 (4.9–8.0)
Diaz-Rubio et al, 2004 [7]	Spain	Random sample of Spanish population aged 40–79 years had a telephone interviews using a validated questionnaire.	Participants with any GERD symptoms in the past year	791	Individuals interviewed with no GERD symptoms	1709	< 25	1.0
							25–30	1.5 (1.2–1.9)
							> 30	1.7 (1.3–2.3)

* All studies were cross sectioned.

Table 2
Characteristics of studies examining obesity and erosive esophagitis

Reference	Country	Study design	Sampling frame	Number of cases	Control group	Number of controls	BMI	Adjusted odds ratio (95% confidence interval)	*p*
Stene-Larsen et al, 1988 [16]	Sweden	Case-control	Patients referred for upper endoscopy at a single hospital	195	All persons enrolled in the study without endoscopic esophagitis	1029	< 25 25–26 26–28 > 28	1.0 0.9 (0.5–1.6) 1.6 (1.0–2.6) 2.5 (1.7–3.5)	< 0.01
Chang et al, 1997 [18]	Taiwan	Cross-sectional	Persons presenting for routine physical exam (upper endoscopy as part of that) to a single institution	102	All persons enrolled in the study without endoscopic esophagitis	1942	< 25 25–30 > 30	1.0 2.1 (1.4–3.3) 4.5 (2.4–8.6)	< 0.01
Ruhl et al, 1999 [20]	United States	Cohort	NHANES I study population-based cohort of 12349; cases were those hospitalized with reflux-related diagnoses.	526	The remaining cohort without hospitalizations for GERD	11823	< 22 22– < 25 25–28 > 28	1.0 1.1 (0.9–1.6) 1.5 (1.1–1.9) 1.9 (1.5–2.5)	< 0.01
Wilson et al, 1999 [17]	United States	Case-control	Upper endoscopy reports at a single hospital were retrospectively searched.	189	Patients without endoscopic esophagitis or hiatal hernia	1024	< 20 20–25 25–30 > 30	1.0 1.0 (0.6–1.5) 1.5 (0.9–2.3) 1.6 (0.9–2.7)	NS

Furukawa et al, 1999 [19]	Japan	Cross-sectional	All persons presenting for routine physical exam (EGD as part of that) in a single institution	977	All persons in the study without endoscopic esophagitis	5023	< 25 > 25	1.0 0.9 (0.7–1.0)	NS
Nilsson et al, 2002 [14]	Sweden	Case-control	All patients referred for EGD at 17 hospitals throughout Sweden	224	Random sample of age-sex-and location-matched controls	224	< 25 25–30 > 30 Women 1.0 0.8 (0.3–2.3) 14.6 (2.6–81)	Men 1.0 1.2 (0.7–2.2) 2.9 (1.1–7.6)	NS < 0.01

nonsteroidal anti-inflammatory drug (NSAID) intake [7–9], five for cigarette smoking [7–10,13], and one for *Helicobacter pylori* status and socioeconomic status [9]; only one study adjusted for physical activity [13]. None of these adjustments significantly changed the association between obesity and GERD symptoms. Adjustments for alcohol [7–10,13] or coffee consumption [7–10], dietary fiber [10], or total energy intake [13] resulted in no significant changes in the odds ratios.

Obesity and erosive esophagitis

The author and colleagues identified three case-control [14–17], two cross-sectional studies [18–19], and one cohort study [20] that examined the association between BMI and erosive esophagitis. The details of these studies are shown in Table 2. Five out these six studies showed a significant positive association between obesity and erosive esophagitis, while only one study conducted in Japan showed no significant association (Fig. 1) [19].

Obesity and esophageal adenocarcinoma and adenocarcinoma of the gastric cardia

Esophageal adenocarcinoma

Seven case-control studies were identified that examined the association between BMI and esophageal adenocarcinoma [21–27]. Four studies examined esophageal adenocarcinoma separate from that of the gastric cardia [21,23,25,26]; one excluded cancers of the cardia [27], and two studies combined the esophagus and gastric cardia [22,24]. In all studies, control groups were identified from noncancer subjects in the general population and matched to cases by age and sex.

Five of these seven studies showed a significant positive association between BMI and esophageal adenocarcinoma, and two showed no significant association (Table 3). Adjustments for age and sex (all studies), race [21,24,26], smoking [21–27], alcohol consumption [21,22,24,25,27], caloric intake [22,24,25,27], history of reflux symptoms [25,27], or education

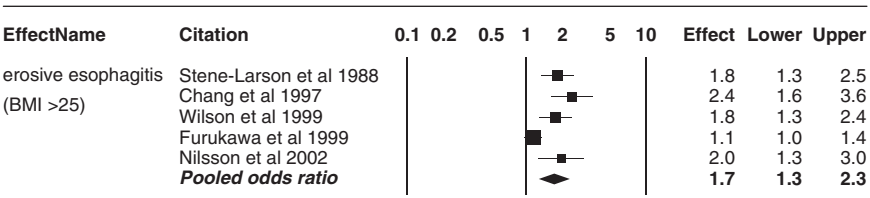

Fig. 1. Unadjusted odds ratios (95% confidence interval) for the risk of erosive esophagitis among overweight (BMI greater than 25) versus normal weight (BMI less than 25) individuals.

level [21,25–27] did not alter the significance or direction of associations. Overall, the risk of esophageal adenocarcinoma is 2.1 times higher in people with BMI greater than 25 compared with normal BMI. These estimates were pooled from all studies except that of Zhang et al [24], which combined the estimates for esophageal and gastric cardia cancers.

Case-control studies are subject to recall bias with regards to self-reporting of body weight. For example, if patients with cancer were concerned that their eating habits and BMI caused their disease process, they were more likely to overestimate their historical weight compared with noncancer controls. The consistency across studies, however, provides some reassurance against recall bias. Importantly, six of the cancer studies had a control group of either squamous cell cancer of the esophagus or distal gastric adenocarcinoma, and BMI was found to have either no association or a significant negative association with these cancer controls.

Because of the concern of significant weight loss at the time of cancer diagnosis, historical weight information was obtained in all studies but one [24]. Further, among the three studies that collected multiple historical heights and weights [23,25,26], there were no significant differences in the magnitude or direction of the association between BMI at different time points and risk of adenocarcinoma.

There were no analytic studies satisfying the author's inclusion and exclusion criteria that assessed the association between obesity and BE. A case-control study by Chak et al reported no significant difference in obesity in 35 patients with BE compared with a control group of patients with GERD and no BE [28]. Because of the small number of cases, however, one cannot be certain that smaller differences were not missed. Another uncontrolled study by Caygill et al reported a BMI greater than 30 in 24% of 102 patients in their case series of 102 patients with BE compared with 13% in the general population of England [29].

Adenocarcinoma of the gastric cardia

Six studies examined the association of obesity and adenocarcinoma of the gastric cardia (Table 3). They included four studies that combined esophagus with gastric cardia and two studies from China that examined only adenocarcinoma of the gastric cardia [30,31]. Four studies showed a significant positive association between obesity and adenocarcinoma of the gastric cardia, with ORs ranging from 1.5 to 4 (Table 3). One study showed a positive association that did not reach statistical significance [21], and one of the Chinese studies showed a significant negative association [31]. The latter study examined BMI 1 year before cancer diagnosis, however; therefore weight loss from the underlying malignancy may have affected these patients. Overall, there was a significant increase (but smaller than esophageal adenocarcinoma) in risk of cancer with obesity with a weighted pooled OR of 1.5.

Table 3
Characteristics of studies examining the association between obesity and esophageal adenocarcinoma or adenocarcinoma of the gastric cardia

Reference	Country	Cancer cases (adenocarcinoma)	Number of cases	Control group	Number of controls	Body mass index	Adjusted odds ratio (95% confidence interval)
Vaughan et al, 1995 [21]	United States	Esophagus or gastric cardia	133	Random sample of age and sex matched population based controls; patients with esophageal squamous cell cancer	724	1% to 10% 11% to 49% 50% to 89% 90% to 100%	1.6 (0.7–3.6) 1.0 1.2 (0.7–2.1) 2.5 (1.2–5.0)
Brown et al, 1995 [22]	United States	Esophagus or gastric cardia combined	194	Random sample of age- and sex-matched population-based controls	750	< 23.1 23.1–25 25.1–27 > 27	1.0 1.1 (0.6–2.1) 1.2 (0.6–2.3) 3.1 (1.8–5.3)
Zhang et al, 1996 [24]	United States	Esophagus or gastric cardia combined	95	Patients undergoing upper endoscopy with no diagnosis of cancer; patients with noncardia gastric cancer	132	BMI as continuous variable	0.9 (0.8–1.0)
Ji et al, 1997 [30]	China	Gastric cardia only	185	Random sample of age-, and sex-matched population-based controls; patients with noncardia gastric cancer	1451		N/A
Chow et al, 1998 [23]	United States	Esophagus or gastric cardia	292	Random sample of age- and sex-matched population-based controls; patients with esophageal squamous cancer; patients with noncardia gastric cancer	694	m < 23 m 23–25 m 25–27 m > 27	1.0 1.3 (0.8–2.2) 2.0 (1.3–3.3) 2.9 (1.8–4.7)

Lagergren et al, 1999 [25]	Sweden	Esophagus or gastric cardia	189	Random sample of age- and sex-matched population-based controls; patients with esophageal squamous cancer	820	< 22 22–25 25–30 > 30	1.0 3.2 (1.6–6.7) 6.9 (3.3–14.4) 16.2 (6.3–41.4)
Cheng et al, 2000 [27]	United Kingdom	Esophagus (cardia excluded)	74	Random sample of age-, sex-, and location-matched population controls	74	< 19.5 19.5–21 21–22.7 > 22.7	1.0 0.9 (0.2–4.3) 4.9 (0.9–28.0) 6.0 (1.3–28.5)
Wu et al, 2001 [26]	United States	Esophagus or gastric cardia	222	Random sample of age-, sex-, and race-matched population-based controls Non-cardia gastric cancer controls	1356	m < 22 m 22–25 m 25–27 m > 27	1.0 1.2 (0.8–1.9) 1.3 (0.9–2.1) 1.8 (1.1–2.7)
Zhang et al, 2003 [31]	China	Gastric cardia only	300	Random sample of control subjects presenting for routine physical examination	258		N/A

Mechanism of obesity-related gastroesophageal reflux disease and its complications

Mechanical

It has been proposed that obese patients may experience extrinsic gastric compression by surrounding adipose tissue, leading to increased intragastric pressures and subsequent relaxation of the lower esophageal sphincter, thus facilitating abnormal reflux [32–34]. The findings of manometric studies, however, have been inconsistent, indicating both decreased [35] and normal [36–39] lower esophageal sphincter pressures in obese persons.

Diet

It also has been postulated that dietary intake, notably fat, rather than obesity, is responsible for GERD. However, the effect of BMI on GERD-related disorders was independent of dietary intake, however, when total caloric intake or dietary intake of fiber, fruits and vegetables, or other macronutrients or micronutrients was examined. Moreover, no consistent association was found between dietary fat and GERD or esophageal adenocarcinoma.

Hiatus hernia

Obese patients may have a higher predisposition to hiatal hernia, which has a role in initiating and promoting GERD [40]. One study found obesity to be associated significantly with esophagitis [41] only in the presence of hiatal hernia. Similarly, a study by Stene-Larson et al [16] found that 68% of patients with esophagitis had concomitant hiatal hernia and that obesity was associated significantly with both conditions. Conversely, Wu et al [14] found no significant association between BMI and hiatal hernia. In a study that examined the association of BMI and grade of esophagitis among people with esophagitis, El-Serag et al [42] also found that obesity remained an independent risk factor for severe versus mild esophagitis while controlling for the presence of hiatal hernia. The cross-sectional nature of these studies, however, makes it impossible to distinguish temporal associations between obesity and hiatal hernia. In addition, the criteria for identifying and measuring hiatal hernia may not have been used correctly or uniformly.

Estrogen

Two studies conducted by the same group of investigators from Sweden observed that the association of obesity and GERD might be mediated by the effect of circulating estrogen [10,14]. The first study reported a significant association between obesity and esophagitis in women, and the use of estrogen in overweight postmenopausal women appeared to potentiate this effect. The second study examined a large population-based cohort and

found that overweight (BMI 25 to 30) women and men had a similarly increased risk of GERD symptoms. However, in that study obese women (BMI >30) had an increased risk of GERD symptoms compared with obese men, however, and the risk was highest among premenopausal women and postmenopausal women on estrogen therapy. Furukawa et al reported that among patients stratified by age and BMI, overweight women older than 70 years old were the only group to have a significantly increased risk of esophagitis; they did not report on estrogen use in these patients [19]. Several other studies, however, have found that the increased risk of acid-related esophageal disease among overweight and obese persons was neither confounded nor modified by gender [14,42].

Management

Weight gain often is associated with onset of GERD or exacerbation of existing symptoms. Nilsson et al found that that a gain greater than 3.5 BMI units was associated with an approximately threefold increase in the risk of developing new reflux symptoms [10]. Some studies found weight loss can improve GERD symptoms and esophagitis in overweight persons [43], while others did not [44]. There are small nonrandomized studies suggesting that weight loss following bariatric surgery for morbid obesity is associated with an improvement in GERD symptoms [45,46]. Lastly, there are no data to suggest that weight loss affects risk of esophageal adenocarcinoma. Therefore, although weight loss often is recommended for patients with GERD [47], there are limited data on its efficacy.

Summary

There is a 1.5- to twofold increase in the risk of GERD symptoms, erosive esophagitis, or esophageal adenocarcinoma with being overweight or obese compared with a normal BMI. The association between obesity and BE is virtually unknown. Obesity satisfies several criteria for a causal association with GERD and its complications. Although not proven, maintaining normal weight may reduce the likelihood of developing GERD and its potential complications.

Obesity and colorectal cancer

Colon cancer is the third most common cause of cancer and the third leading cause of cancer-related mortality in the United States. Known risk factors for colorectal cancer (CRC) include age, colon polyps, family history of CRC, genetic alterations including familial adenomatous polyposis and hereditary nonpolyposis colon cancer, and inflammatory bowel disease. Obesity has been proposed as a risk factor for colon cancer. This section reviews evidence for such a link and its possible underlying mechanisms.

Colorectal carcinoma

Obesity first was observed to be associated with colon cancer in 1940. Several epidemiological studies over the past 25 years have investigated obesity as a risk factor for colon cancer [48,49]. Studies on the association between obesity and colon cancer include cohort and case-control studies.

There is a strong case for an association between obesity and risk of developing colon cancer in men. Several prospective and retrospective studies have reported a 1.5- to 2.8- fold increase in the relative risk for those in the highest tertile of BMI as compared with the lowest. Similarly, mortality related to colorectal cancer is increased in obese individuals [50]. Five selected cohort studies evaluating the risk of CRC with obesity are shown in Table 4 [51–55]. Three studies showed a significant positive association between obesity and CRC; in all three, the effect was relatively modest, with an increased risk of about 1.5- to threefold. In two studies, there was a positive association that did not reach statistical significance. The association was found to be weaker for women than for men.

Of prospective studies that examined the risk of CRC separate for men and women, some have supported an association between BMI and colon cancer in women, but at least three other studies did not find a significant association. Further, in women, age and menopausal status seem to modify the relationship between BMI and colon cancer. The BMI-related risk of colon cancer is increased in younger aged women and is less evident in older aged women. Similarly, the risk is increased in premenopausal but not postmenopausal women. The findings of case controls are inconsistent for evidence of association between BMI and colon cancer risk for men, and even less consistent for women. It is hypothesized that in premenopausal women, obesity is associated with high estrogen in addition to high insulin [56].

A recent meta-analysis of six studies on excess weight and colorectal cancer found a 3% increase (95% confidence interval 2% to 4%) in risk of colorectal cancer per 1 unit increase in BMI [57]. There was also a dose–response relationship, with a 15% increase in the risk of colorectal cancer for an overweight person compared with a person having normal weight and a 33% increase in the risk for an obese person.

In summary, obesity consistently has been associated with colorectal cancer in men, with relative risks of 1.5 to 2. The association is weaker and less consistent in women, with relative risks (RRs) of 1.2 to 1.5. Further, obesity is associated with an increased risk in premenopausal but not postmenopausal women. The RRs are higher for the colon than the rectum.

Colon polyps

Several studies have examined the role of obesity in the risk of colon adenomas (presence and size). Obesity doubles the risk of the development of colon adenomas [58–60]. Weight gain also is associated with an increased

Table 4
Cohort studies examining the association between body mass index and the risk of colorectal cancer*

Study	Design	Cohort size	Number of CRC	BMI	Adjusted relative risk	Adjustments
Moore et al, 2004 [51]	Prospective	1661 males	69	> 30	2.0 (0.98–4.2)	Age, sex, smoking, alcohol, height,
		2141 females	80		1.9 (0.98–3.5)	physical activity
Lee et al, 1992 [52]	Prospective	17,595 males	290	> 26	1.52 (1.06–2.17)	Age, exercise, family history
Calle et al, 2003 [53]	Prospective	404,576 males	3,494 males	30–35	1.47 (1.30–1.66)	Age, race, education, smoking, alcohol,
		495,477 females	3,012 females		1.33 (1.17–1.51)	exercise, diet
Ford 1999 [54]	Retrospective	5402 males	104 males	> 30	2.95 (0.99–8.74)	Age, race, smoking, alcohol, education, exercise,
		7796 females	118 females		2.74 (1.04–7.25)	serum cholesterol
Murphy et al,	Prospective	379,167 males	1,792 males	> 30	1.75 (1.49–2.05)	Age, race, smoking, alcohol, diet, exercise,
2000 [55]		496,239 females	1,616 females		1.25 (1.06–1.46)	family history, aspirin use

* All studies were conducted in the United States.

risk of colon polyps. The risk appears higher in men than women. The data suggests that obesity increases the risk of large (greater than 1 cm) and high-risk adenomas (greater than 2 cm, multiple, tubulovillous), but not small adenomas. The obesity related risk of adenomas is increased further by abdominal obesity and possibly female gender.

Mechanism(s) of obesity-related colorectal carcinoma

Abdominal obesity and insulin resistance

Abdominal obesity is a stronger risk factor for colon cancer than truncal obesity or BMI. In some studies, abdominal obesity (waist hip ratio, and waist circumference) had higher risk estimates than BMI, and independent of BMI. Abdominal obesity is more common in men, and this might explain the stronger effect of obesity in men (versus women). In women, there is limited information to suggest a trend toward increased risk of colon cancer with abdominal obesity measured as waist to hip ratio.

Abdominal obesity reflects visceral fat deposition, which is associated with insulin resistance and higher circulating levels of insulin growth factor (IGF-1). The mechanism by which insulin and IGF increase the risk of colorectal cancer has been reviewed in detail elsewhere [49]. Obesity as measured by BMI is correlated strongly with plasma insulin levels. Further, there is a strong correlation between plasma insulin levels and measures of visceral adiposity, including waist circumference and waist to hip ratio.

Estrogen

Estrogen may influence colorectal cancer risk [56]. Postmenopausal hormone use has been shown in several observational studies to be associated with reduced risk of colon and rectum cancer [61]. The role of endogenous estrogen has not been well-studied, however, and it is speculated to play a role in obesity-related increased CRC risk. BMI might be an important determinant of estrogen levels in postmenopausal women where the conversion of androgens to estrogens takes place in adipose tissue. It has been postulated that postmenopausal estrogen may counteract the effect of insulin/IGF. In premenopausal women, however, obesity increases the level of insulin, but it is a relatively unimportant source of estrogen (which is produced by the gonads), thus having a net effect of increasing the risk of CRC.

Physical activity

Physical activity directly increases insulin sensitivity and reduces plasma insulin levels. Physical activity is also a major determinant of obesity, which increases insulin resistance. Several prospective and retrospective studies reported significant associations between physical inactivity and colon cancer. A review of the literature reported an approximately 50% reduction in colon cancer risk in active individuals [62]. In one large well-designed study, the levels of physical activity seem to explain part of the effect of

BMI. When assessed, dietary factors did not affect the association between physical activity and colon cancer.

Diet

Part of the effect of BMI on the risk of colon cancer may be confounded by dietary intake. Dietary factors including high consumption of red meat, low consumption of fresh fruit and vegetables, low-fiber diets, and diets low in certain vitamins and minerals including calcium and folate have been associated with increased risk of colon cancer. In addition, in a review published in 1994, high sucrose intake has been associated with increased risk of colon cancer in 12 of 14 studies that qualified for inclusion in that review [63]. It is unclear, however, the extent to which dietary intake explains the effect of obesity.

Management

The International Agency for Research on Cancer Working Group on the Evaluation of Cancer-Preventive Strategies concluded in a recent report that avoidance of weight gain reduces the risk of several cancers including esophageal and colonic adenocarcinoma. These conclusions were based on the epidemiological association between overweight/obesity and these cancers, not on studies that examined the effect of weight loss [6]. Given that few individuals manage to maintain weight loss after initial intentional weight reduction, however, it is difficult to examine the risk of relatively rare cancer outcomes in a large number of individuals. This might become possible with the rapid proliferation of bariatric surgery.

The increasing rates of obesity and the significant conditions associated with obesity suggest that obesity-related conditions will be major health issues for gastroenterologists for several years to come. The widespread use of bariatric surgery also means that a significant proportion of these patients will have several additional GI-related disorders.

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Gastroenterol Clin N Am
34 (2005) 83–90

GASTROENTEROLOGY
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Diet Options of Obesity: Fad or Famous?

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"Diets;" the wise man said, "those that work are unpalatable; those that are palatable don't work." Thus, over the years, Americans have been consumed with dieting and have witnessed a variety of approaches to combat the rising problem of obesity, most of which have not achieved the desired long-term effects of lowering the rate of obesity and its consequences. None have failed more miserably than the low-fat concept that eventually became synonymous with healthy eating in the United States. In the past 30 years, the average American's fat consumption has dropped to 34% of total calories from 40% of total calories. During that time, despite an impressive rise in the number of low-fat products sold and consumed in the United States, the rate of obesity has risen to an all-time high. The rate of obesity, which remained fairly constant from the 1960s through 1980, has surged higher since then, from 14% to 22% of the population. The rate of diabetes mellitus also has increased to match this rate; this includes a rise in the rate of type II diabetes mellitus among teenagers, particularly boys. It is tempting to think that this low-fat dietary approach that swept the United States in the past 30 years has been the wrong approach. There are many factors that account for the perpetuation of the low-fat craze, including the promulgation of government recommendations based on soft scientific data and the fact that the production and marketing of reduced-fat food products have become big business. Perhaps the best exponent of the dilemma is the report of the Harvard Nurses Health Study and its two follow-up studies [1]. In these studies, data on the diet and health of over 300,000 Americans were obtained over a 10-year period. Results suggest that total fat consumed has no relation to heart disease risk and that saturated fats are little worse, if at all worse, than the pasta and other carbohydrates that are suggested strongly by the US Department of Agriculture food pyramid. According to Gary Taubes [2], writing in the *New York Times Magazine*, "the history of

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0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.007 *gastro.theclinics.com*

the national conviction that dietary fat is deadly and its evolution from hypothesis to dogma is one in which politicians, bureaucrats, the media, and the public have played as large a role as the scientists and the science.''

Now the low carbohydrate craze has developed on its own through several published books beginning with Robert Atkins, MD, in the 1970s. This craze developed despite the official government recommendations being directly in contradiction and the unofficial opposition of many groups with vested interest in maintaining the status quo. The first Atkins book was ignored and snubbed by the mainstream medical community as efforts were concentrated on the evils of dietary fat. Eventually the pendulum swung in the opposite direction. The past few years have begun to show a subtle change in the scientific consensus regarding the low-carbohydrate diets. A few key scientists finally are taking seriously what the many best selling diet books have been saying for years. An increasing number of researchers now say that low-fat weight loss diets have proved to be dismal failures in clinical trials. The new hypothesis (which is the underpinning of the diets described in this article) has become at least something that can be discussed and not rejected outright. High-glycemic carbohydrates such as potatoes and white rice are absorbed quickly into the bloodstream and cause a quick rise in blood glucose followed by a surge in insulin production. This in turn eventually results in lower blood sugar levels than before eating. The body then senses that it has run out of fuel, although the insulin level remains high enough to prevent the body from burning its own fat. The result is hunger and craving for more carbohydrates, a vicious cycle producing a situation ripe for obesity. Recent data point to the growing trend and widespread use of low- carbohydrate or correct carbohydrate diets with the emphasis put on carbohydrates rather than fat. The British Federation of Bakers recently announced that bread sales have declined 2% per year since 1997, two years after Sugar Busters first was published nationally and the year that the Atkins Diet was re-released. News reports have credited these diets with increasing beef sales in the United States in 12 of the last 14 quarters. Consumption of bacon and eggs are at 10-year highs, and beef jerky sales are up more than 40% in the past 2 years. In short, it now appears that the diet pendulum has swung fully away from the low-fat side and has moved rapidly to the low-carbohydrate side. This article highlights the different dietary approaches that have evolved and become popular over the past few years. Whether these are fads or truly represent important changes in the way people eat and that ultimately will lead to a lower rate of obesity and improved health is impossible to know.

The Atkins diet

The grand daddy of them all, this approach was first published in the 1970s and reintroduced again about 10 years ago as ''Dr. Atkins' New Diet

Revolution'' leading to what many have termed the ''low-carb mania'' in the United States and many other countries. This book has been a bestseller for years, and millions have tried this diet [3].

The diet works by promoting a 2-week induction phase during which one is permitted to eat no more that 20 g of carbohydrates per day. This is a very severe restriction, and Atkins makes no distinction between high-glycemic carbohydrates such as white bread and low glycemic ones such as beans. The approach translates into a diet that consists mainly of meats, poultry, seafood, cheeses, oils, eggs, butter, and margarine.

One may wonder about the 20 g of carbohydrates and where one can find such a tiny amount other than in traces found in dressings, cheeses, and lettuce greens. During the 14-day induction period, carbohydrate-containing foods such as milk, fruits, grains, and cereals cannot be consumed, and particular attention is paid to avoidance of potatoes, peas, corn, and carrots. After the first 2 weeks, carbohydrates can be introduced at the rate of about 5 g per week, and the recommendation for the long-term or maintenance phase is that the dieter should stick to a diet containing no more than 40 to 90 g of total carbohydrates per day. Even this is a very small amount when compared with the amount allowed by the food pyramid and major health organizations.

Although there has been virtually no scientific evidence to back such a restrictive approach to dieting or eating habits, there have been several studies comparing the Atkins approach with other dietary approaches. In two studies, participants on the Atkins diet had a larger decrease in serum triglyceride levels and a greater increase in high-density lipoprotein (HDL) cholesterol levels when compared with a traditional low-fat group. Changes in total and low-density lipoprotein (LDL) cholesterol were similar in both groups, and at the end of 1 year, both groups achieved similar levels of weight loss. In these two studies there were some important facts about diets in general and Atkins specifically that are worth noting. First, about 40% of dieters in each group dropped out of the study prematurely because of their inability to adhere to the diets. For the average person, this indicates a 60% chance that one will be able to stick to either one of these plans even for a year, let alone for a lifetime. The second point is that Atkins group lost an average of 15 pounds after 6 months but by the end of the year the total weight loss was only 9.7 pounds. These data appear to confirm what has been known about most diets, particularly those with severe restrictions of any type, that they are extremely difficult for most people to follow in the long term and that many regain lost weight because of difficulties adhering to the restrictions. The long-term effects of restrictive diets such as the Atkins Diet remain to be seen. There are no long-term studies for this approach, just as there are no long-term studies for any dietary approach. Still, it is a valid criticism that any approach that restricts one of the major food groups may in the long term prove to be harmful.

Sugar Busters

This diet plan is based on the glycemic index of carbohydrates, which can vary widely. The glycemic index is the area under the curve of a carbohydrate determined by the measurement of blood sugar level against time after ingestion of a given carbohydrate (Fig. 1). Most glycemic indexes have been determined using glucose or a slice of white bread as the standard reference. These standards arbitrarily are given an index of 100, and all measured glycemic responses are defined against this standard. For example, a standard serving of white potato has a glycemic index of 90 to 95, very close to pure glucose, whereas a serving of lima beans has a glycemic index of 35. Carbohydrates with glycemic indexes above 70 are thought to be high, whereas those with an index of less than 45 are thought to be low. Glycemic index tables are available for most carbohydrates consumed in Western countries; however, some carbohydrates consumed in other countries have not been tested, and one can deduce their glycemic index only by what type of carbohydrate they are. The theory behind this diet is that high-glycemic carbohydrates have a greater stimulus on insulin production, which over a period of time, has the effect of promoting fat storage and preventing lipolysis, thus leading to increased fat deposition and insulin resistance, high insulin levels and perpetuation of this process. This dietary approach then is suited to those individuals who have been consuming high-carbohydrate diets, particularly those rich in high-glycemic carbohydrates such as sugar, white rice, white potatoes, and white bread, and who have gained weight and become insulin insensitive or overt diabetics. Glycemic index tables

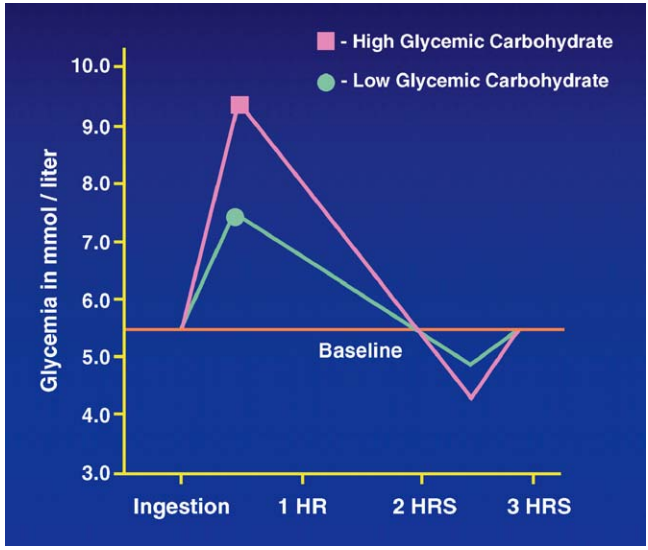

Fig. 1. Glycemic index of carbohydrates.

have been developed over the years, especially in Australia and New Zealand, where these have been used in the dietary treatment of diabetes. In the United States, Jenkins et al first reported on the potential of the glycemic index in 1981, but this concept was not adopted widely until the publication of "Sugar Busters! Cut Sugar to Trim Fat" in 1996. The book, authored by Leighton Steward; Morrison Bethea, MD; Samuel Andrews, MD; and Luis Balart, MD, became an instant best-seller, and it has sold millions of copies throughout the United States and Europe [4].

When compared with the Atkins diet revolution, Sugar Busters offers a more complete dietary approach in that it does not prohibit an entire food group. Instead, Sugar Busters makes a distinction between low- and high-glycemic carbohydrates and allows the dieter to select low-glycemic carbohydrates instead of the high ones, a correct carbohydrate approach. This leads to a modulation of insulin production and thence to weight loss and other improved metabolic functions. Sugar Busters encourages the consumption of monounsaturated fats such as olive and canola oils and the avoidance of saturated and trans fats to reach a balanced and favorable overall nutritional concept. The hidden sugars in many of the shelf products such as salad dressings, breakfast cereals, and ketchup is stressed, as these can be a source of high-glycemic carbohydrates that otherwise would go unnoticed. The reading and interpretation of labels on foods is very important to this concept and is a featured part of the book. The authors even have proposed a modified food pyramid in which they stress moderation in portion size and the consumption of whole-grain products, fruits, legumes, and vegetables in addition to trimmed and lean meats and seafood. There is no induction phase or lead-in time as there is for Atkins. The authors strongly recommend that this dietary approach be incorporated for life more as a lifestyle change than a diet. A recently published scientific article has provided support for the correct carbohydrate approach advocated by Sugar Busters. Ludwig et al [5] reported on a study showing that dieters consuming low-glycemic carbohydrates fared better in the magnitude of the decrease in triglycerides and decrease of C-reactive protein when compared with those on a low-fat diet. These researchers also found that hunger pangs were less common among low-glycemic dieters. Beneficial effects of this dietary approach include weight loss, increased energy levels, improved blood glucose levels, lower triglyceride levels, higher HDL cholesterol levels, and disappearance of gastroesophageal reflux symptoms. Diabetics appear to benefit greatly from this dietary regimen as reported to the authors by many diabetic patients who have used the Sugar Busters approach. It appears that the traditional diabetic diet may be incorporating this concept in an attempt to better control diabetes by diet. It should be pointed out, however, that, similar to other diets, no long-term studies are available to compare this approach with other diets. Additionally, in terms of adherence, there are no long-term studies available, but it would make sense that because this is not a restrictive diet, adherence over a long period

of time may be much better than with a low-fat approach or a very restrictive approach such as Atkins.

South Beach diet

The South Beach diet, created by Arthur Agatston, MD, through a book of the same name has become the latest in the low-carbohydrate diets to become wildly popular [6]. Since its publication several years ago, millions of copies of this book have been sold, and it has been on the best seller list for months. The concept is basically a phase 1 part called the strict part of the diet. It calls for limiting fat to the good fats and limiting carbohydrates to those with lowest glycemic index needed for blood sugar control (eg, no bread, rice, pasta, baked goods, or fruits). This is where the most rapid weight loss occurs. In phase 2, a more liberal part, healthy carbohydrates are allowed to be introduced slowly. These include carbohydrates with low glycemic index. According to the author, compared with phase 1, weight loss slows down, but the point is to continue losing weight while increasing the carbohydrate intake. If weight returns during this phase, however, then one can return to phase 1 for a short period of time. During phase 2, the author recommends that each dieter's reaction to carbohydrates be monitored by their weight to make changes necessary to continue losing weight. This seems impractical, as small changes in weight may occur for a myriad of reasons, and most would find it difficult, if not impossible, to fine tune the intake of carbohydrates to this extent. Finally, phase 3 is a continuation of phase 2 that is supposed to be a lifelong maintenance phase.

The South Beach diet incorporates the elements of the Atkins diet in the first 2 weeks but in a less severe or restrictive form, what could be termed Atkins Light. After the first 2 weeks, phase 2 is very similar to the Sugar Busters diet, that is, avoiding high-glycemic carbohydrates and saturated fats and including monounsaturated fats and other healthy oils.

The zone diet

This diet concept, created by Barry Sears, PhD, and published as a book in 1994, has become popular over the years. This diet recommends a balanced approach of 40% carbohydrates, 30% protein, and 30% fat [7]. The premise is a rather interesting and appealing one that 100,000 years ago people were meat eaters and human bodies were designed to handle the demands of a meat-based diet. As people have evolved, more and more carbohydrates have been introduced into human diets, causing an imbalance. The reason for the increased rate of obesity is attributed to the many grains and starches in modern diets. The zone calls for a return to the diets of human ancestors, where meats, fruits, and vegetables were the main dietary items.

The zone works by achieving the correct ratio of carbohydrates to proteins and fats to control the insulin in the bloodstream. Sears stresses that by using the zone diet people are optimizing the body's metabolic function and that through the regulation of blood sugar one allows the body to burn excess body fat. Foods with high fat and carbohydrate content such as grains, starches, and pastas should be avoided, while fruits and vegetables are the preferred source of carbohydrates. Monounsaturated fats such as olive oil, almonds, and avocados are the ideal choice of fats. Critics of this concept say that this diet is too complicated and scientific for the average person and that it is too expensive to follow, and time-consuming and inconvenient. Advocates say that the diet is a low glycemic diet with an adequate amount of protein. Sears himself says that the diet is not complicated, citing that this is a misconception dating to his first book, which was aimed at cardiologists who are more scientifically oriented. As with most diets, no long-term studies have been done to test the effectiveness of weight loss over the long haul.

The protein power diet

This diet concept by Michael and Mary Dan Eades is similar in many ways to the Atkins diet [8]. The fundamentals of this concept are the reduction of carbohydrate intake until the body switches over to using fat for fuel. After this, one can reintroduce low-glycemic carbohydrates back into the diet slowly, until one is eating slightly more carbohydrates than protein. The key to this diet is the drastic reduction in carbohydrates in the initial phases. Phase 1 of this program is for people who are 20% and over their ideal body weight. These dieters reduce carbohydrate intake drastically to a maximum of 30 g per day much like the initial 14 days of the Atkins program. Phase 2 is for those less than 20% over their ideal body weight, and these dieters reduce their carbohydrate intake to 55 g a day. As opposed to Atkins, where if one doe not exceed daily carbohydrate intake one does not have to worry about counting calories, on the protein power diet, the daily caloric intake is tied directly to the protein requirement. Active individuals will require more protein that those who are sedentary, and that becomes a problem with this diet. Sedentary individuals may have a very low caloric intake, in many cases below 1200 calories, which may be too drastic and slow metabolism significantly.

Other criticisms of this diet are that one can experience significant hunger, and that the amount of protein may be excessive and lead to cancer, heart disease, renal failure, and osteoporosis. The author's review of the available literature on these claims fails to establish any link between high protein consumption and any of these diseases. The fact is that when high-protein diets are consumed in balance with enough water, fat, fat-soluble vitamins, and vegetables, they are in fact healthy.

Gastroenterologists frequently are asked advice on diets and weight loss, and many may feel inadequate in knowledge of what is medically acceptable and indicated. Whereas many clinical situations may demand a special diet that requires referral to a clinical dietitian, when the need is simply weight loss, this has not worked for the author's patients. One clinical setting in which a low-glycemic approach may be perfect is nonalcoholic fatty liver disease. These patients frequently are found to have many of the indicators of the metabolic syndrome, and it seems reasonable to expect that low-glycemic diets will lead to a more profound improvement in their abnormalities. Prospective studies should be done to test this hypothesis. The author finds it very rewarding and within time constraints in a busy practice to recommend that patients buy any of the more balanced approaches such as Sugar Busters or South Beach and that they read and understand the concepts and try to lose weight. If successful, the author recommends that they change their lifestyle forever.

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Gastroenterol Clin N Am
34 (2005) 91–104

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Pharmacological Therapies for Obesity

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The development of effective pharmacological therapies has been both the greatest hope and one of the greatest disappointments in the field of obesity. At its root, obesity is a complex, but ultimately understandable, metabolic and behavioral disorder that disrupts normal body weight regulatory mechanisms. Logically, both the metabolic and behavioral components should be amenable to pharmacological treatment, and several agents have been developed that influence eating behavior, food intake, nutrient absorption, and energy expenditure. They also cause weight loss, but to a lesser extent and for a shorter period than would be considered ideal by either patients or physicians. Moreover, many of these agents have been associated with unacceptable adverse effects, in many cases as a direct result of their therapeutic mechanism of action. These adverse effects, including the euphoric and addictive effects of amphetamines, the hypertensive and arrhythmogenic effects of the adrenergic agents, the cardiac valvular effects of fenfluramine, and the steatorrhea associated with orlistat, have curtailed the use of these drugs significantly and in some cases have required their complete withdrawal from the market.

Recent studies of the physiology of body weight regulation have demonstrated the complexity of this control system and have identified numerous novel targets for therapeutic intervention [1,2]. These studies provide hope that new, more specific agents will provide more effective and durable treatment of obesity with fewer adverse effects. The very complexity of weight regulation; however, and the powerful systems to defend against real or perceived starvation, make it unlikely that a single pathway, cell or molecule will prove to be the Achilles heel of obesity. Thus, long-term

This work was supported by grants DK99010, DK43351 and DK46200 from the National Institutes of Health.

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doi:10.1016/j.gtc.2004.12.002 *gastro.theclinics.com*

effective treatment is likely to require a multi-modal approach, using multiple drugs aimed at different targets or novel combinations of specific pharmacological, nutritional, endoscopic, and surgical approaches.

Goals of pharmacological therapy

Available pharmacological treatments for obesity can be effective adjuncts to diet- and exercise-based behavioral therapies, typically increasing the amount of weight loss by 4% to 6% (eg, from a weight loss of 4% to a weight loss of 8%) over 1 to 2 years [3]. In all cases, however, the maximal effect appears to occur within the first year of therapy, often the first 6 months, with partial regain of lost weight thereafter [3,4]. In addition, the response to each medication varies widely from patient to patient, with a few patients (typically 2% to 5%) exhibiting considerably more weight loss than average and a significant portion experiencing no effect of the drug on their weight [5].

For the available weight loss medications (regardless of the mechanism of action), the criterion of a 4-pound weight loss in 4 weeks is a helpful guideline. Weight loss of lesser magnitude provides good evidence that the medication is having little effect. Given the potential for adverse effects, it is a strong indication for stopping the drug. For patients who lose 4 or more pounds in the first month, it is not clear how much additional weight loss should occur for the drug to be continued. Many physicians require that patients lose 4 pounds per month for a minimum of 3 months (12 pounds total) to consider the medication clinically effective. Thereafter, if a patient maintains the lower weight, the drug is still considered effective, because it is likely preventing the weight regain that occurs in more than 90% of patients upon cessation of treatment. For each of these drugs, human and animal studies suggest that they work less by causing weight loss than by causing the weight regulatory system to adjust the weight and energy set point downward. For each drug and for each patient, there appears to be a maximum achievable weight loss. Continuing the drug is usually necessary to maintain all or most of the lost weight, and cessation is commonly associated with rapid regain of the lost weight.

Weight loss medications usually are reserved for patients who have failed more standard behavioral interventions, including various combinations of diet- and exercise-based approaches. Box 1 shows the standard criteria for use of these agents.

Medications approved for treating obesity

Table 1 lists the medications most commonly used for the treatment of obesity. The first three drugs, phentermine, sibutramine, and orlistat, are approved by the Food and Drug Administration (FDA) specifically for this

Box 1. Clinical criteria for pharmacological therapy for obesity

Body mass index (BMI) > 30 kg/m^2 or BMI > 27 kg/m^2 in association with significant medical complications
Failure of behavioral approaches, including diet and exercise regimens
No strong contraindications to the medication used
For continued treatment, weight loss of ≥ 4 pounds per 4 weeks for each of the first 3 months

indication. The others are approved for other indications but have been found in one or more clinical studies to exhibit a significant weight loss effect. Two drugs, phendimetrazine and benzphetamine, are approved by the FDA but classified as Schedule III drugs by the Drug Enforcement Administration because of their high potential for abuse. These drugs have little or no role in the routine management of obesity and are not considered further in this article.

Phentermine

Phentermine is an adrenergic reuptake inhibitor that augments adrenergic signaling in the brain and peripheral tissues. It is thought to promote

Table 1
Medications for treatment of obesity

A. Approved by the FDA specifically for weight loss indication*

Medication	Typical dosing	Classification	Common adverse effects
Phentermine[a]	15–37.5 mg/d	Adrenergic agent	Tachycardia, hypertension
Sibutramine[a,b]	10–15 mg/d	Serotonergic/adrenergic	Hypertension, tachycardia
Orlistat	120 mg three times daily	Lipase inhibitor	Malabsorption, steatorrhea

B. Approved by the FDA for other indications**

Medication	Typical dosing[c]	Primary indications	Common adverse effects
Bupropion[a]	150–300 mg/d	Depression	Anticholinergic; agitation
Metformin	500–1000 mg/d	Type 2 diabetes	Hepatic oxidative injury
Topiramate	50–100 mg/d	Seizure disorder	Cognitive impairment
Zonisamide	400–600 mg/d	Seizure disorder	Cognitive impairment

* Phentermine is approved by the FDA for short-term use, and sibutramine and orlistat are each approved without time limitation [6]. Use in clinical practice varies widely.

** These agents typically are approved for life-long use for their specific indication.

[a] Use of phentermine, sibutramine or bupropion in patients taking monoamine oxidase inhibitors (MAOIs) is strongly contraindicated because of the risk of severe cardiovascular events.

[b] Use of sibutramine in patients taking serotonin-selective reuptake inhibitors (SSRI) is relatively contraindicated because of the risk of serotonin syndrome.

[c] Typical dosing for use as a weight loss agent. Effective doses for primary indication may be higher.

weight loss by activation of the central and sympathetic nervous systems, with a resulting decrease in food intake and increased resting energy expenditure.

Phentermine is the weak but safe half of the ''phen-fen'' combination therapy introduced by Weintraub et al in the 1990s. Unlike fenfluramine, phentermine has no known effects on cardiac valves. As an adrenergic agonist, however, it can be associated with tachycardia, and, less commonly, hypertension. Thus, phentermine should be used with caution in people at significant risk for hemodynamic or cardiovascular complications of tachycardia and those with uncontrolled hypertension. All patients taking this medication should be monitored closely for changes in heart rate or blood pressure, particularly during the first several weeks of therapy and at times of dosage elevations. Abnormal heart rate or blood pressure should be treated as necessary, or the phentermine should be withdrawn.

Because phentermine no longer is covered by patent protection and there are several proprietary and generic formulations available, it is the least expensive of the widely used medications for weight loss [7]. It comes in two major forms, phentermine resin (eg, Ionamin) and phentermine-HCl. Normal dosing is 15 to 30 mg per day for phentermine resin and 18.75 to 37.5 mg per day for phentermine-HCl. An acceptable therapeutic response is considered as 4 pounds/4 weeks for at least the first 8 to 12 weeks of therapy, when given with or without associated dietary and exercise counseling.

Although approved by the FDA for only 3 months' use, many experts advocate longer-term use in patients who demonstrate a good therapeutic response during the first 3 months. As with other weight loss medications, the weight loss generally stops within 3 to 6 months of initiation. For patients who have lost a significant amount of weight during this time, continuation of the drug is nonetheless valuable to prevent weight regain.

Sibutramine

Sibutramine, a monoamine reuptake inhibitor, enhances adrenergic, serotonergic, and dopaminergic signaling in the brain. Thus, it has pharmacological characteristics that are similar to, if weaker than, those of the phentermine–fenfluramine combination that was introduced in the mid-1990s. Unlike fenfluramine, which has been withdrawn because of the risk of carcinoid-like cardiac valvular disease, sibutramine's serotonergic effects have not been associated with valvular abnormalities [8].

Sibutramine treatment is associated with an average weight loss of approximately 5% to 8%, compared with 2% to 4% in participants receiving placebo [9]. Most of the randomized, controlled trials include dietary or exercise counseling for participants in the treatment and placebo groups, which likely accounts for the weight loss in the placebo group. Thus, sibutramine itself appears to be associated with an average weight loss of approximately 3% to 4% during the first 6 to 12 months of treatment.

Extension of therapy for up to 2 years is associated with an average regain of approximately half of the weight lost initially. In one large trial, however, of the participants who experienced at least 5% weight loss on sibutramine, more than 25% maintained the full weight loss when sibutramine treatment was continued for an additional year [10]. As with other pharmacological therapies for obesity, however, there is a wide patient-to-patient variation in response. A small percentage of patients exhibits dramatic weight loss, and a significant number accrue no weight loss benefit at all [5]. To date, no reliable predictors of outcome after sibutramine or other weight loss medications have been identified.

The normal dosing for sibutramine in adults is 10 to 15 mg per day taken once daily. Many physicians prefer to start with 10 mg per day and increase to 15 mg per day as clinically required. Doses higher than 15 mg per day have not been demonstrated to have increased efficacy, and they are associated with a greater risk of adverse effects, most notably hypertension and tachycardia. Patients who lose at least 4 pounds in 4 weeks are considered sibutramine responders; this medication generally is continued in these individuals for as long as weight loss continues at this rate. With longer-term sibutramine therapy, weight loss generally stops after approximately 3 to 6 months. Nonetheless, for patients who have lost a significant amount of weight by this time, continuing treatment appears to decrease the rate and magnitude of weight regain. During the second year of continued therapy with sibutramine, patients typically regain approximately 50% of the initial weight lost [10]. As with initial weight loss, however, there is substantial patient-to-patient variation. Many obesity specialists will continue to use this medication in individual patients for as long as weight loss persists, extending on occasion beyond 2 years of treatment. Some practitioners prefer to use this medication on an intermittent, as needed, basis, although the efficacy of this approach has not yet been examined carefully.

In most patients, the major adverse effects of sibutramine relate to its adrenergic properties. Approximately 10% to 15% of patients experience new-onset hypertension that can be managed by antihypertensive therapy; fewer than 3% of patients need to discontinue this drug because of uncontrolled hypertension [11]. Patients with pre-existing hypertension undergoing sibutramine therapy need to be monitored closely for exacerbation of their hypertension; their antihypertensive regimens should be adjusted as required. A few patients exhibit tachycardia with sibutramine, and this drug should be avoided in patients at elevated risk for life-threatening tachyarrhythmias and those who are unlikely to tolerate tachycardia of any cause. Other, generally less severe and dangerous adverse effects include insomnia and anticholinergic-like effects such as dry mouth and constipation.

Use of sibutramine in patients taking serotonin-selective reuptake inhibitors (SSRIs) is relatively contraindicated because of an increased

risk of serotonin syndrome, which is marked by some combination of flushing, diarrhea, and mild hypotension [12]. As a result, sibutramine should only be prescribed to patients on SSRIs when both agents are indicated strongly and when the patient is supervised closely by a physician well-versed in the use of these agents taken alone and in combination.

Orlistat

Orlistat, an inhibitor of pancreatic and intestinal lipases present in the intestinal lumen, prevents the breakdown of ingested triglycerides into absorbable fatty acids and monoacylglycerols. When taken with meals, orlistat is capable of inhibiting the absorption of up to 30% of ingested fat [13]. Clinical trials have revealed that orlistat treatment (120 mg three times daily with meals) in the setting of nutritional counseling is associated with a weight loss of approximately 10% at 1 year [14,15]. Subjects receiving a placebo along with the counseling lost nearly 6%, suggesting that orlistat itself is responsible for approximately 4% body weight loss on average [14–17]. Extension of orlistat therapy to 2 years is associated with a regain of approximately one-third of the weight initially lost, versus regain of two-thirds of the initial loss in those who took placebo during the second year [14,15]. Some clinicians preferentially prescribe orlistat to patients who consume a high-fat diet; there is no evidence, however, that such patients respond better to this agent. Moreover, although conceptually attractive, there is no good evidence that the diminishing effects of orlistat in the second year of treatment results from substitution of carbohydrates for fats in the patients' diets. Some patients decrease their intake of fats to limit the gastrointestinal (GI) adverse effects of the drug, but there is substantial intake fat (and fat malabsorption with orlistat) even on such low-fat diets.

As seen with other approaches and medications, weight loss from orlistat treatment is associated with improvements in several comorbidities of obesity, including high blood pressure, insulin resistance, and serum lipid levels [3,17]. The magnitude of weight loss on orlistat is somewhat less in patients with type 2 diabetes mellitus, a phenomenon seen with several therapies for obesity [18]. Widespread use of orlistat is inhibited by its limited efficacy and the high rate of GI adverse effects. These side effects include flatulence, steatorrhea, increased stool frequency, fecal incontinence, and oily rectal discharge. The associated malabsorption can lead to deficiencies of the fat-soluble vitamins A, D, E, and K, and all patients on orlistat should receive a daily supplement enriched for these vitamins, given at least 2 hours before or after each orlistat dose. Because of the higher rate of vitamin D deficiency in people with obesity and the associated risk of metabolic bone disease, vitamin D levels should be measured before starting orlistat and periodically (eg, every 6 months) during therapy, with supplementation to achieve a serum 1,25-OH-vitamin D level of at least 20 IU/mL [1,3,16,17].

Medications approved for other indications

Bupropion

Unlike many other psychotropic agents that induce weight gain, bupropion treatment for depression often is associated with modest weight loss. In short-term trials (up to 26 weeks) in patients with obesity, bupropion SR has led to weight loss of 4% to 5%, compared with less than 2% in placebo-treated controls [19]. As with other weight loss-promoting drugs, short-term success may not translate into long-term weight loss, and longer studies are needed to assess the potential utility of bupropion for obesity. Nonetheless, given the paucity of pharmacological options, many providers are trying a course of bupropion, particularly for patients with mild-to-moderate obesity who have symptoms of depression. A growing use of this agent is as a replacement for one of the SSRIs, when those agents have led to significant weight gain. The mechanisms of action of SSRIs and bupropion for depression are different, however, and not all patients respond similarly to the two classes of drugs. For patients with SSRI-induced weight gain (which occurs more commonly with citalopram, escitalopram, and paroxetine), it is often effective to switch to another SSRI that is less likely to generate weight gain, such as fluoxetine or sertraline. It is important to note, however, that in different patients each of these agents can be associated with weight gain, weight loss, or have no effect on weight, so empiric evaluation of their effect is needed in each individual treated.

Metformin

Nearly all of the available medications to treat type 2 diabetes mellitus are associated with weight gain. Insulin therapy promotes an increase in fat deposition and total body fat, and sulfonylureas exert the same effect by enhancing secretion of endogenous insulin from pancreatic beta cells. Although the degree of weight gain varies, the amount can be substantial in some patients. The thiazolidinediones, including pioglitazone and rosiglitazone, typically cause only minor weight gain, but recent studies have suggested that body fat may be redistributed more centrally with their use. In contrast to these other agents, metformin (Glucophage and others) is either weight neutral or causes moderate weight loss. In the long-term Diabetes Prevention Program trial, the metformin-treated group lost approximately 4% of their initial body weight over 1 to 2 years, which was approximately half of the weight loss seen in the group that underwent an intensive lifestyle intervention. Although the effectiveness of metformin was diminished by year 4, weight loss remained significantly greater than the placebo-treated group. In this trial, metformin treatment led to a 31% decrease in the incidence of diabetes, compared with a 58% decrease for the lifestyle intervention group. Based on these results and similar outcomes in shorter duration studies, many clinicians recommend metformin as the agent of first choice in patients with

obesity and type 2 diabetes. In addition, metformin is being used with increasing frequency in nondiabetic patients with obesity and insulin resistance. One group worth specific mention is patients with obesity and nonalcoholic fatty liver disease. Animal studies and small series in people suggest that metformin treatment may decrease fat deposition in the liver. Whether these findings will be borne out in larger, controlled studies remains to be seen. Nonetheless, metformin-induced weight loss is likely to have a beneficial effect in these individuals. The normal dose of metformin is 500 to 850 mg, once or twice daily. Metformin should not be used in patients with significant renal dysfunction (creatinine of at least 1.5 mg/dL) or ketoacidosis; lactic acidosis is a rare but serious complication of metformin use.

Topiramate

Promotion of weight gain is the most troubling adverse effect of many of the newer antipsychotic drugs, mood stabilizers and anticonvulsants, and physicians using these medications have sought effective ways of mitigating this complication. Topiramate, an anticonvulsant with mood stabilizing properties, is unusual among these drugs in that it promotes weight loss rather than weight gain. In several uncontrolled studies, topiramate treatment has led to partial or complete reversal of weight gain induced by other psychotropic drugs. This effect recently led to the investigation of topiramate as a primary treatment for obesity. Although studies of this broader use are continuing, doses above 100 mg per day are associated with a high rate of cognitive impairment that is unacceptable to most patients. For reasons that are not clear, this effect appears less common or troubling in patients receiving other psychotropic agents. To avoid adverse effects, this medication should be started at low doses (eg, 25 mg per day) and increased slowly to a maximum of 100 mg per day. Although doses up to 200 mg per day commonly are used to treat seizures and mood disorders, the available data suggest that doses above 100 mg per day confer little additional weight loss and are associated with increased cognitive deficits.

Zonisamide

Zonisamide is an atypical anticonvulsant that has been found to induce weight loss in patients receiving other antiepileptic agents. This observation provoked a short-term, randomized, controlled trial that demonstrated significant weight loss in patients with moderate obesity (average BMI = 36 kg/m^2). In this trial, patients receiving 400 to 600 mg per day zonisamide lost an average of 6% of their initial body weight, compared with a 1% loss in the control group [20]. The major adverse event reported in this study was fatigue. This study has generated much interest in zonisamide as a possible primary treatment of obesity. Confirmatory and longer-term studies are needed, however, before it can be recommended for widespread use.

Discredited medications

Fenfluramine

Fenfluramine and its biologically active enantiomer dexfenfluramine are monoamine secretagogues. They act by making more serotonin available at serotonergic synapses, and one effect of this increased synaptic serotonin is to diminish appetite and promote energy expenditure. The combination of fenfluramine and phentermine, an adrenergic agonist, was shown in the early 1990s to have dramatically improved effects (both numbers of positive responders and degree of weight loss) over either phentermine or fenfluramine alone [21,22]. Widespread use of this combination began in 1995 and was accelerated by FDA approval of dexfenfluramine for weight loss in 1996. In 1997, however, a high rate of cardiac valvular abnormalities, most notably fibrosis reminiscent of carcinoid/serotonin-associated heart disease, was seen in patients taking these agents [23,24]. Further epidemiological examination linked these abnormalities with the fenfluramine, which was withdrawn from the market. Phentermine, as noted above, remains in widespread use for obesity treatment. It has none of the valvular effects associated with fenfluramine. Notably, in the years since fenfluramine was withdrawn, the risk of associated valvular disorders has been re-evaluated and, while still significant, the risk has been found to be substantially lower than originally thought [25]. Fortunately, many patients who exhibited valvular abnormalities from this medication have experienced partial or complete regression of these changes since the drug was discontinued [24,25].

Ephedrine and phenylpropanolamine

These agents had been sold as over-the-counter weight loss remedies until they were withdrawn in 2000 and 2004, respectively, after the FDA determined that they were unsafe for routine use. Despite their widespread use in dietary supplements and herbal formulations, there have been few studies of their short- or long-term effectiveness in promoting weight loss. These agents have been associated with an increased risk of cardiovascular complications, including strokes and life-threatening arrhythmias, however, which led to the FDA recommendations that they be withdrawn [26–28]. Current formulations of dietary supplements and other OTC weight loss therapies sold in the United States do not include these compounds.

Pharmacological treatment of drug-induced weight gain

Many medications are associated with weight gain, including steroid hormones, thiazolidinediones, insulinotropic agents, and several classes of psychotropic drugs (Box 2). Treatment for drug-induced obesity is similar to

Box 2. Medications associated with weight gain

Steroid hormones
Glucocorticoids
Progesterone

Neurotropic and psychotropic medications
Olanzepine, clozapine
Valproic acid
Lithium
Phenothiazines
Antidepressants
- SSRIs
- Tricyclics
- MAOIs

Diabetes treatments
Sulfonylureas
Insulin
Thiazolidinediones (Actos, Avandia)

that for essential obesity, with a heavy reliance on behavioral therapies to improve diet and increase physical activity. In some cases, however, drug-induced obesity may be more amenable to pharmacotherapy than other weight disorders. Weight gain associated with treatment of diabetes may be ameliorated or reversed by inclusion of metformin in the antidiabetic regimen, either in lieu of or in addition to thiazolidinediones or sulfonylureas. Although insulin, sulfonylureas, and thiazolidinediones promote weight gain and central fat redistribution, metformin often promotes weight loss. Even in the absence of weight loss, per se metformin tends to be weight-neutral, and substitution of other antidiabetic agents with metformin often results in modest weight loss. For patients with seizure or mood disorders in whom pharmacological treatment has been associated with significant weight gain, topiramate and zonisamide may be particularly helpful. Both of these agents are approved by the FDA for treatment of seizure disorders. In addition, they have been found to have mood stabilizing properties, making them reasonable alternatives to weight-promoting mood stabilizers such as olanzapine and clozapine. In some cases of seizure and mood disorders, it is possible to change from these latter medications to ones that have fewer weight-promoting effects, including topiramate and zonisamide. Alternatively, these weight loss-promoting mood stabilizers and anticonvulsants are often effective when added to the patient's regimen. Different practitioners follow widely different practice patterns relating to these medications. Where equivalent efficacy can be achieved with agents that inhibit further weight

gain (or promote reversal of previous obesity), this approach is generally favored.

Medication use after weight loss surgery

Although GI weight loss surgery is a highly effective therapy for severe obesity, its efficacy varies considerably among individual patients. After Roux-en-Y gastric bypass, patients lose an average of 65% to 70% of their excess body weight within the first 1 to 2 years after surgery and maintain the loss of 50% to 55% of their excess body weight over more than 10 years [29,30]. The author has observed, however, that weight loss in individual patients varies from 20% to 120% of excess body weight at 1 year. For many patients at the lower end of the weight loss distribution, the results of surgery are disappointing. Some clinicians have used medications in an attempt to enhance weight loss after surgery. No formal trials of this approach have been reported, but the centrally acting agents, including phentermine, sibutramine, and topiramate are attractive because of their ability to curb appetite in many patients. Orlistat in this setting appears inadvisable, because it can exacerbate deficiencies of fat-soluble vitamins already depleted by the surgery itself. Prescribing any weight loss medication after surgery should be viewed as experimental, however, and generally should be limited to controlled trials by clinicians experienced in obesity treatment.

Future considerations

The increasing understanding of the normal mechanisms of weight regulation has given rise to numerous targets for new pharmacological therapies, and more than 150 drugs are under active development for the treatment of obesity [31]. These newer agents act on a broad spectrum of available targets (Fig. 1), and most are more narrowly directed than currently available options; thus, there is hope that they will have a better adverse effect profile. Two of them, ciliary neurotrophic factor (CNTF) and rimonabant, were recently studied in large-scale, randomized controlled trials. CNTF is a central- and peripherally acting nerve growth factor that has been found to exhibit appetite suppressing activity in animal studies. In animal and human studies directly specifically at obesity, it has the distinction of being the first weight loss agent to exert effects that continue for some time after the drug is discontinued. Unfortunately, however, its use is associated with the development of neutralizing antibodies that limit its effectiveness and may be associated with immune complex disease.

Rimonabant is an antagonist of the cannabinoid type 1 receptor, one of two receptors that mediate the effects of endogenous cannabinoids and marijuana. It has been developed as an aid for smoking cessation and as

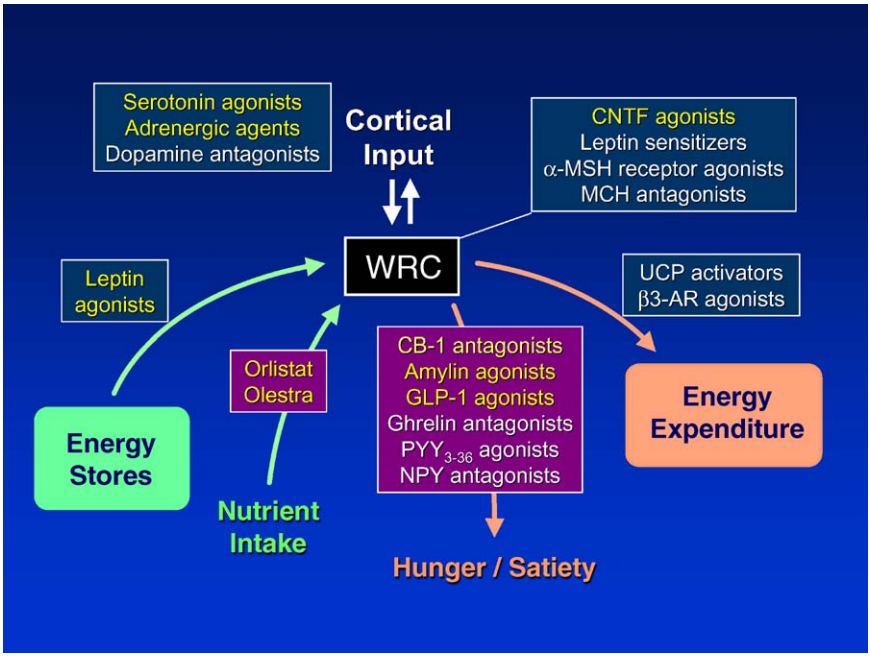

Fig. 1. Selected targets for obesity pharmacotherapy. Increased understanding of the mechanisms of normal weight regulation has revealed numerous potential targets for novel weight loss medications. Compounds that affect each of these targets are in varying stages of development. *Abbreviations:* β3-AR, beta-3 adrenergic receptors; CB-1, cannabinoid type 1 receptors; CCK-A, cholecystokinin type A receptors; CTNF, ciliary neurotrophic factor; GLP-1, glucagon-like peptide 1; MCH, melanin-concentrating hormone; α-MSH, alpha-melanocortin; NPY-Y1/Y5, neuropeptide Y type 1 or type 5 receptors; NPY-Y2, neuropeptide Y type 2 receptors; UCP, uncoupling protein; WRC, weight regulatory centers of the brain, including several nuclei within the hypothalamus, hindbrain, and reward centers.

a treatment for obesity. In one, as-yet-unpublished, large-scale clinical trial, treatment with 20 mg per day rimonabant for 1 year was associated with an increased rate of smoking cessation and an average weight loss of 18 pounds, compared with an 8-pound weight loss in the placebo group. It also was associated with a significant improvement in high-density lipoprotein cholesterol, suggesting that it may have broad benefits in reducing cardiovascular risk. Whether these effects are durable remains unknown, and additional long-term studies are needed to assess efficacy and safety. Nonetheless, this agent is an example of the potential for novel therapies aimed at specific targets within the body's weight regulatory apparatus.

Because the physiological mechanisms of weight regulation are complex, and redundant systems are likely to be present to guard against starvation, it is unlikely that any single agent will be completely effective in treating obesity. Effective long-term control of weight by pharmacological therapies

likely will require multiple agents used in combination to defeat the requisite number of redundant pathways. The large number of drugs under development suggests that several moderately effective agents will emerge. Combinations of different moderately effective agents, or combinations of these agents with other therapies (eg, dietary manipulation, intestinal infusions, electrical stimulation, or endoscopic or laparoscopic surgery), likely will generate the greatest sustainable weight loss. Design of some of these combinations will be guided by advancing knowledge about the physiological effects of weight loss surgery and the array of mechanisms used by this very effective treatment to induce durable weight loss. The identification of increasingly safe and effective medications for obesity likely will be the basis for new and even more effective combination approaches, even if they have limited utility as single agents. Such combinations should facilitate sufficient control of obesity in many patients to begin reversing this epidemic problem.

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Gastroenterol Clin N Am
34 (2005) 105–125

GASTROENTEROLOGY
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Gastrointestinal Management of the Bariatric Surgery Patient

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For patients with severe and medically complicated obesity, gastrointestinal (GI) weight loss surgery is the most effective means of achieving substantial and durable, weight loss [1]. Roux-en-Y gastric bypass (RYGB), the most effective procedure in widespread use in the United States, leads to an average loss of 65% to 70% of excess body weight (usually considered the portion of one's body weight above a body mass index [BMI] of 25 kg/m^2) within 1 to 2 years after the operation [2]. After this surgical intervention, patients typically maintain a 50% to 55% excess body weight loss for 15 years or longer, in most cases for life [1,3]. This long-term weight loss is associated with dramatic and durable improvements in the medical complications of obesity. The effect of surgery on metabolic (eg, diabetes) and structural (eg, obstructive sleep apnea) complications can be profound [1,2]. The benefits come with a cost, however. People with obesity are at increased risk of complications from all types of abdominal surgery, and weight loss surgery involves major operations selectively performed in patients with severe or medically complicated obesity [4]. Appropriate selection of patients, preoperative preparation, and postoperative follow-up are essential to promoting the best possible outcomes after these procedures.

Each type of weight loss surgery is associated with a distinct group of risks and adverse effects that must be considered when evaluating and preparing patients and when managing them postoperatively. RYGB includes a gastric separation and two anastomoses. Common complications include stomal ulcers or stenosis, particularly at the gastrojejunal anastomosis; gastrogastric fistulae or staple line rupture; and selective malabsorption of iron,

This work was supported by grants DK99010, DK43351 and DK46200 from the National Institutes of Health.

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doi:10.1016/j.gtc.2004.12.004

vitamin B_{12}, calcium, and vitamin D [2,5]. Biliopancreatic diversions, including the duodenal switch procedure, are associated with an even higher rate of micronutrient malabsorption and a variable degree of protein-calorie malabsorption [6,7]. In contrast, gastric restrictive operations, including laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG), generally are not associated with malabsorption. The major long-term complications after these procedures are more reflective of the associated anatomical changes, and include stenosis or erosion at the band site, band migration, gastroesophageal reflux, and occasional esophageal dysmotility [8,9].

Optimal management of the patient undergoing weight loss surgery requires a multi-disciplinary approach with a team that includes experts in nutrition, psychology, medicine, and surgery. Patients who require these procedures often have multiple medical complications of the obesity itself. For many patients, input from one or more medical subspecialists (eg, in cardiology, pulmonology, endocrinology, or diabetes) is required to optimize clinical outcome and minimize perioperative risk. During the past few years, the role of gastroenterologists in the management of patients undergoing weight loss surgery has become increasingly apparent. Involvement of gastroenterologists is particularly beneficial in the postoperative period. Most of the late complications of weight loss surgery arise from the GI tract, either because of structural disease—ulceration, stenosis, obstruction, fistula or reflux—or micronutrient malabsorption, which is extremely common after gastric bypass and the various forms of biliopancreatic diversion. Gastroenterologists can also contribute to the preoperative evaluation of these patients, to help prevent complications of weight loss surgery and to manage the common GI complications of obesity itself: gastroesophageal reflux, colorectal polyps, and fatty liver disease (FLD).

The roles of the gastroenterologist

Preoperative evaluation

Preoperative GI evaluation serves two major roles: identification and treatment of disease that requires preoperative management or postoperative follow-up, and evaluation and management of chronic GI disorders that may complicate postoperative care or adversely affect outcomes.

Weight loss surgery involves manipulation of the GI tract, either by restricting the flow of food through the stomach (VBG and adjustable gastric banding) or by reordering the flow of food and visceral secretions through the alimentary tract (gastric bypass, biliopancreatic diversion). After these surgical manipulations, some parts of the GI tract become less accessible to endoscopic or radiological visualization and therapy. Thus, it is often important to exclude disease in these segments before surgery is

undertaken. Endoscopic visualization of the distal stomach (gastric remnant) is often difficult or impossible after RYGB. This is particularly true for procedures that employ a longer (eg, 100 to 150 cm) Roux limb, which are becoming more common in many centers. In addition, the long biliopancreatic limb prevents oral contrast from refluxing back into the gastric remnant, limiting the use of contrast radiography or CT for disorders of the distal stomach. Similar anatomic limitations exist for the endoscopic evaluation of biliopancreatic disease after gastric bypass. It is therefore important to consider the risks of gastric, biliary, and pancreatic disease in each patient and to pursue an appropriate preoperative assessment.

The second major role of the gastroenterologist in the preoperative evaluation is to evaluate and manage disorders that may complicate perioperative or postoperative management. The most important of these disorders are GI blood loss and chronic liver disease. All patients should be screened for iron deficiency before weight loss surgery and further evaluated as necessary. Patients older than 50 (or with a family history of colorectal neoplasia) should be brought into compliance with recommended cancer screening protocols.

Gallstones are present in up to 20% of patients who undergo weight loss surgery [10]. In patients undergoing laparoscopic gastric bypass or LAGB, many surgeons obtain preoperative sonograms. If gallstones are present, they will include a laparoscopic cholecystectomy at the time of the weight loss surgery. Because of the altered postoperative GI anatomy and the technical difficulties and complications associated with laparoscopic common duct exploration, it is generally easiest and most effective to perform an endoscopic retrograde cholangiopancreatography (ERCP) before the surgery.

Biopsy series have demonstrated that approximately 90% of patients who undergo weight loss surgery have FLD; in 3% to 7% of patients, the liver disease has progressed to cirrhosis [11,12] Patients with evidence of cirrhosis should be evaluated for portal hypertension and esophagogastric varices. The presence of varices in the area of the esophagogastric junction and gastric cardia presents a serious operative challenge and thus a strong contraindication to gastric surgery. Whether such patients should undergo biliopancreatic diversion for weight loss remains an open question.

Postoperative care

GI care after weight loss surgery generally is focused in two areas: evaluation and management of GI complications of the surgery itself, and surveillance and management of nutritional complications.

The GI complications of surgery usually present as nausea, vomiting, constipation, diarrhea, pain, or bleeding. In the early postoperative period, these symptoms are most commonly a direct effect of the operation and are often managed by the surgeon, although in some centers, gastroenterologists participate even at this early stage. Later on, these symptoms are more likely

to represent complications only indirectly related to the operation, such as band or anastomotic ulceration, stricture, staple line disruption, gastrogastric fistula, dumping syndrome, or chronic diarrhea. In many cases, they require more extensive GI evaluation or endoscopic treatment.

The potential nutritional complications of weight loss surgery vary depending on the type of operation used. For gastric bypass and biliopancreatic diversions, deficiency of iron, vitamin B_{12}, or calcium are common [2,5,6,13]. These complications are unusual after gastric banding or VBG; however, persistent vomiting from partial obstruction after these procedures has been associated with profound thiamine (vitamin B_1) deficiency [14,15]. In many centers, dietitians or nutritionists take responsibility for evaluating and managing potential nutritional complications of weight loss surgery. When gastroenterologists are integral to the multidisciplinary team, however, they often take responsibility for the initial evaluation of these nutritional complications. This is particularly true for iron deficiency, for which the differential diagnosis includes occult GI blood loss and iron malabsorption.

Preoperative gastrointestinal evaluation

The major goals of the preoperative GI evaluation are: (1) to exclude distal gastric disease, (2) to exclude ongoing active or occult GI bleeding, (3) to identify relevant hepatobiliary disease, (4) to exclude esophageal dysmotility in patients undergoing gastric restrictive procedures, and (5) to identify and correct preoperative nutritional deficiencies in patients undergoing potentially malabsorptive procedures. Table 1 outlines the most common components of the preoperative GI evaluation.

Screening for gastric disorders

The most commonly used operations for weight loss involve modifications of the stomach. In restrictive operations, such as adjustable gastric banding and VBG, a segment of the stomach is narrowed by an external band to slow passage of food from the cardia to the distal organ. For gastric bypass, the proximal gastric pouch is separated completely from the distal stomach by several rows of surgical staples, with or without division, and a gastrojejunal anastomosis is created from the pouch. Most biliopancreatic diversions with the so-called duodenal switch include sleeve resection of the gastric body. Because of these manipulations, the stomach is a frequent site of complications after weight loss surgery. Little is known about the factors that predispose to gastric complications. Ulcerations are thought to result primarily from local ischemia that results from microvascular changes around the anastomosis. The possible role of *Helicobacter pylori* is not known. Nonetheless, many clinicians prefer to negate any potential contribution of *H. pylori* infection by eradicating the organism preoperatively.

Table 1
Preoperative gastrointestinal evaluation

Goal	Indications and approach
Exclude distal gastric disease	For patients undergoing Roux-en-Y gastric bypass, *Helicobacter pylori* testing; Endoscopy only for clinical indication
Exclude occult GI bleeding	For patients undergoing Roux-en-Y gastric bypass, fecal occult blood testing, hematocrit and/or, iron studies; Follow-up endoscopy and/or colonoscopy as clinically indicated
Ensure colorectal cancer screening is up to date	Colonoscopy or flexible sigmoidoscopy as indicated
Exclude esophageal dysmotility	Relative contraindication to adjustable gastric banding or vertical banded gastroplasty; For patients undergoing these procedures with dysphagia, symptoms of severe gastroesophageal reflux disease or esophageal spasm, upper GI series, motility studies as clinically indicated
Exclude gastroparesis	Relative contraindication to adjustable gastric banding or vertical banded gastroplasty; For patients undergoing these procedures with diabetes and evidence of neuropathy, upper GI series
Identify hepatobiliary disease	Serum hepatic enzymes; Viral hepatitis serology as clinically indicated; Abdominal ultrasonography to exclude gallstones (especially before laparoscopic surgery); ERCP as clinically indicated
Exclude gastric varices	In patients with known or suspected cirrhosis, upper GI endoscopy and abdominal CT to exclude perigastric varices
Exclude micronutrient deficiency	For patients undergoing gastric bypass, biliopancreatic diversion or duodenal switch procedure, serum iron studies, vitamin B_{12}, calcium, albumin, vitamin D, and parathyroid hormone

After gastric bypass, to visualize the distal stomach endoscopically, the endoscope must traverse the gastric pouch and Roux limb and then proceed retrograde through the biliopancreatic limb and the pylorus. Such procedures are performed best by experienced endoscopists, and even then they are successful in only a fraction of patients. Ability to reach the distal stomach appears to be strongly dependent on the Roux limb length, and success is rare in patients with limb lengths that approach 150 cm. The inability to evaluate the gastric remnant after bypass has led many gastroenterologists to recommend endoscopic evaluation before this operation. The utility and cost-effectiveness of this approach has not been well examined, however, and preoperative endoscopic evaluation does not help in evaluating the most difficult postoperative problem: occult GI blood loss that may reflect inflammation, erosion, or ulceration in the (distal)

gastric remnant. As a result, the author generally recommends against routine preoperative endoscopy in these patients, reserving it for patients with standard indications. Instead, we evaluate each patient serologically for *H. pylori* and treat everyone who tests positive with a single course of combination therapy. In patients who are at particularly high risk for *H. pylori* infection or in whom serological testing may not be reliable (eg, within 1 year after a course of therapy), it may be helpful to complement serology with *H. pylori* breath testing or stool antigen testing.

In the rare patient from East Asia who requires gastric bypass, it may be worthwhile to do a screening upper GI endoscopy. Some people from this region have a higher risk of gastric carcinoma, and endoscopic evaluation of the distal stomach may not be possible after the bypass. In populations at substantially increased risk of development of gastric cancer, gastric banding may be the more appropriate procedure, because it generally does not preclude later examination of the distal stomach.

Irrespective of *H. pylori* status, the author generally keeps patients on proton pump inhibitors (PPIs) for 6 months after gastric bypass surgery. The purpose of this strategy is to decrease the risk of gastritis or ulceration in the distal stomach (gastric remnant) during the early postoperative period. Although its efficacy is unproven, this approach is unlikely to engender serious adverse effects. It should be noted that in more than 90% of patients, the pH of fluid in the small gastric pouch is at least 4, so PPIs are not generally effective for prevention or treatment of pouch gastritis or anastomotic ulcers. Sucralfate is the treatment of choice for these disorders in the setting of a near neutral or elevated pH.

Screening for iron deficiency and occult gastrointestinal bleeding

The main reason to exclude iron deficiency and occult GI bleeding during the preoperative evaluation of patients undergoing gastric bypass, biliopancreatic diversion, or the duodenal switch procedure is that these patients are at high risk for iron malabsorption after the surgery. To avoid confusion about the nature of iron deficiency detected during the postoperative period, it is valuable to assess hematocrit, hemoglobin, and iron stores preoperatively and evaluate further as clinically indicated. If no treatable source of blood loss is identified within the GI tract or elsewhere, oral or parenteral supplementation should be given as needed to normalize iron stores before the surgery. This approach ensures that anemia or iron deficiency detected after surgery reflects perioperative or postoperative events.

Obesity is associated with a significantly increased risk of colorectal polyps and cancer [16]. Despite this association, people with obesity undergo colon cancer screening at a significantly lower rate than those of normal weight [17]. The dichotomy between increased obesity-associated risk and decreased surveillance also has been observed for breast, cervical, and prostate cancer

screenings. The period of preoperative evaluation and intensive preparation for weight loss surgery provides an excellent opportunity to ensure that all cancer, lipid, hypertension, and diabetes screenings are up to date. When clinically indicated, preoperative screening for colorectal cancer is particularly important for patients undergoing gastric bypass or biliopancreatic diversion, given the high rate of postoperative iron deficiency associated with these procedures.

Screening for esophageal and gastric dysmotility

Restrictive weight loss operations, while generally easier and safer than gastric bypass or biliopancreatic diversion, can be associated with complications related to the restriction itself. With VBG and adjustable gastric banding, stenosis from the band itself, or from local mucosal inflammation, can cause obstruction, pouch dilatation, gastroesophageal reflux, and on occasion, esophageal dysmotility. Pre-existing esophageal dysmotility syndromes are thus a relative contraindication to these procedures. Because severe gastroparesis may exacerbate the obstructive nature of these operations, it also may prove to be a relative contraindication. Thus, for patients slated to undergo these purely restrictive procedures, the preoperative evaluation should include careful clinical screening for symptoms or heightened risk of dysmotility syndromes. Suggestive findings include severe gastroesophageal reflux disease (GERD) symptoms, symptoms of esophageal spasm, dysphagia, or evidence of diabetic neuropathy. When any of these symptoms is present, more detailed assessment of esophageal or gastric motility may provide an indication to choose a different weight loss operation or to defer weight loss surgery entirely. In most cases, an upper GI series is sufficient to identify severe dysmotility; however, in some patients, formal motility studies may be required to evaluate the risks adequately.

Screening for hepatobiliary disease

The most common GI disorder associated with severe obesity is FLD. A recent study at the author's center revealed that 92% of patients undergoing weight loss surgery have FLD based on intraoperative liver biopsy, and similar findings have been reported from other centers [11,12]. Importantly, approximately 50% of patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD) have normal serum transaminases levels. These false-negative enzyme levels are seen with all stages of FLD, including simple steatosis, steatohepatitis, and bridging fibrosis or cirrhosis. Although NAFLD is common in this population, its presence does not have significant impact on patient management unless it has progressed to cirrhosis.

In patients with established or suspected cirrhosis from NAFLD or any other cause, it is important to assess the severity of the cirrhosis and the nature of associated complications, if any. Although hepatic encephalopathy,

ascites, edema, or coagulopathy are not absolute contraindications to weight loss surgery, they require careful assessment and aggressive treatment to minimize the risk of perioperative metabolic abnormalities, infection, and bleeding. For these patients, the author generally recommends minimally invasive assessment of portal hypertension and perigastric varices, because varices pose a serious risk of intraoperative bleeding and are a strong contraindication to a gastric procedure. This assessment can be done by endoscopy to identify lower esophageal varices, in combination with abdominal sonography or CT to identify perigastric varices. In larger patients (up to the 450 pound table limit), CT is generally the more sensitive imaging test, because a thick layer of subcutaneous abdominal fat interferes with the ultrasonic signal.

For patients undergoing laparoscopic weight loss surgery (eg, laparoscopic gastric bypass or adjustable gastric banding), preoperative identification of cholelithiasis can be valuable in helping the surgeon plan for laparoscopic cholecystectomy at the time of the weight loss surgery. For patients with gallstones who are slated for laparoscopic gastric bypass, a preoperative ERCP is helpful by either excluding or facilitating endoscopic treatment of associated choledocholithiasis.

In patients with abnormal transaminases or with risk factors for chronic hepatitis B or C infection, preoperative serological screening for these viruses is indicated. In the absence of cirrhosis, chronic viral hepatitis does not contraindicate weight loss surgery. Knowledge of the infection, however, will alert the surgical team to use extra care in handling tissues and specimens. In addition, abnormal transaminases or risk factors for chronic hepatitis B or C should prompt obtaining an intraoperative liver biopsy. Because viral hepatitis and FLD act synergistically to promote progressive liver disease and cirrhosis, knowledge of the liver histology would be valuable in directing the long-term approach to managing these patients.

Screening for micronutrient deficiency

Micronutrient malabsorption and deficiency are common complications of gastric bypass or biliopancreatic diversion. Deficiencies of iron, calcium, vitamin B_{12}, and vitamin D are common, and magnesium, zinc, vitamin K, and folate deficiency occasionally can occur as well. Vitamin D deficiency is a particular problem, because it is common in people with severe obesity (before weight loss surgery) [18], and metabolic bone disease is a major long-term complication of gastric bypass and biliopancreatic diversion [6,13,19]. Because of these risks, it is important to ensure that patients undergoing these procedures have adequate preoperative stores of iron, calcium, vitamin B_{12}, and vitamin D. The author generally measures serum levels of these nutrients at the first opportunity and begins any required replacement therapy immediately. It is also helpful to obtain a parathyroid hormone level at the same time (and again after any required supplementation with

calcium or vitamin D). Secondary hyperparathyroidism is very common after gastric bypass and biliopancreatic diversion. Seventy percent of patients undergoing gastric bypass at the author's center have elevated parathyroid hormone (PTH) levels at some point after surgery, and it requires aggressive supplementation with calcium and vitamin D to reverse. The degree to which the hyperparathyroidism observed after gastric bypass is predictive of bone density loss has not yet been determined. It is likewise not known whether correction of the PTH abnormality prevents this complication. Because bone loss is a common late complication after weight loss surgery, however, it seems prudent to treat this problem aggressively until the results of such studies are available.

Postoperative gastrointestinal management

The major goals of GI management after weight loss surgery are to prevent avoidable GI complications; to recognize, diagnose, and treat unavoidable complications as efficiently and effectively as possible; and to identify and treat micronutrient deficiencies. Table 2 outlines the most common postoperative GI symptoms, their causes, and effective treatment.

Preventing gastrointestinal complications of weight loss surgery

Dumping syndrome

Dumping syndrome is a hormonally-driven constellation of symptoms that can results from rearrangement of the proximal GI tract. These symptoms vary from patient to patient but typically include some combination of facial flushing, lightheadedness, palpitations, sudden and profound fatigue, and diarrhea during or immediately after eating. The symptoms are induced most commonly and dramatically by concentrated sweets and highly processed starches (eg, white bread or pasta). Early studies of RYGB suggested that dumping syndrome occurred in more than 15% of patients. With improved dietary management, more recent studies estimate that persistent, clinically significant dumping syndrome occurs in fewer than 2% of patients [1,2,5]. The most effective approach to preventing dumping syndrome after RYGB is intensive dietary counseling. Patients should be advised to avoid carbohydrates at the beginning of each meal, reserving them until after they have ingested a significant amount of protein and fats. They also should be instructed to eat slowly, because more rapid eating appears to be associated with overfilling the small gastric pouch, which may induce an overexuberant satiety response that is accompanied by dumping symptoms.

Gastritis, erosions and ulcers

Mucosal damage after weight loss surgery can arise from physical injury (eg, band stenosis or food stasis secondary to partial obstruction), microvascular ischemia (the likely cause of anastomotic ulcers), and the pathological effects of *H. pylori,* stress, or drugs. The gastric mucosa after

Table 2
Common gastrointestinal complications of weight loss surgery

Problem	Presentation*	Evaluation and treatment
Dehydration	Early after surgery, constipation, hypotension	Vigorous hydration
Dietary noncompliance	Early after surgery, nausea, vomiting, upper abdominal pain	Slow eating, stop when full; Avoid foods that are not tolerated (most common are sugars, bread, pasta, and beef)
Dumping syndrome	Early after RYGB, at time of eating: lightheadedness flushing watery diarrhea extreme fatigue	Avoid sugars and processed starches at beginning of meals; Start meals with protein; Octreotide for refractory symptoms
Bile salt toxicity	Early after RYGB, watery diarrhea	Colesevelam Cholestyramine
Anastomotic ulcer	Most common after RYGB or duodenal switch; More likely at gastrojejunal anastomosis; Abdominal pain, nausea	Evaluate by upper GI endoscopy; If pouch pH < 3, proton pump inhibitor; If pouch pH ≥ 4, sucralfate suspension; Exclude bile reflux into pouch; if present and symptoms persist, consider lengthening Roux limb
Anastomotic stricture	Most common at gastrojejunal anastomosis after RYGB, Nausea, vomiting, abdominal pain	Evaluate by upper GI series and endoscopy; Treat for presumed anastomotic ulcer, Vigorous and repeated balloon dilatation
Band stricture	After banded gastroplasty or LAGB; gastroesophageal reflux, nausea, vomiting	Evaluate by upper GI series and endoscopy, loosen LAGB, Limited balloon dilatation for VBG
Band erosion/ ulcer	After VBG or LAGB, Abdominal pain, GI bleeding	Evaluate by upper GI endoscopy; Proton pump inhibitor; Partially deflate LAGB; Surgical revision if needed
Band migration	After LAGB, abdominal pain, obstruction, perforation	Evaluate by abdominal CT scan, surgical revision
Partial bowel obstruction	Abdominal pain, nausea and vomiting	Upper GI series, abdominal CT scan; Reverse obstruction (endoscopically or surgically)

Table 2 (*continued*)

Problem	Presentation*	Evaluation and treatment
Staple line disruption	After gastric bypass with nondivided stomach, Substantial weight regain; Abdominal pain rare	Upper GI series, upper GI endoscopy; Endoscopic repair (sewing or clips), surgical revision
Gastrogastric fistula	After gastric bypass with divided stomach, Abdominal pain; Modest weight gain	Upper GI series, upper GI endoscopy; Endoscopic repair (sewing or clips), surgical revision
Micronutrient deficiency	After gastric bypass or biliopancreatic diversions, Thiamine deficiency with persistent vomiting after VBG or LAGB	Prophylactic calcium supplementation, Prophylactic iron supplementation depending on risk (eg, menstruating women), Surveillance serum levels of iron, vitamin B_{12} calcium, vitamin D, PTH
Macronutrient malabsorption	After biliopancreatic diversions, Diarrhea, steatorrhea, hyperphagia, ketosis	Calorie-dense, high-protein diet, Revisional surgery to lengthen common channel
Fatty liver disease	New onset or worsening after surgery, Associated with rapid weight loss, Rarely symptomatic	Follow serum liver enzymes; Liver biopsy if enzymes remain elevated after weight loss slows; ultrasonography rarely helpful unless preoperative study revealed no fatty liver
Gallstones	New onset after surgery, Abdominal pain, rare jaundice	Serum liver enzymes; Abdominal ultrasonography; Laparoscopic cholecystectomy; ERCP as clinically indicated, if technically possible; if not, magnetic resonance cholangiopancreatography and/or transhepatic cholangiography

* Reference to biliopancreatic diversions includes duodenal switch procedure.

RYGB appears to be particularly susceptible to nonsteroidal anti-inflammatory drug (NSAID)-induced injury; its response to *H. pylori* is not understood well. Unfortunately, there is little objective information on which to base strategies to prevent postoperative mucosal injury. Absent these data, a reasonable, three-pronged approach would be:

Detection and eradication of *H. pylori* infection before surgery, regardless of whether infection is associated with discernible pathology

Avoidance of NSAIDs, especially during the first postoperative year, with use of the available Cox-2-selective inhibitor when NSAIDs are absolutely required for management of inflammation or pain

Prophylactic use of PPIs during the first several months after surgery. For most patients who have undergone gastric bypass, PPIs will have no effect on the gastric pouch, because it is generally acid-free. There may be benefit, however, to inhibiting acid secretion in the distal gastric remnant, perhaps preventing mucosal injury and its complications in that segment.

Micronutrient deficiencies

Micronutrient deficiencies after RYGB and biliopancreatic diversion arise primarily from selective or nonselective malabsorption of these compounds. Deficiencies of iron, vitamin B_{12}, calcium, and vitamin D are the most common after gastric bypass or biliopancreatic diversion [1,2,6,11,13]. After biliopancreatic diversion, deficiencies in the other fat-soluble vitamins (A, E, and K) and other electrolytes also are seen [13]. To prevent whole-body calcium deficiency, secondary hyperparathyroidism, and osteopenia, most practitioners recommend prophylactic calcium supplementation with 1000 to 1500 mg per day of elemental calcium in divided doses of no more than 500 mg each. Recent evidence suggests that calcium citrate is absorbed more efficiently than calcium carbonate and that this effect may be magnified in patients who have undergone RYGB.

In many centers, people at higher risk of iron deficiency (eg, menstruating women) who undergo these procedures are treated with prophylactic iron supplementation, but prophylactic iron supplementation is not generally used in all patients.

To prevent development of micronutrient deficiency, careful preoperative and postoperative monitoring of relevant blood levels, with supplementation or replacement as required, is most often effective. In many centers, serum iron, iron-binding capacity, ferritin, vitamin B_{12}, folate, calcium, magnesium, vitamin D, PTH, and prothrombin time are measured at initial evaluation, and deficiencies are corrected as needed. Postoperatively, these levels are measured on a periodic basis (eg, at 2, 6, and 12 months after surgery, and yearly thereafter), and supplements are given or adjusted based on absolute deficiencies or trends that suggest impending deficiency. For vitamin D and calcium, target levels are a normal calcium, and a serum vitamin D level of greater than 25 IU/mL, with additional calcium and vitamin D supplementation as needed to keep the PTH in the normal range. A persistently elevated prothrombin time is treated with three 10 mg doses of vitamin K. The author only rarely has seen abnormally low levels of folate or vitamin E and has stopped routine measurement of vitamin E metabolites.

For adolescents who undergo weight loss surgery, and for all patients in whom LABG or VBG is planned, many centers measure preoperative thiamine levels and follow blood levels after surgery is complete. Profound thiamine deficiency has been described in a few adolescents who have undergone RYGB and in a few patients who experienced prolonged vomiting after restrictive weight loss surgery (LAGB or VBG) [14,15].

Assessment of constipation

Constipation is the most common complication during the first few months after weight loss surgery, arising primarily as a symptom of moderate dehydration. Dehydration results from decreased water consumption associated with the postoperative loss of appetite, along with increased metabolic use and breakdown of water during active lipolysis and fat mobilization. When postoperative dehydration is severe, patients may present with orthostatic hypotension, ketosis, and anorexia, but even mild dehydration in this setting appears to provoke disproportionate constipation. Treatment consists of encouraging increased daily fluid intake (a common target is 64 ounces daily) and use of stool softeners as needed. Although laxatives can provide transitory relief, when used alone they generally exacerbate the dehydration, leading to recurrent constipation.

Assessment of abdominal pain, nausea and vomiting

The differential diagnosis of abdominal pain after weight loss surgery is broad. In many patients who have undergone LAGB, VBG, or gastric bypass, eating too fast allows the proximal pouch to overfill before satiety mechanisms can be activated. It is postulated that this excess food prevents complete closure of the lower esophageal sphincter, leading to spasm of the sphincter muscle and associated epigastric and lower substernal pain. This type of pain is treated most effectively by encouraging and training patients to eat more slowly.

Early after surgery, abdominal pain commonly can result from abdominal muscle injury, liver injury during retraction with capsular distention, ileus with visceral distention, or bloating from increased swallowing of air (caused by changed patterns of chewing and swallowing after the surgery). It is important to discriminate these common, relatively benign causes of abdominal pain from pain caused by potentially catastrophic complications such as gastric remnant distention (with risk of perforation), anastomotic leak, abscess, wound infection, or obstruction. These surgical complications typically occur early in the postoperative course and are managed by the surgical team. Given the size of these patients, the mainstay of evaluation is an abdominal CT scan, which in conjunction with vital signs, abdominal exam, and white blood cell count can distinguish most of the serious causes of postoperative abdominal pain.

Beyond the immediate postoperative period, the most common causes of new onset abdominal pain are mucosal injury (eg, gastritis, erosion, or ulceration, Fig. 1) or partial obstruction from stenosis, with increased intraluminal pressure and possible dilatation proximal to the obstruction. After LAGB or VBG, the most common site for stenosis is in the region of the band, with mucosa injury or edema of the underlying tissue and luminal

narrowing. After RYGB, there are several potential sites of stenosis. They include:

- The gastrojejunal anastomosis (most commonly as a result of an anastomotic ulcer)
- The midportion of the Roux limb (where it traverses the mesocolon in procedures where this limb is placed behind the stomach and transverse colon)
- The jejunojejunal anastomosis (which can cause dangerous dilatation of the distal gastric remnant)
- At sites of adhesions

In the absence of vomiting (which could suggest high-grade obstruction) or evidence of perforation or infection, the most useful diagnostic studies are upper GI series and abdominal CT. In patients with GI blood loss, associated dyspepsia, known mucosal injury, or NSAID use, early endoscopy can be helpful in identifying and treating proximal lesions. It should be noted that the normal gastric pouch often includes multiple staples and sutures visible endoscopically (Fig. 2). Their presence does not require any specific evaluation or intervention, and, in general, no attempt need be made to remove them.

Treatment of postoperative stenosis varies depending on the site of stenosis. For band-related stenosis after VBG or LAGB, the goal is to ease the

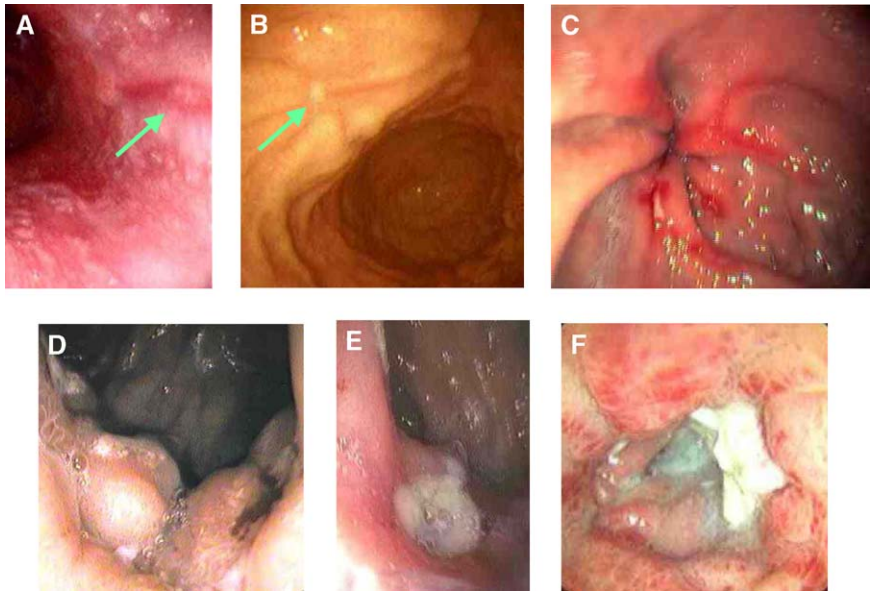

Fig. 1. Mucosal injury after gastrointestinal weight loss surgery. (*A*) Gastric erosions after LAGB *(arrow)*. (*B*) Erosion of band through stomach wall after VBG *(arrow)*. (*C*) Gastric erosions secondary to excessive restriction after VBG. (*D,E,F*) Gastrojejunal anastomotic ulcers after RYGB.

stenosis without substantially increasing the diameter of the lumen. In patients who have undergone LAGB, this often can be accomplished by deflating the balloon slightly. In patients with deflated LAGB balloons or who have undergone VBG, modest endoscopic dilatation (eg, with a maximum 12 mm balloon) can relieve symptoms without affecting the intended restriction from the device (Fig. 3). In contrast, the goal in dilating a tight anastomotic stricture after RYGB is to optimize the patency of the anastomosis. Achieving this goal often requires multiple sessions with increasingly larger balloons or rigid dilators, up to a maximum of an 18 to 20 mm diameter device (Fig. 4). Similarly, effective dilatation of a stenosis at the site of passage through the mesocolon typically requires a large diameter balloon dilator.

Treatment of mucosal injury, including anastomotic ulceration, requires removal of the inciting cause and agents to promote mucosal healing. Gastritis, esophagitis, erosion, and ulceration after VBG or LAGB are treated best with PPIs to decrease secreted acid, and by discontinuing any NSAIDs that the patient may be taking. Retesting and treating *H. pylori* infection likely will be helpful, although in many centers, this infection would have been detected and treated preoperatively. Treatment of ulceration after RYGB is more complex. Possible contributors include some combination of ischemia, acid, bile salts, NSAIDs, and *H. pylori*, and

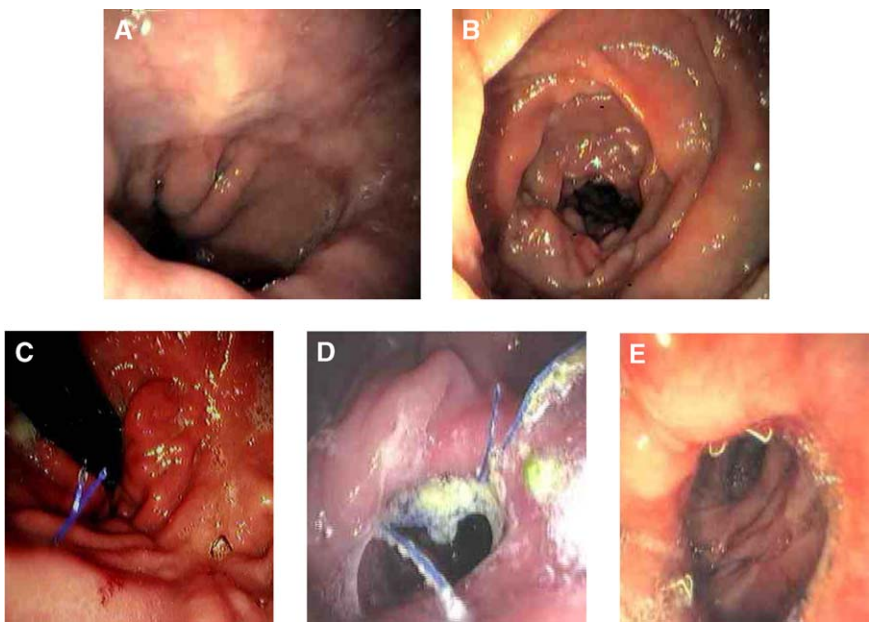

Fig. 2. Normal endoscopic appearance after RYGB. (*A*) Proximal view of esophagogastric junction and gastric pouch. (*B*) Gastrojejunal anastomosis and proximal postanastomotic jejunum. (*C*) Suture and staple within normal gastric pouch. (*D*) Sutures within normal gastric pouch. (*E*) Staples within normal gastric pouch.

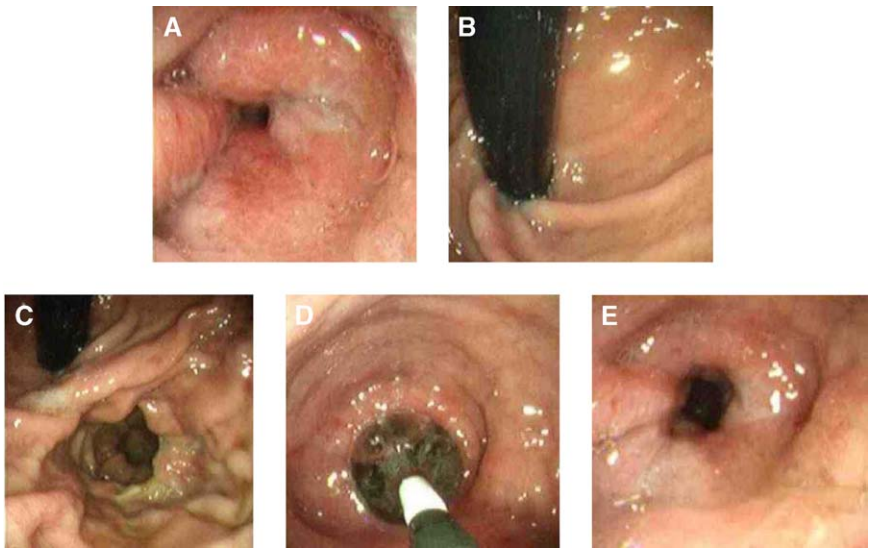

Fig. 3. Balloon dilatation of band stenosis after VBG. (*A*) Anterograde view from proximal gastric pouch. (*B*) Retrograde view from distal stomach. Note tight fit of 8 mm endoscope at level of band. (*C*) Normal appearance of distal stomach. (*D*) Single dilatation with 12 mm endoscopic balloon. (*E*) Postdilatation anterograde view from proximal gastric pouch.

each of these possibilities should be investigated by appropriate endoscopic or chemical testing and therapy instituted appropriately. At the time of endoscopy, it is useful to determine the pH of the lower esophageal or gastric pouch fluid before entering the jejunum. If the fluid is neutral or alkaline, the ulcer is unlikely to benefit from acid suppression therapy. In that case, sucralfate treatment is likely the best option. Given the limited grinding activity in the small gastric pouch, the suspension formulation would seem to be better than the pill form, but no studies have compared the two directly. Common dosing is 1 g by mouth four times daily, but this dose may need to be modified or reduced to avoid interactions with other drugs, vitamins, and micronutrients. If bile reflux is a prominent finding, a bile acid binder such as cholestyramine or colesevelam may be helpful. In any case, because of the multiple possible contributors to mucosal injury in these patients and the varied responses to therapy, it is helpful to assess healing endoscopically after a generous course of therapy. In the small number of patients with anastomotic ulcers not amenable to medical eradication, surgery to revise the gastric pouch is sometimes necessary.

Assessment of diarrhea

There are several common causes of diarrhea in patients who recently have undergone weight loss surgery. They include bile salt intolerance after RYGB or biliopancreatic diversion, exacerbation of pre-existing, subclinical lactose

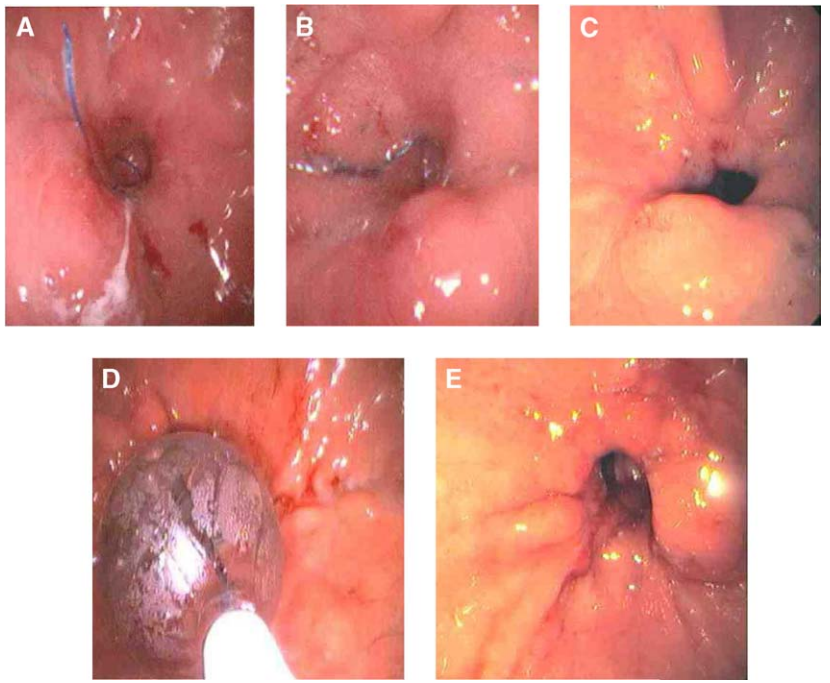

Fig. 4. Balloon dilatation of anastomotic stricture after RYGB. (*A*,*B*) Anterograde view of tight stricture at gastrojejunal anastomosis from gastric pouch. (*C*) Close-up view of stricture. (*D*) Last of sequential dilatations with increasingly large CRE balloons (up to maximum of 15 mm diameter during this setting). (*E*) Appearance of stenotic region after dilatation. This patient subsequently underwent further dilatation to a maximum CRE balloon diameter of 20 mm.

intolerance, exacerbation of pre-existing irritable bowel syndrome, and, in patients undergoing biliopancreatic diversion or long-limbed gastric bypass, maldigestion or malabsorption. Less common causes include bacterial overgrowth in the setting of longer blind loops or diverticula, *Clostridium difficile* colitis, and dumping syndrome (which has become much less common with improved dietary management). Evaluation of diarrhea after weight loss surgery is similar to evaluation of diarrhea in other patients, with the approach keyed to the severity and duration of the symptoms. Exclusion of common bacterial pathogens, including *C. difficile*, modification of diet to reduce the likelihood of dumping syndrome, therapeutic trials of bile salt binders, anticholinergic agents, lactose-free diets and, occasionally, a gluten-free diet, are indicated. In some patients, empiric probiotic therapy has been helpful, although careful study of the effectiveness of this approach is lacking.

Assessment of gastrointestinal bleeding

Gastrointestinal bleeding after weight loss surgery is rare. Acute bleeding within the first 72 hours after surgery is typically the result of an

intraoperative event or anastomotic ischemic ulceration. These events can be associated with significant arterial hemorrhage requiring emergent surgical intervention. Endoscopic evaluation this early after surgery should be used only if absolutely necessary and with great care to avoid causing visceral distention and possible suture line leakage. In addition to the effects of the bleed loss itself, major intraluminal bleeding early after RYGB can lead to transient obstruction from clotting at the distal (jejunojejunal) anastomosis, with proximal intraluminal hypertension and an increased risk of perforation of the gastric remnant or at the proximal (gastrojejunal) anastomosis.

Upper GI bleeding after the first postoperative week most commonly is associated with erosion or ulceration, from excessive restriction or band erosion after VBG or RYGB, and from anastomotic ulceration after RYGB or duodenal switch. It also commonly is associated with gastritis, erosion, or ulceration from NSAIDs used to treat pre-existing arthritis, back pain, or other pain syndromes associated with severe obesity and that may not fully resolve after surgery. Evaluation is primarily by upper GI endoscopy. In patients who have undergone RYGB and in whom no bleeding site is seen on upper endoscopy, it may be useful to repeat the procedure with a longer endoscope (or colonoscope) to examine the jejunojejunal anastomosis and common channel. Because of the Roux-en-Y anatomy, it is often difficult to visualize the gastric remnant, but evidence of blood at the distal anastomosis or in the common channel selectively would implicate a distal gastric or duodenal source.

Treatment of upper GI bleeding from gastritis, erosions or ulcers after VBG or LAGB is similar to that in nonoperated patients, with endoscopic intervention as needed, cessation of any NSAID use, PPI therapy, and identification and eradication of an associated *H. pylori* infection. The protocol is somewhat different for patients who have undergone RYGB. At the time of endoscopy, it is useful to look for evidence of bile reflux into the gastric pouch or proximal Roux limb (by the tell-tale yellow coloration or foaming of the intraluminal fluid). It is also helpful to collect fluid from the distal esophagus or gastric pouch for pH measurement before continuing into the jejunal Roux limb. If the pH of the gastric fluid is less than 3, it is likely that the pouch includes a significant number of parietal cells, and treatment with a PPI is indicated. If the gastric pouch pH is at least 4, however, additional PPIs are unlikely to be helpful. In that case, treatment with sucralfate suspension (1g two to four times daily as tolerated) in combination with the pre-existing PPI regimen, likely will be more helpful. Sucralfate should not be taken within an hour of a PPI, or iron or calcium supplementation, so it is occasionally difficult for these patients to accommodate a four times daily schedule for this drug. Because of the risk of recurrent bleeding, follow-up endoscopy in 8 to 12 weeks to assess healing at the bleeding source is helpful in guiding further evaluation or therapy.

Occult GI blood loss after weight loss surgery most often represents milder manifestations of the same pathological processes that cause gross

bleeding, and evaluation should proceed in a similar fashion, starting with upper endoscopy. Because obesity is associated with an increased risk of colorectal polyps and cancer, however, evaluation of occult blood loss or isolated iron deficiency should include colonoscopy, unless a source is identified by upper GI endoscopy. Even in that case, careful follow-up for recurrent occult bleeding or iron deficiency should be done after resolution of the upper GI source. Ensuring that colorectal cancer screening is up to date before surgery can obviate the need for postoperative colonoscopy for isolated iron deficiency or occult GI blood loss.

Treatment of micronutrient deficiency

Iron

Evaluation of iron deficiency that develops after RYGB should include consideration of GI blood loss. That said, in most patients with post-operative iron deficiency, the cause is iron malabsorption, and treatment is oral supplementation. Ferrous sulfate and ferrous gluconate commonly are associated with increased constipation, which is already a problem in many of these patients. In addition, these preparations require multiple daily doses and appear to be less well absorbed than preparations containing elemental iron complexed with a polysaccharide. Many of these newer preparations contain vitamin C to promote iron absorption and can be taken as single daily doses of 100 to 200 mg of elemental iron each. Iron studies should be followed closely in these patients, and if they fail to respond adequately with escalating doses of oral iron and trials of different oral preparations, a course of intravenous iron therapy is indicated. Although the risk of anaphylaxis from newer formulations of intravenous iron has been reduced dramatically, this therapy should be administered only by well-trained personnel familiar with its use.

Vitamin B_{12}

Vitamin B_{12} deficiency after RYGB most often resolves after several weeks of treatment with 700 to 2000 μg per week (taken daily, twice weekly or weekly). B_{12} deficiency after biliopancreatic diversion or duodenal switch may require a higher supplementation dose. The therapeutic goal is normalization of serum levels. If needed, dosing with up to 1000 μg daily of oral vitamin B_{12} can be used. If high-dose oral vitamin B_{12} fails to normalize serum levels, it is worthwhile trying one of the newer sublingual preparations before advancing to injection therapy.

Calcium and vitamin D

Frank hypocalcemia is rare after weight loss surgery. Decreased calcium absorption after RYGB or biliopancreatic diversion, however, often leads to

calcium mobilization from bone to maintain serum levels. This process also can be caused or accelerated by vitamin D deficiency, which is common in people with obesity and can be induced by gastric bypass or biliopancreatic diversion surgery. As noted previously, in patients who have undergone RYGB, high circulating levels of vitamin D may be required for full physiological effect. Inadequate calcium absorption or vitamin D deficiency leads to a compensatory elevation of PTH (secondary hyperparathyroidism). PTH drives calcium absorption and facilitates vitamin D action. The author has observed that up to 70% of patients who have undergone RYGB have elevated circulating PTH levels at some time after surgery. Long-term deficiency of calcium or vitamin D is associated with bone loss from osteoporosis and osteomalacia, respectively. Thus, it is essential to monitor for these deficiencies and to correct them as quickly and effectively as possible. In patients with secondary hyperparathyroidism, the author treats with up to 2500 mg of elemental calcium as calcium citrate, in divided doses to improve absorption. Calcium citrate appears to be better absorbed than calcium carbonate in these patients. In addition, vitamin D is given at doses of up to 50,000 units twice weekly to maintain serum levels in the high normal range (30 to 45 IU/mL).

A cautionary note must be made about using bisphosphonates (Fosamax and others) in patients who have undergone RYGB or biliopancreatic diversions. Bisphosphonates prevent bone loss by inhibiting osteoclast-mediated resorption [20]. Because the primary cause of bone loss in these patients appears to be decreased calcium absorption, bisphosphonate therapy in the absence of adequate calcium intake or absorption theoretically could precipitate acute hypocalcemia. Pending further studies to determine the safety and efficacy of bisphosphonates in this population, it is prudent to avoid them altogether.

Summary

Beyond the acute perioperative period, the most common complications of weight loss surgery relate to GI tract structure, function, and mucosal integrity. As a result, gastroenterologists have a major role in the management of patients undergoing these procedures. Optimal care of the bariatric surgical patient requires a multi-disciplinary team to address the medical complications, nutritional management, and psychological and behavioral implications of obesity. Because of their important role in preoperative assessment and postoperative management, gastroenterologists should be integral members of these multi-disciplinary teams. A model of close collaboration among gastroenterologists, bariatric surgeons, and other members of the team will help optimize care of the bariatric patient and set the stage for effective development, testing, and use of the many new laparoscopic, endoscopic, intraluminal, and pharmacological GI-based therapies for obesity that are under development.

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Gastroenterol Clin N Am
34 (2005) 127–142

GASTROENTEROLOGY
CLINICS
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Surgical Options for Obesity

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Obesity is a complex disease influenced by the interaction of several genetic, endocrine, metabolic, and environmental factors. It has gained epidemic proportion in the United States, with nearly 20% of the adult population affected. An estimated 40 million Americans are overweight, and nearly 11.5 million people nationwide are morbidly obese. With obesity comes an array of debilitating and life-threatening comorbidities, including adult-onset diabetes mellitus, hypertension, hypercholesterolemia, obesity hypoventilation and sleep apnea syndrome, cholelithiasis, cardiovascular disease, renal disease, and osteoarthritis. Others include necrotizing panniculitis; hypercoagulable states; psychosocial problems; and an increased risk of uterine, colon, and breast cancer. Several obesity-related illnesses including overflow incontinence, pseudotumor cerebri, sex hormone imbalance, and gastroesophageal reflux may cause significant physical and emotional disability. Overall, obesity-related illnesses consume nearly 5% of the total health care costs in the United States, a staggering $100 billion.

The most accurate method of defining the relationship between body weight and frame size is the body mass index (BMI). Obesity is defined as a BMI of greater than 30 kg/m^2. The 1991 National Institutes of Health (NIH) Consensus Panel on Gastric Surgery for Severe Obesity defined morbid obesity as a BMI of 35 kg/m^2 or greater with severe obesity-related comorbidity or 40 kg/m^2 or greater without comorbidities. Superobese patients are defined as having a BMI of 50 kg/m^2 or greater. Other definitions of morbid obesity include patients who weigh at least 200% of their ideal body weight.

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doi:10.1016/j.gtc.2004.12.005

No dietary approach has achieved long-term success for treating morbid obesity. Several weight-reducing agents including Phentermine Redux and Fenformin were associated with an unacceptably high incidence of cardiac valvular disease and pulmonary hypertension and thus were removed from the market by the Food and Drug Administration (FDA). Currently available Sibutramine (Meridia) and orlistat are associated with only a 10% weight loss in most studies. Surgery has been the only method proven effective in maintaining long-term weight loss, with current options including restrictive or malabsorptive procedures or a combination of both.

With the evolution of bariatric surgery and its techniques, the number of gastrointestinal surgeries performed annually for severe obesity has increased from about 16,000 in the early 1990s to about 103,000 in 2003 [1]. This increase is because of several factors, including an increase in the overall number of people who are extremely obese; failure of diets, exercise, and medical therapy; and the advent of minimally invasive surgery procedures. Similarly, the number of bariatric surgeons who are members of the American Society for Bariatric Surgery has increased from 258 in 1998 to 1070 in 2003.

It must be remembered that an effective bariatric procedure is one that results in a sustained excess weight loss (EWL) of greater than 50% and resolution of comorbid conditions. Any surgical procedure that does not achieve these goals cannot be classified as a successful weight loss operation. This article reviews the evolution of bariatric surgery through the last several decades, with emphasis on development of minimally invasive surgical techniques. The common bariatric procedures in practice and some of the controversies existing in obesity surgery are discussed in detail. These procedures can be divided into two major groups: malabsorptive or restrictive procedures or a combination of both.

Malabsorptive procedures

Jejunoileal bypass

The history of bariatric surgery dates back to 1950s when Kremen et al reported the first case of jejunoileostomy for weight loss [2]. Payne et al reported the first clinical series of 11 jejuno–colic bypass patients in 1963. This jejuno–colic shunt was performed by an end-to-side anastomosis of the proximal 15 cm of the jejunum to the transverse colon. This procedure incurred effective weight loss but resulted in significant nutritional adverse effects including severe protein calorie malnutrition (PCM), vitamin deficiencies, severe diarrhea, electrolyte imbalances, liver failure, and a resultant high mortality [3]. The jejuno–colic shunt was condemned widely and finally abandoned [4].

Several modifications were made to this operation that included an intestinal anastomosis proximal to the ileocecal valve, namely the jejuno–ileal bypass (JIB). This was constructed using an end-to-side jejunoileostomy,

anastomosing the proximal 35 cm of the jejunum (the biliopancreatic limb) to the distal ileum (the common channel), 10 cm proximal to the ileocecal valve (Fig. 1). Payne and DeWind reported their experience with this procedure in 58 patients [5]. Important data including percentage of EWL and follow-up of these patients, however, were not reported. The JIB underwent various modifications that included variations in the length of distal ileum and the distance from the ileocecal valve. In their report of 200 patients who underwent JIB in 1977, Scott et al compared their results with Payne's series [6]. In their construct of the JIB, the jejunum was anastomosed in an end-to-end fashion to different lengths of the distal ileum with the excluded small bowel decompressed by an end-to-side ileocolostomy. Despite achieving sustained weight loss in nearly 70% of the patients, intractable diarrhea continued to be a major problem. Other long-term complications in these patients included repeated hospitalizations for electrolyte imbalance, hypoalbuminemia, hypokalemia, hypocalcemia, calcium oxalate kidney stones, migratory polyartharlgias, elevated liver enzymes, and hyperbilirubinemia.

In another study reported by Griffin et al in 1977, JIB and gastric bypass were compared in a randomized prospective trial [7]. Mean weight loss at 1 year and peri-operative complication rates were not significantly different in the two groups. Long-term complications including diarrhea, urolithiasis, PCM, vitamin deficiencies, and liver failure were more prevalent in the JIB group. Liver function studies were of minimal value in predicting the development of liver disease, necessitating frequent liver biopsies to assess

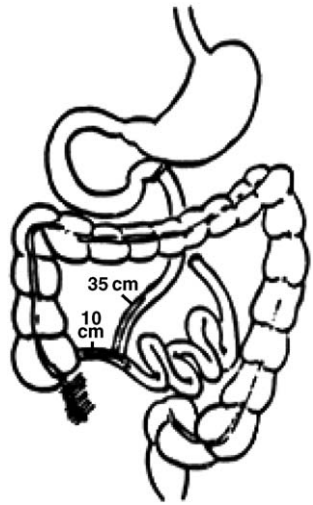

Fig. 1. Jejuno–ileal bypass. The original operation described by Payne involved an end-to-side jejunoileostomy, anastomosing the proximal 35 cm of the jejunum to the distal ileum, 10 cm proximal to the ileocecal valve.

liver damage. Requarth et al reported the largest series of JIB patients with a follow-up period of 15 years [8]. The incidence of liver failure was 10%, urolithiasis 29%, and renal failure 9% at the end of 15-years of follow-up. Nearly 25,000 JIBs have been performed in the United States since the 1980s, and most converted to a gastric bypass or other less malabsorptive procedure. Because of the high incidence of metabolic complications, diarrhea, renal, and hepatic disease, the JIB no longer is recommended as a weight loss procedure for the morbidly obese, and it has been abandoned.

Biliopancreatic diversion

Biliopancreatic diversion (BPD) is a variant of the JIB first reported by Scopinaro in 1979 [9]. It is a malabsorptive procedure that consists of a distal gastrectomy and a proximal 200 to 500 mL gastric pouch with a long Roux-en-Y reconstruction (Fig. 2). The small intestine is divided 250 cm from the ileocecal valve and an enteroenterostomy made 50 cm from the ileocecal valve, thus creating a 200 cm alimentary limb and a 50 cm common channel. The weight loss results primarily from reduction in gastric volume and the dumping syndrome, with appetite and eating capacity restored within 1 year after the procedure [9,10]. In their series of 2000 patients, Scopinaro et al reported EWL averaging between 73% and 78% [11]. At

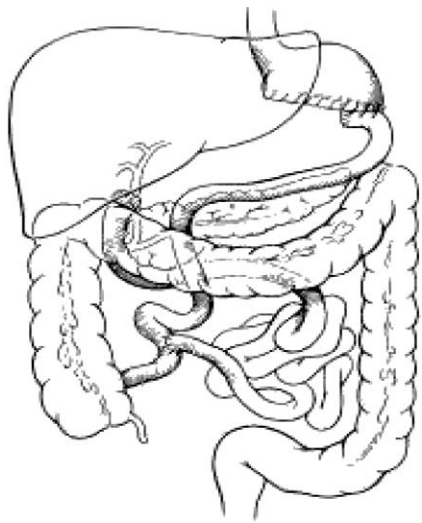

Fig. 2. Biliopancreatic diversion. After a subtotal gastrectomy, the distal alimentary (Roux) limb, created by dividing the ileum 250 cm proximal to the ileocecal valve, is anastomosed to the 200 mL proximal gastric remnant. The biliopancreatic (jejunum to proximal ileum) limb is anastomosed end-to-side to the distal ileum 50 cm proximal to the ileocecal valve, leaving a 50 cm common channel between the biliopancreatic and the distal alimentary limbs. (*From* Schirmer BD. Operative treatment of morbid obesity, Townsend: Sabiston textbook of surgery. 16th edition. 2001 Philadelphia: WB Saunders Company; 2001; with permission.)

15-year follow-up there was little or no weight regain. Despite low mortality, late complications continued to plague this patient population, with PCM occurring in 12% of patients, with a higher incidence in Southern Italy, where the diet was mostly carbohydrate-based. Several modifications were required to reduce the incidence of PCM, bone demineralization, and anemia in these patients. These included varying the size of the gastric pouch; increasing patient compliance; changing dietary habits; and supplementation with iron, folate, vitamin B12, and calcium.

Mun et al compared their results of BPD in 11 superobese patients with 26 patients undergoing the long-limb Roux-en-Y gastric bypass using a 100 cm common channel [12]. There was one death in the BPD group from hepatic failure, and development of bone disease in two patients. These complications were not seen in the gastric bypass group, although EWL was reduced to 15% at 4 years. Most BPD patients resolved their comorbid conditions following the procedure, with improvement in diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea [9,11,13]. Despite excellent results with this procedure, the experience with BPD is limited to a few case series, and its widespread application cannot be recommended yet.

Biliopancreatic diversion with duodenal switch

Although the BPD continued to be a successful bariatric procedure producing adequate weight loss in most clinical series, several complications including marginal ulceration, diarrhea, and PCM were seen more commonly than in gastric bypass patients. A modification to the BPD with a duodenal switch consisting of a sleeve gastrectomy and a duodenoileostomy proposed by Hess and Marceau appeared to reduce the incidence of these complications (Fig. 3) [14]. Hess et al reported results of BPD with duodenal switch (BPD-DS) in 440 patients [15]. Their common channel was 50 to 100 cm in length, whereas the alimentary limb measured variably from 225 to 350 cm. Their results were excellent, with reported mean EWL of 80% at 2 years and 70% at 8 years. There were no cases of marginal ulceration reported in this series, and the overall mortality was 0.5%. A small number of patients required revision for PCM and excessive diarrhea, whereas 9% of patients developed iron-responsive microcytic anemia. Marceau et al compared BPD patients with a common channel of 50 cm with DS patients with common channel of 100 cm [16]. Although peri-operative morbidity and overall mortality was similar in both groups, the DS patients had EWL of 73%, whereas BPD patients had EWL of 61%. The DS patients also had a lower incidence of diarrhea, mineral bone disease, and vomiting.

Several other reports of BPD-DS confirm excellent weight loss in morbidly obese patients. Rabkin et al reported a retrospective analysis of 32 BPD, 105 DS, and 138 gastric bypass patients. All had similar weight loss, although some BPD-DS patients required reversal for protracted diarrhea. The laparoscopic experience with BPD-DS is limited to a few case

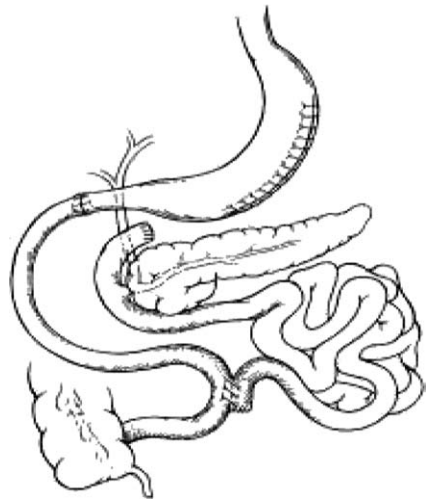

Fig. 3. Biliopancreatic bypass with a duodenal switch. The greater curvature of the stomach is resected to create a sleeve gastrectomy. After dividing the duodenum 5 cm distal to the pylorus, the distal alimentary limb, created by dividing the ileum 250 cm proximal to the ileocecal valve, is anastomosed end-to-end to the proximal duodenum. The biliopancreatic limb is anastomosed end-to-side to the distal ileum 100 cm proximal to the ileocecal valve, leaving a 100 cm common channel between the biliopancreatic and the distal alimentary limb. (*From* Schirmer BD. Operative treatment of morbid obesity, Townsend: Sabiston textbook of surgery. 16th edition. Philadelphia: WB Saunders Company; 2001; with permission.)

series. Ren et al reported their experience in 40 patients [17]. Their perioperative morbidity was significantly higher in patients with BMI greater than 65 than in those with a lower BMI.

Overall, BPD with or without duodenal switch appears to be an effective weight loss procedure for the morbidly obese. Long-term follow-up data suggest that both procedures are more effective in and should be reserved for the superobese (BMI greater than 50). As evident from most studies, metabolic complications, including vitamin deficiencies, PCM, liver disease, and diarrhea still occur in these patients, although with a lower incidence than JIB. Therefore, these patients should be followed closely, and aggressive vitamin and mineral supplementation should be performed. No large studies comparing BPD or BPD-DS with gastric bypass are available to suggest the supremacy of one procedure over other.

Restrictive procedures

Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass (RYGBP) first was described by Mason nearly 30 years ago, and it is the gold standard bariatric procedure. The NIH Consensus Conference in 1991 declared RYGBP and vertical band

gastroplasty (VBG) as the two most suitable weight loss procedures with excellent outcomes and low morbidity. This consensus led most bariatric surgeons to perform either VBG or RYGBP as the predominant weight loss procedures. The RYGBP is constructed using a small 15 to 20 mL gastric pouch and a Roux-en-Y gastrojejunostomy (Fig. 4). This procedure creates malabsorption by bypassing the distal stomach, proximal duodenum, and a variable length of the jejunum depending on the length of the Roux limb. It also restricts food intake by creating a small gastric pouch [18]. Because this procedure creates a risk of malabsorption related to nutrient and vitamin deficiencies compared with malabsorption of caloric intake alone, it is better classified as causing altered absorption to differentiate it from truly malabsorptive procedures like BPD and BPD-DS.

Several randomized controlled trials report a significantly higher and sustained weight loss and resolution of obesity related comorbidities in subjects undergoing RYGBP. In a report by Griffin et al, a comparison of RYGBP and JIB was published [7]. This study established the superior long-term weight loss benefits of RYGBP over JIB without the long-term complications of diarrhea seen in the JIB group. In similar studies by Law and Pories et al, patients undergoing RYGBP were compared with those undergoing purely restrictive gastric partitioning procedures [19,20]. The data suggest the superior weight loss benefits in RYGBP patients without the long-term sequelae of band erosion, reflux, and vomiting. Sugerman et al reported results of their randomized prospective study comparing VBG and RYGBP [21]. This study documented the superior long-term weight loss benefits of RYGBP over VBG (EWL of 71% versus 55%) although with a slightly higher complication rate in the RYGBP group. Most of the

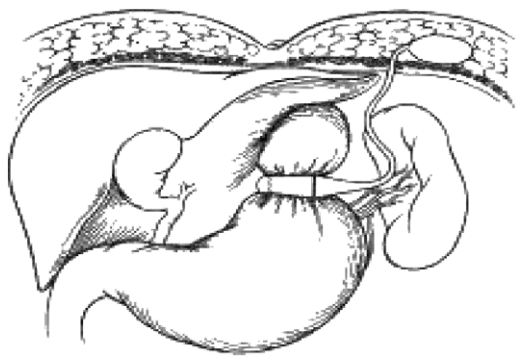

Fig. 4. Roux-en-Y gastric bypass. A Roux limb, created by dividing the proximal jejunum 60 cm distal to the ligament of Trietz, is anastomosed end-to-side to a 30 mL gastric pouch. The proximal jejunal (biliopancreatic) limb is anastomosed end-to-end to the Roux limb 60 cm distal to the gastroenterostomy. The proximal gastric pouch and distal stomach can be stapled in continuity (*A*) or stapled and divided (*B*). (*From* Schirmer BD. Operative treatment of morbid obesity, Townsend: Sabiston textbook of surgery. 16th edition. Philadelphia: WB Saunders Company; 2001; with permission.)

nutrient and vitamin deficiencies caused by the gastric bypass (iron deficiency anemia and vitamin B12 deficiency) were correctable with vitamin supplementation.

Other studies documenting the superior results of RYGBP over VBG include those by Hall and Mclean. In the Adelaide study, despite no difference in the overall morbidity, only 48% of patients undergoing the VBG demonstrated 50% EWL or more, whereas nearly 67% of the RYGBP patients demonstrated more than 50% EWL [22]. Mclean reported similar results with 58% of his RYGBP patients losing more than 50% of EWL compared with 39% of those undergoing VBG [23]. Sugerman et al reported their experience with VBG and conversion rates to RYGBP [24]. Fifty-eight morbidly obese patients underwent conversion for either failed weight loss or complications of VBG. These included two patients referred with anastomotic leak and peritonitis, three with band erosion, 15 with staple-line disruption, and 23 with stomal stenosis. Postoperatively, EWL in 53 patients after conversion increased from 36% to 67%. Although average follow-up after 5 years was only 45%, EWL was equal to weight loss after a primary gastric bypass with significant resolution of comorbid conditions.

Minimally invasive surgical techniques have revolutionized the world of bariatric surgery. Several large studies documenting the safety and efficacy of laparoscopic Roux-en-Y gastric bypass (LRYGBP) are available in the surgical literature. These have paralleled the weight loss and resolution of comorbidities seen with the open approach [25–27]. The authors' own case control data at the Medical College of Virginia suggest similar weight loss results between laparoscopic and open gastric bypass over 12 months of follow-up. In terms of complications, the operative mortality for gastric bypass is in the range of 0.5% to 1.0% in open and laparoscopic gastric bypass series. Long-term nutritional issues include a similar risk of iron deficiency anemia and the need for vitamin B12 supplementation. In contrast to purely malabsorptive procedures, protein calorie malnutrition is rare in gastric bypass patients. In terms of immediate postoperative complications, multivariate analysis of the authors' series of 3000 open and laparoscopic gastric bypass patients suggest that older, heavier male patients with multiple comorbid conditions are at increased risk for anastomotic leak and higher mortality and therefore should be avoided by surgeons in early part of their training [28].

Laparoscopic gastric bypass also has been compared with open gastric bypass in a prospective randomized trial by Nguyen et al in which longer operative time for the laparoscopic group was found but with less overall blood loss and shorter hospitalization [29]. Higher operating room expenses were offset by lower hospital costs in laparoscopic patients, and a significant reduction in wound complications including hernia and wound infections were recognized in the laparoscopic group. One year follow-up data showed a similar EWL between the two groups. In contrast, in a study from Sweden, 23% of the patients undergoing laparoscopic gastric bypass were converted

to an open procedure, and another 26% underwent subsequent surgery for bowel obstruction in the postoperative period [30]. This study thus found significant differences, with the laparoscopic group requiring a shorter hospital stay and fewer narcotics.

In all studies combined comparing the open and laparoscopic approach, the LRYGBP produces comparable and sustained weight loss compared with the open approach, with improvement in obesity related comorbidities. In most studies LRYGBP affords an improved short-term recovery from surgery, a shorter hospital stay, and a lower incidence of incisional hernias. The incidence of anastomotic strictures and increased hospital cost is reportedly higher in some clinical series. The evidence suggests gastric bypass is the weight loss procedure of choice for the morbidly obese, with a good outcome and acceptable morbidity and mortality.

Vertical band gastroplasty

VBG first was described by Mason in 1982. Before the advent of the gastric bypass, VBG was the most commonly performed bariatric procedure in the United States [31]. This procedure was performed with a 5 cm circumferential Marlex band placed around a gastric pouch created by stapling the gastric fundus. Thus, it was a purely restrictive procedure, decreasing food intake and resulting in subsequent weight loss (Fig. 5). It is

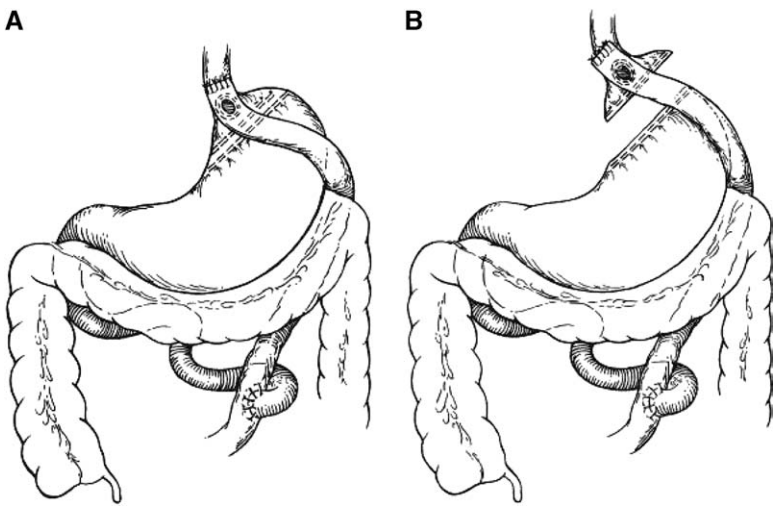

Fig. 5. Vertical banded gastroplasty. A stapled vertical gastric pouch is constructed by firing a stapler at a point 3 cm from the lesser curve and 6 cm below the angle of His and by firing a linear noncutting stapler between the angle of His and the gastric window created by the circular stapler. The gastric pouch outlet (stoma) is reinforced with a 1.5 cm wide and 5.0 cm circumference mesh collar. (*From* Schirmer BD. Operative treatment of morbid obesity, Townsend: Sabiston textbook of surgery. 16th edition. Philadelphia: WB Saunders Company; 2001; with permission.)

performed infrequently today because of less favorable long-term weight loss and significant adverse effects, including gastroesophageal reflux, vomiting, and solid food intolerance [32,33]. VBG in most clinical series has demonstrated acceptable weight loss (meaning EWL of at least 50%) in only 40% of patients after a follow-up period of 3 to 5 years. The average EWL at 3 to 5 years reported in most series appears to be 30% to 50% [33,34]. Long-term follow-up of VBG patients shows a reduction in effectiveness of this procedure with time. Laparoscopic approaches to VBG are available and result in reduced perioperative morbidity with weight loss results similar to the open procedure [35,36].

In 1982, a prospective study to evaluate and compare VBG and RYGBP was performed by Fobi et al [37]. One hundred patients had the VBG, and a similar number underwent RYGBP. At 10 years follow-up, VBG compared favorably with GBP for control of morbid obesity in terms of weight loss and resolution of comorbid conditions, although RYGBP yielded better weight loss and maintenance at all times of follow-up. Both procedures were found to be equal in terms of morbidity and mortality. Other series also have reported acceptable results with this procedure. Suter et al reported their experience with VBG in 197 patients over a 14-year period [38]. In their practice, three different types of banding were used, including the Silastic band, marlex mesh, and an adjustable sphincter. Overall EWL was 66% after 12 to 24 months follow-up and remained between 50% and 60% up to 9 years postoperatively. There was no significant difference between the three groups. Complications reported in the series included stomal stenosis (20%), staple-line disruption (11%), incisional hernia (13%), severe esophagitis (7%), and band migration (1.5%). Stenosis developed more often with a Silastic band or an adjustable sphincter, and severe esophagitis was more prevalent after the adjustable sphincter. The overall reoperation rate was 29.4%, with more reoperations reported in the Silastic and adjustable sphincter groups compared with the Marlex mesh group.

Capella et al reported their experience with a recently described combined VBG-RYGBP procedure in a series of 652 patients [39]. The patients were followed to 5 years and had an initial mean weight of 140 kg and a BMI of 50 kg/m^2. Superobese individuals made up 42% of the study group. The incidence of early reoperation and late complications that required reoperation was reported at 0.5%. There were two deaths in the study from pulmonary embolism for a mortality of 0.3%. At 5 years follow-up, the patients had lost an average of 58 kg with EWL of 77%. Their BMI was reduced to 29 kg/m^2, and 93% of patients had more than 50% EWL. Although this combined procedure appears to produce drastic weight loss, especially in the superobese, lack of long-term follow-up in this series prevents widespread use from being recommended.

Vertical band gastroplasty has been compared with other bariatric procedures in several prospective randomized trials. Of interest, when open

VBG is compared with open RYGBP, every study has shown superior and sustained weight loss after gastric bypass. Sugerman et al compared VBG with RYGBP in a similar study that included preoperative separation of sweets eaters versus nonsweets eaters [33]. Patients who underwent VBG had 37% EWL compared with 64% EWL in the RYGBP group. Although there was no significant difference between the loss of excess weight in sweets eaters or nonsweets eaters after RYGBP at 1 year, sweets eaters who had VBG lost significantly less excess weight (36%) than did nonsweets eaters in the same group (57%) or sweets eaters who had RYGBP. No significant differences were noted for electrolytes or renal or liver dysfunction between the two groups. The RYGBP group had lower serum vitamin B12 levels correctable with supplementation. Few patients in the RYGBP developed late complications, including stomal stenosis and marginal ulcer, which were managed nonoperatively. RYGBP was found to be superior to VBG for sweets eaters, probably because of the development of dumping syndrome symptoms. These and several other studies support the supremacy of gastric bypass over VBG in achieving successful and sustained weight loss in the morbidly obese [21–24,32,34] resulting in an almost near abandonment of the latter by bariatric surgeons.

Adjustable gastric banding

The concept of silicone gastric banding was introduced by Kuzmak in the early 1980s [40]. His original description of the adjustable gastric band involved encircling the stomach with Silastic material to create a small gastric pouch with a narrowed efferent tract. The silicone band later was modified to include an adjustable portion to enhance weight loss. Functionally, this device encircles the proximal stomach and is connected by tubing to a reservoir implanted deep on the abdominal fascia in the patient's upper abdomen. The reservoir can be accessed using a needle under fluoroscopy to inflate or deflate the band (Fig. 6).

Initial studies by Kuzmak reported more than 60% reduction in excess body weight over a 3-year follow-up period and concurrent resolution of comorbid conditions. Kuzmak's adjustable silicone gastric band, currently called the Lap Band (Inamed Corporation, Carpinteria, California) was approved by the FDA for use in the United States in 2001. The Lap-Band has had excellent results in most European and Australian studies and is the most commonly performed bariatric procedure in these countries. Relative advantages of this device include technical ease for laparoscopic placement and no intestinal anastomoses, thus excluding the risks of anastomotic leak. Furthermore, postoperative vomiting may be decreased with the Lap-Band compared with VBG, because the gastric pouch outflow tract can be widened by band adjustment.

After the laparoscopic placement of the first Lap Band by Belachew et al in 1993, several large Lap-Band series with excellent weight loss results

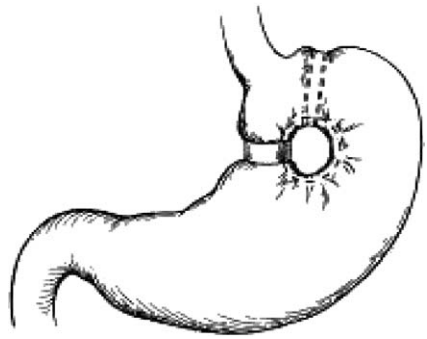

Fig. 6. Gastric banding. A saline-injectable locking gastric band placed around the proximal stomach. The reservoir is buried subcutaneously and sutured to the anterior rectus sheath. (*From* Schirmer BD. Operative treatment of morbid obesity, Townsend: Sabiston textbook of surgery. 16th edition. Philadelphia: WB Saunders Company; 2001; with permission.)

have been reported from Europe [41]. Angrissani reported the results of the Italian Collaborative Study Group for the Lap-Band system [42]. Laparoscopic adjustable gastric banding (LAGB) was performed on 1863 patients recruited in the study, with a mean BMI of 43.7 kg/m^2. Weight loss was evaluated at 6, 12, 24, 36, 48, 60, and 72 months with BMI of 37.9, 33.7, 34.8, 34.1, 32.7, 34.8, and 32, respectively. The overall mortality was 0.53%, whereas the open conversion rate was 3.1%, being higher in superobese (BMI greater than 50) than in morbidly obese patients (BMI less than 50). Most common complications reported were tube port failure, gastric pouch dilatation, and gastric erosion. No data on resolution of obesity-related comorbidities were provided in this study.

In another study from Italy, Favretti et al [43] reviewed 830 consecutive patients undergoing laparoscopic placement of the adjustable band. Major complications requiring reoperation occurred in 4% of patients (36 patients), including one gastric perforation, early (one case) and late (17 cases) gastric prolapse, nine malpositionings, four gastric erosions, three psychological intolerance, and one HIV conversion (band removed). Overall, their data revealed that 30% of patients (142 of 479 patients) experienced poor weight loss (less than 30% EWL) over 3 years of follow-up, although the manuscript incorrectly suggests this figure to be 20%. Reoperation for complications and failure of laparoscopic banding procedures will become increasingly common as more of these procedures are done in the United States.

The Swedish counterpart, called the Swedish Adjustable Gastric Band (SAGB, AB Obtech, Sweden), was developed in the 1980s. Forsell and Hellers [44] reported a 4-year follow-up in 50 patients who underwent open SAGB placement. BMI decreased from 46 to 27.5 kg/m^2, with a mean weight loss of 80 kg. These results could not be duplicated in other series, in which the reoperation rate was as high as 35%. The most common

complications requiring reoperation were band erosion and erosive esophagitis [45], while others included gastric pouch dilatation, invagination of distal gastric wall through the band, leakage from the balloon, and overall patient dissatisfaction.

The results of European and Australian studies have not been duplicated in most United States trials. The authors performed 36 Lap-Band insertions at the Medical College of Virginia Hospitals between March 1996 and May 1998 as part of the 'A trial' of the device in the United States under an Investigational Device Exemption from the FDA [46]. All patients accepted for Lap-Band placement included those specifically requesting the procedure, patients with a preoperative BMI less than 50 kg/m^2, patients with no or limited previous abdominal operations, and patients in whom dietary screening did not reveal significant (greater than 10%) calorie intake in the form of sweets. To date, 18 of 36 (50%) Lap-Bands have been removed. Indications for removal and conversions included failed weight loss, failed weight loss with esophageal dilatation, failed weight loss with leaking band, and esophageal dilatation with frequent emesis. Fourteen of 18 were converted to a gastric bypass involving either laparoscopic ($n = 8$) or open ($n = 5$) techniques. Overall mean percentage EWL was 62% (range 29% to 106%). The majority, of weight loss (43%) was after conversion to a gastric bypass, whereas only 19% was after Lap-Band placement. African-American patients demonstrated relatively poor weight loss compared with Caucasians following LAGB. The reduction in comorbidities after LAGB was also modest, with major resolution occurring after conversion to RYGBP. Of the 18 patients with the Lap-Band in place, the mean percentage of excess weight loss was only 32%.

Recent United States studies suggests that LAGB is associated with 40% to 55% EWL with modest resolution in comorbid conditions without significant long-term complications. In the presence of successful bariatric procedures with excellent long-term results like the LRYGBP, however, the LAGB would require long-term follow-up data to be advocated in morbidly obese patients.

Summary

Several bariatric procedures are available that have excellent long-term weight loss results and are backed by several large clinical trials. Purely restrictive procedures like VBG have fallen out of favor because of inadequate long-term weight loss. Gastric bypass and the BPD are well-studied and show significant resolution of obesity-related comorbidities. Long-term nutritional consequences are seen more commonly after malabsorptive procedures like the BPD than after hybrid malabsorptive–restrictive procedures like the gastric bypass. Because compliance and long-term nutritional follow-up are mandatory after any bariatric procedure, purely

malabsorptive procedures should be reserved for superobese patients who are at risk for inadequate long-term weight loss. Furthermore, minimally invasive techniques have evolved and essentially have eliminated the high incidence of postoperative wound complications and incisional hernias frequently seen after open gastric bypass. Until the development of a similarly successful procedure, gastric bypass will continue to be the gold standard bariatric procedure with its concurrent sustained weight loss benefits and resolution of comorbidities.

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Gastroenterol Clin N Am
34 (2005) 143–150

GASTROENTEROLOGY
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Endoscopic Treatments for Obesity: Past, Present and Future

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Obesity represents an increasing major health problem in the United States and most industrialized countries, with substantial morbidity, mortality, and economic impact. Dietary programs, drug treatments, behavior therapy, and physical training have shown short-term effectiveness, but long-term results are often disappointing.

Gastroenterologists are involved in the care of obese patients, primarily for treatment of diseases such as gastroesophageal reflux disease and cholelithiasis, which are prevalent in this subpopulation, and the management of patients following bariatric surgery.

As the prevalence of obesity continues to escalate, however, greater attention is turned toward minimally invasive endoscopic therapies as an important tool for managing this disease. The idea of using an endoscopically placed intragastric device for control of obesity first was described in 1982 [1]. Since then, various intragastric space-occupying devices, primarily balloons, have been evaluated for short- and long-term results. More recently, novel endoscopic procedures directed at duplicating gastric restrictive and bypass surgeries have been attempted in preclinical studies. Currently, endoscopic therapy for obesity in the United States is only investigational.

Past devices

Garren-Edwards gastric bubble

The Food and Drug Administration (FDA) approved the Garren-Edwards gastric bubble (GEGB, American-Edwards Laboratories, Irvine, California) as an adjunct to diet, behavior therapy, and exercise in 1985. The

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0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.001 *gastro.theclinics.com*

GEGB was a polyurethane cylindrical device, with a self-sealing valve at one end through which a removable air insufflation catheter was inserted (Figs. 1, 2). A lengthwise tunnel or interior wall traversed the center of the bubble. The device was inserted into the stomach using an adapted gastric tube that was passed gently down the esophagus into the stomach. The bubble was released from the gastric tube and then inflated with 220 mL of air by means of the detachable insufflation catheter. The gastric tube and catheter then were removed, and the implanted bubble floated freely in the stomach. GEGB removal was accomplished endoscopically by puncturing the bubble using a rat-tooth forceps [2].

The Garren-Edwards gastric bubble was used in the United States until 1988, with more than 25,000 devices inserted despite the lack of controlled data [3]. Between 1987 and 1989, several well-designed controlled studies subsequently were published, which uniformly concluded that the GEGB was no more successful in inducing weight loss than diet and behavior modification alone [4,5]. A double-blind controlled crossover study with 61 patients compared bubble–sham, sham–bubble and bubble–bubble in two successive 12-week periods [6]. All groups participated in diet and behavioral modification therapy. This study showed no significant differences in weight loss between the groups at 12 or 24 weeks, with a change in body mass index (BMI) of 3.1, 2.3, and 2.9 at 12 weeks for the respective bubble–sham, sham–bubble and bubble–bubble groups. The major weight loss occurred during the first 12 weeks irrespective of bubble or sham therapy. A sham-controlled study from the authors' institution involving 22 patients (11 with GEGB; 11 sham procedure) showed no significant differences in weight loss between the groups (5.8 kg with GEGB; 2.8 kg with sham) at 2 to 3 months follow-up [7].

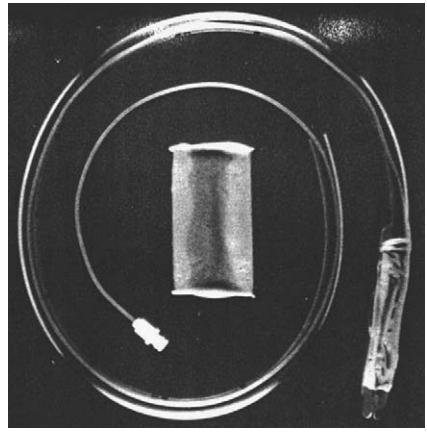

Fig. 1. Garren-Edwards gastric bubble and introducer tube. (*From* Lindor KD, Hughes RW Jr, Ilstrup DM, et al. Intragastric balloons in comparison with standard therapy for obesity—a randomized, double-blind trial. Mayo Clin Proc 1997;62(11):992–6; with permission.)

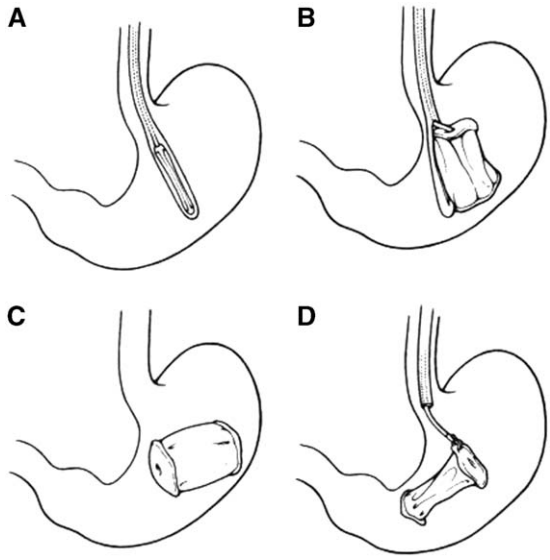

Fig. 2. (*A*) Insertion of overtube containing deflated bubble. (*B*) Insufflation with 200 mL of air. (*C*) Overtube removed, bubble left in place. (*D*) Removal with endoscopic graspers after puncture and deflation. (*From* Hogan RB, Johnston JH, Long BW, et al. A double-blind, randomized, sham-controlled trial of the gastric bubble for obesity. Gastrointest Endosc 1989;35(5):381–5; with permission.)

Another sham-controlled crossover study with 23 patients showed no differences in mean weight reduction between the gastric bubble period and sham period (5.4 kg versus 5.2 kg). Bubble implantation reduced weight significantly more than the sham procedure initially, but the mean weight loss at 12 weeks was not different [8].

Complications reported were significant and included gastric erosions (26%), gastric ulcers (14%), small bowel obstruction (2%), Mallory-Weiss tear (11%), and esophageal laceration (1%) [6,9,10]. Because of the significant adverse events and the lack of data to support efficacy, GEGB no longer is used, nor is it commercially available.

Other balloons

Subsequent to the advent and demise of the GEGB, several modified intragastric balloons were introduced and evaluated in small studies. The lack of efficacy and safety of GEGB was attributed by some to the small volume used in the bubble and the composition material [4]. The Taylor intragastric balloon (Dunlop Limited, Leicestershire, England) was a pear-shaped, smooth silicone balloon filled with 550 mL of saline. The device was introduced endoscopically. A single prospective, multi-center study showed an 11.4% decrease in BMI over 16 weeks [11]. This was a single, uncontrolled study with limited follow-up. The Ballobes intragastric balloon

(DOT ApS, Rodovre, Denmark) was another balloon that was inflated with approximately 475 mL of room air. A double-blind, sham-controlled, crossover study on 28 supermorbidly obese patients using this system showed no additional benefit to the balloon compared with diet, physical training, and behavior modification [12]. Several further variations on inflatable intragastric balloons have been reported in the literature, including silicone-rubber and polyurethane balloons that are kept in position using a nasogastric catheter taped to the nose [3,13,14]. Despite the modifications to the original concept of an intragastric space-occupying device, none of these balloons were shown to be effective or free from complications, and as a result, they are not applied in clinical practice.

Present

BioEnterics intragastric balloon system

The Bioenterics intragastric balloon system (BIB, BioEnterics Corporation, Carpinteria, California) is designed to partially fill the stomach and mimic an intragastric bezoar (Fig. 3). Although widely used internationally, it is not approved for use in the United States. BIB is made of transparent silicone elastomer and forms a sphere when inflated (eg, 500 mL will give a 13 cm diameter) [15]. The balloon has a self-sealing radio-opaque valve to which a silicone catheter is attached to facilitate balloon filling. The balloon generally is filled with 400 to 700 mL of sterile saline. It is intended for temporary weight loss, with a recommended maximum placement period of 6 months because of the higher risk of balloon deflation beyond this time. The BIB and filling catheter are advanced gently down the esophagus into the stomach. Its position within the stomach is verified endoscopically as is the filling of the balloon. Once filling is complete, the catheter is detached and removed along with the endoscope. An appeal of the BIB is the ability to vary the balloon volumes, increasing the volume to promote further satiety or decreasing the volume to minimize adverse effects such as vomiting or abdominal pain [16]. Nonetheless, reintubation of the BIB valve can be difficult. As the BIB has no grasping parts and is smooth, finding the valve and then positioning the reintubation catheter within it can prove challenging. Food also can obstruct the valve. Some authors have suggested that reintubation may result in a leaky valve and lead to early balloon deflation and recommend avoiding this practice [15]. BIB removal should be done with general anesthesia. An endoscope initially is passed into the gastric lumen and the balloon punctured using a needle. Once most of the saline is eliminated, the balloon is removed using foreign body graspers. Before removal through the esophagus, intravenous buscupan or glucagon is recommended.

Although the BIB device has been used for short-term weight loss for over 5 years, there has been no sham-controlled study in the literature. As

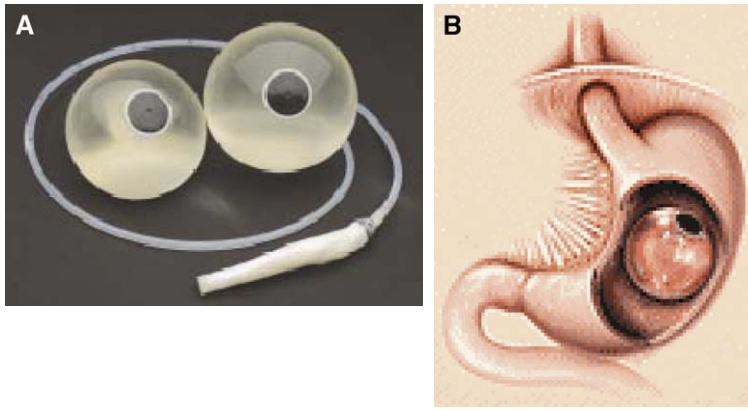

Fig. 3. (*A*) BioEnterics intragastric balloon system filled with 400 mL and 700 mL, and with the uninflated system in the foreground. (*B*) Inflated BioEnterics intragastric balloon in the stomach. (*From* BioEnterics Corporation, Carpinteria, California; with permission.)

suggested by past experience with the GEGB, sham-controlled crossover studies are essential in identifying a successful treatment. A mean reduction of BMI of 4.8 was reported after 4 months of balloon treatment in a study with the largest number of implanted devices in the literature over a 4-year period (349 BIB devices in 303 patients) [17]. All patients were placed on a 4.2 Kcal per day diet. The same authors also evaluated weight loss over an 18-month period in patients treated with diet alone versus BIB and diet (42 patients diet alone, 31 BIB for 4 months and diet) [18]. After 4 months, the mean weight loss was 13.9 kg, and the mean reduction in BMI was 4.8. The weight loss in the BIB and diet group was slightly higher at 4 months. Whether this was significant is unclear (no p value available). At 18 months, all patients regained weight. Other studies with large patient numbers have shown a mean weight loss of 9.5 to 15.4 kg postballoon placement at 3 to 6 months follow-up [19,20]. Most of the weight loss occurred during the first 3 months, and not all patients lost weight.

Although complications are less frequent with the BIB than with earlier intragastric balloons, similar complications are reported. Complications include intolerance to the balloon (7.4%), gastric ulcer (0.5%), gastric erosions (0.8%), esophagitis (4.8%), spontaneous balloon deflation (3.7%), vomiting for 1 week (90%), vomiting for more than 3 weeks (18%), gastroesophageal reflux (11.5%), and abdominal pain (12.5%) [17,19]. A few case reports of gastric perforations, small bowel obstruction, and gastric dilatation have been described [21–24]. To minimize the risk of small bowel obstruction, the balloon can be filled with both methylene blue dye and saline to allow for early detection of balloon deflation, as methylene blue turns urine green [25]. It is important to remember, however, that propofol, which is administered commonly for balloon placement, is known to

infrequently cause green urine. The cause is unclear and generally disappears within 2 days of discontinuing the infusion.

There are no other known endoscopic approaches to weight loss currently used in clinical practice.

Future

Intragastric space-occupying devices

The use of intragastric devices is based on the finding that bezoars cause weight loss [26]. The exact mechanism for weight loss is unclear, with several proposed suggestions that include delayed gastric emptying, placebo effect, hormonal, mechanical satiety, behavior modification and neuronal effects. The ideal intragastric space-occupying device should be effective in inducing long-term weight loss. The basic design features must include:

- Ease of instillation allowing device placement under intravenous conscious sedation
- Avoid the use of an overtube
- Short procedure time of approximately 20 minutes or less
- Resides exclusively within the stomach and will not pass the pylorus or be regurgitated
- Can be removed on demand or for scheduled replacement
- Can be modified for added therapeutic effect
- Device safety is crucial.

Presently, a device called the Butterfly (Wilson Cook, Winston-Salem, North Carolina) is being evaluated in preclinical and pilot clinical work [27]. It is a shift away from the traditional balloon concept and instead is comprised of a continuous ribbon of low-density polyethylene folded over on itself over a total length of approximately 36 m.

Gastric restrictive and bypass endosurgery

These procedures are designed to duplicate bariatric surgical procedures. Such an approach potentially would offer more durable weight loss and avoid issues related to long-term foreign body presence from space-occupying devices. The basic design features of such an approach must include:

- Transmural suturing to provide durability
- Intravenous conscious or deep sedation
- Procedure time within 45 minutes
- Minimal intraluminal space requirement for performing the procedure
- Maximally flexible accessories that would allow easy access to all luminal surfaces

Ongoing work in the authors' Developmental Endoscopy Unit animal laboratory over the past few years has been directed at attempting to

duplicate gastric partitioning, specifically vertical-banded gastroplasty, Magenstrasse sleeve gastroplasty, and creating a small 20 mL proximal gastric pouch [28]. Preclinical work also is being undertaken by other investigators on refining an endoscopic gastrojejunostomy technique. The possibility of endoscopically accomplishing effective gastric restrictive and bypass procedures remains indeterminate.

Summary

Obesity is recognized as a serious, chronic illness affecting all ages. The cause for obesity is multi-factorial, which makes successful management complex and challenging. Meaningful weight loss is frequently difficult to achieve, particularly when the goal is not merely to lose weight but to maintain this loss. The efficacy of future endoscopic approaches needs to be validated through well-designed controlled studies, and verification of safety is essential. Endoluminal therapies must have a sound physiologic basis for their development. The availability of specialized radionuclide imaging of gastric capacity and accommodation provide a useful tool in constructing interventions. Endotherapy is likely best suited for nonmorbid obese individuals with BMI ranging from 30 to 39 or as a budge to bariatric surgery. This specific BMI range has been targeted by the National Institutes of Health for emerging technologies. Presurgical weight loss to reduce surgical risk is another potential target group. Regardless of which endoscopic methods prevail, patients will continue to require a comprehensive, multi-modality management approach to this complex disease.

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Gastroenterol Clin N Am
34 (2005) 151–166

GASTROENTEROLOGY
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Endoscopy in the Bariatric Surgical Patient

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In 1996, a National Institutes of Health Consensus Panel recognized bariatric surgery as the only effective long-term treatment for morbid obesity [1]. As the problem of obesity in the United States has grown, the number of patients undergoing bariatric surgery has risen dramatically. The American Society for Bariatric Surgery estimated that 140,000 bariatric operations would be performed in 2004, compared with approximately 23,000 in 1997. Although most patients achieve successful outcomes following surgery in terms of excess weight loss and improvement of comorbid conditions, many patients develop untoward postoperative gastrointestinal (GI) symptoms. These symptoms are often difficult to interpret clinically and frequently require investigation with upper GI barium studies and upper endoscopy. As the performance of bariatric surgery rises, an increase in the number of patients referred for evaluation and endoscopy is expected. Therefore, gastroenterologists must become familiar with the surgically altered anatomy and the possible endoscopic findings in these patients to perform upper endoscopy in a safe and facile manner.

Understanding the anatomy in the bariatric surgical patient

The major types of bariatric procedures that gastrointestinal endoscopists may encounter are discussed here. A basic understanding of the anatomical

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0889-8553/05/$ - see front matter
doi:10.1016/j.gtc.2004.12.013

changes that occur after bariatric surgery is critical before endoscopy is performed.

Gastric bypass

The Roux-en-Y gastric bypass (RYGBP) is the most commonly performed bariatric procedure in the United States (Fig. 1) [2]. Although there are several modifications of the RYGBP, in the standard procedure a small gastric pouch (typically less than 30 mL) is created along the lesser curvature and transected from the remainder of the stomach. The pouch is anastomosed to a Roux limb in an end-to-side fashion, creating a gastrojejunostomy with a stomal diameter of approximately 10 to 12 mm. The length of the Roux limb is typically 60 to 75 cm, but varies depending on the degree of malabsorption that is desired, and can be as long as 150 cm in the long-limb RYGBP. The original gastric bypass was fashioned with a loop gastrojejunostomy (Fig. 2) [3], which subsequently was abandoned because of problems with alkaline reflux into the pouch.

Vertical banded gastroplasty

Vertical banded gastroplasty (VBG) is a purely restrictive operation that still is performed today, although it is inferior to RYGBP in terms of long-term excess weight loss [4,5]. The key components of this operation include a vertically oriented gastric channel (pouch) that has a volume of 15 mL or less and an outlet (stoma) from the channel into the remainder of the stomach (Fig. 3). The stoma is reinforced by a polypropylene mesh collar or a Silastic ring to prevent stomal dilation. The remainder of the stomach and small intestine are unaltered in VBG.

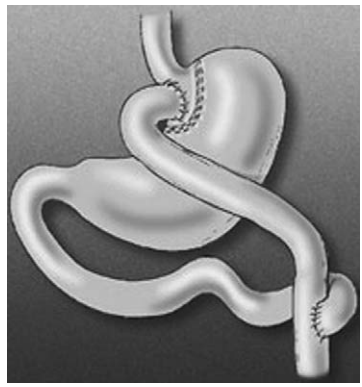

Fig. 1. Roux-en-Y gastric bypass. (*From* the American Society for Bariatric Surgery, Gainesville, Florida.)

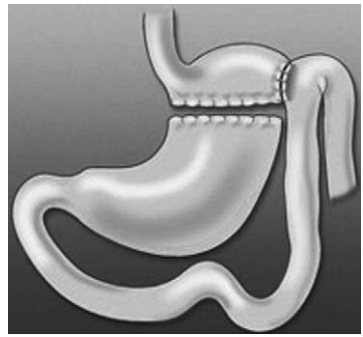

Fig. 2. Illustration of the original gastric bypass operation with loop gastrojejunostomy. (*From* the American Society for Bariatric Surgery, Gainesville, Florida.)

Gastric banding

Gastric banding is another purely restrictive procedure in which a constricting prosthetic band is placed around the proximal stomach, creating a small proximal pouch and a large remnant in an hourglass configuration (Fig. 4) [6]. An adjustable band lined by an inflatable balloon connected to a subcutaneous saline port subsequently was developed, allowing for changes in the degree of restriction [7]. This procedure now is performed laparoscopically, the so-called laparoscopic adjustable silicone gastric banding (LASGB) operation [8].

Biliopancreatic diversion and duodenal switch

Biliopancreatic diversion (BPD) is primarily a malabsorptive procedure with two key components: a distal gastrectomy, which results in mild reduction of oral intake, and construction of a long limb Roux-en-Y

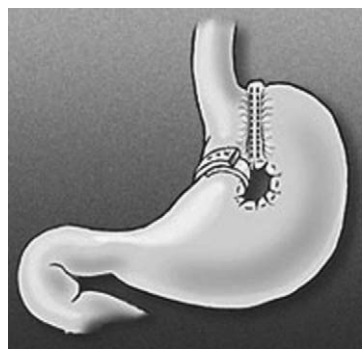

Fig. 3. Illustration of the vertical banded gastroplasty. (*From* the American Society for Bariatric Surgery, Gainesville, Florida.)

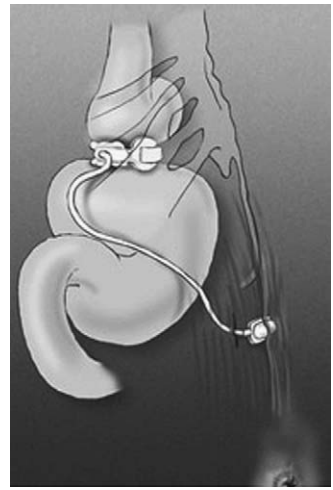

Fig. 4. Illustration of the laparoscopic adjustable silicone gastric banding procedure. (*From* the American Society for Bariatric Surgery, Gainesville, Florida.)

anastomosis with a short (50 cm) common alimentary channel (Fig. 5) [9,10]. A modification of the BPD is the duodenal switch procedure, which uses a sleeve gastrectomy rather than distal gastrectomy, and anastomosis of the jejunal limb end-to-end with the proximal duodenum (Fig. 6) [11,12]. These procedures comprise less than 15% of all bariatric operations performed in North America.

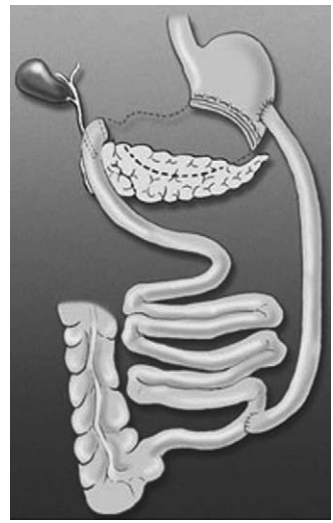

Fig. 5. Illustration of the biliopancreatic diversion. (*From* the American Society for Bariatric Surgery, Gainesville, Florida.)

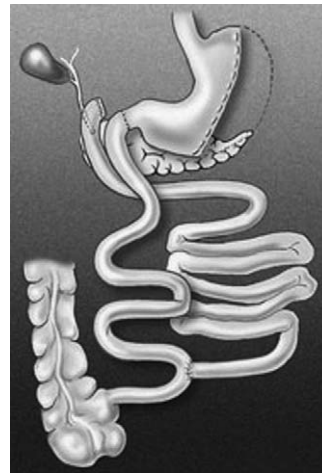

Fig. 6. Illustration of the biliopancreatic diversion with duodenal switch. (*From* the American Society for Bariatric Surgery, Gainesville, Florida.)

Indications for endoscopy

In general terms, the most common indications for endoscopy in bariatric surgical patients are the evaluation of symptoms (such as nausea, vomiting, abdominal pain, dysphagia, and weight regain or the failure to lose weight) and the treatment of complications. In the authors' experience, the most common symptoms reported by patients referred for endoscopy are epigastric abdominal pain (53%), nausea/vomiting (35%), and dysphagia (16%) [13]. The etiology of these symptoms is often multi-factorial. Dumping syndrome, inappropriate eating habits, and poor food selection frequently contribute, but upper endoscopy should be performed to exclude structural abnormalities in the surgically altered GI tract.

Upper GI hemorrhage is a relatively uncommon indication for endoscopy after bariatric surgery [14–16]. Early postoperative GI hemorrhage usually arises from the staple lines of the gastrojejunostomy, gastric remnant, and jejunojejunostomy [16]. Late GI hemorrhage is commonly from a marginal ulcer at the gastrojejunostomy, but it is important to consider the excluded gastric segment and duodenum as potential sites of bleeding [15].

Failure to lose weight or the presence of weight regain after gastric bypass or gastroplasty may indicate the development of a staple line dehiscence, although these symptoms may not predict this complication [17]. An excessively large stoma at the gastrojejunal anastomosis can also present as weight gain [13], presumably because of less restriction of food intake. Weight gain after VBG or LASGB also commonly occurs with band erosion (intragastric band migration), which is diagnosed best by endoscopy.

Heartburn has been reported to be a common complication of gastric banding [18–20], but the actual effect of this procedure on gastroesophageal reflux (GER) is controversial, as some studies report a decrease or no effect of banding on GER [21,22]. One key factor that may determine how GER is affected by gastric banding is the presence and size of the gastric pouch proximal to the band. Reflux and esophagitis appear to be worsened when a large gastric pouch is present (as can occur with band slippage), but improved when the band is placed at or just below the gastroesophageal junction, thereby augmenting the effect of the lower esophageal sphincter [23]. One word of caution: heartburn in a patient after gastric banding may be caused by an excessively tight band, and endoscopy in this setting may lead to perforation [23]. A contrast radiological study should be performed first to assess the degree of constriction and the position of the band. Endoscopy should be performed if heartburn persists after band deflation.

Endoscopic principles

Before performing upper endoscopy in the bariatric surgical patient, the endoscopist should adhere to the following basic principles, as outlined by Stellato et al [24]:

- Discuss the specific bariatric operation with the patient's surgeon to understand the altered anatomy, as modifications to the standard operations are commonplace.
- Review the operative report, pertinent perioperative records, and all available postoperative abdominal imaging studies.
- Select the most appropriate type of endoscope and accessories based on the indication for the procedure and information gathered from investigations. Obtain any specially designed accessories that may be necessary beforehand.

For most RYGBP patients, a standard diagnostic upper endoscope can be used to evaluate the esophagus, gastric pouch, gastrojejunal anastomosis, and proximal portion of the Roux limb. A pediatric colonoscope or enteroscope may be required to examine the jejunojejunal anastomosis, particularly in patients with a long-limb RYGBP.

Retrograde evaluation of the bypassed stomach and biliopancreatic limb is challenging, but this can be accomplished with the use of a pediatric colonoscope or enteroscope long enough to traverse the Roux limb [25,26]. A long-limb RYGBP or acute angulation at the jejunojejunostomy may preclude successful intubation of the bypassed segments, for which intraoperative enteroscopy or antegrade examination by means of percutaneous gastrostomy [27–29] may be required.

Abdominal imaging studies play an important role in the diagnosis of complications following bariatric surgery [30]. Barium studies are particularly useful in defining the postsurgical anatomy and identifying stomal

stenosis and staple line dehiscence; therefore the authors routinely obtain barium studies in most patients before performing endoscopy.

Endoscopic findings in normal postsurgical anatomy

Gastric bypass

The esophagus and gastroesophageal junction should appear normal following gastric bypass. Following RYGBP, the normal gastric pouch is small, so minimal air should be insufflated. Special attention should be paid to the gastrojejunostomy, which normally has a stoma measuring 10 to 12 mm in diameter (Fig. 7). Being an end-to-side anastomosis, there is typically a short, blind limb of jejunum just distal to the gastrojejunostomy in addition to the Roux limb. Endoscopists should be aware of variations such as the loop gastrojejunostomy, which was part of the original gastric bypass procedure. Another variation is in the length of the Roux limb, which typically measures approximately 60 to 75 cm but can be as long as 150 cm in the long-limb RYGBP. This limb should be examined (in patients with nausea and vomiting) to evaluate for evidence of obstruction, which can occur with adhesions or internal hernias.

Vertical banded gastroplasty

Endoscopy following VBG is relatively straightforward. The vertical lesser curvature channel permits easy endoscopic visualization. The stoma is located at the lower end of the channel, typically 7 to 8 cm distal to the gastroesophageal junction. The stoma should be approximately 10 to 12 mm wide, and endoscopically it may appear similar to the pylorus or the diaphragmatic narrowing of a hiatal hernia (Fig. 8A). After passing the endoscope beyond the stoma, complete examination of the unaltered

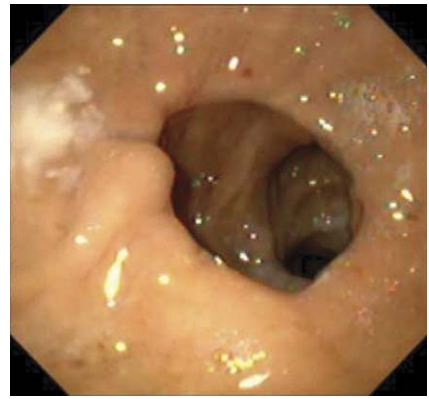

Fig. 7. Endoscopic appearance of a normal gastrojejunostomy after gastric bypass.

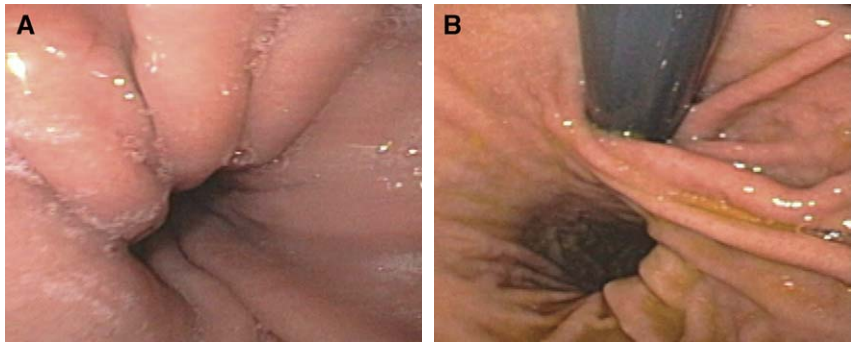

Fig. 8. (*A*) Endoscopic appearance of a normal stoma after vertical banded gastroplasty. (*B*) Retroflexed endoscopic view from the antrum after vertical banded gastroplasty.

antrum, pylorus, and duodenum can be performed. Retroflexion of the endoscope within the antrum reveals the gastric partition, greater curvature, and gastric fundus (Fig. 8B).

Common endoscopic abnormalities

Among symptomatic patients following RYGBP, the most common endoscopic abnormalities are marginal (anastomotic) ulcer, stomal stenosis, and staple line dehiscence [13].

Marginal ulcer

Marginal ulcers, which are defined as ulcers at the gastrojejunal anastomosis, occur in up to 16% of patients following RYGBP (Fig. 9) [31–34]. Their etiology remains unclear, but potential contributory factors include gastric acidity (especially in the presence of a staple line dehiscence and gastrogastric fistula), pouch orientation and size, nonsteroidal anti-inflammatory drug use, *Helicobacter pylori* infection, and local ischemia and tension at the anastomosis [33,35–38]. Marginal ulcers frequently are located on the jejunal side of the anastomosis, so special attention should be paid to this area during endoscopy. The detection of a marginal ulcer should prompt biopsies for *H. pylori* and a careful search for a gastrogastric fistula, both of which have been implicated in the formation of marginal ulceration [33,37].

Stomal stenosis

Stomal stenosis is another important complication of bariatric surgery, occurring in approximately 3% to 12% of patients following RYGBP, with reported rates as high as 27% following laparoscopic RYGBP [30,34,39–43].

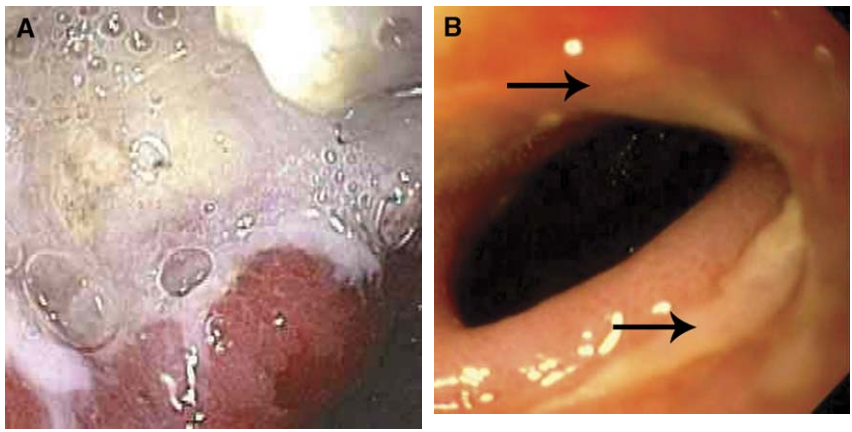

Fig. 9. (*A*) Endoscopic appearance of a large, clean-based marginal ulcer. (*B*) Endoscopic appearance of a marginal ulcer, encompassing 75% of the stomal circumference *(arrows)* and resulting in mild stomal stenosis.

In the authors' experience, after RYGBP, nearly 20% of symptomatic patients had some degree of stomal stenosis. Significant stomal stenosis is identified endoscopically as a pinhole orifice, precluding passage of the endoscope beyond the gastrojejunal anastomosis (Fig. 10). Other potential findings include gastric pouch dilatation, undigested food in the pouch, or foreign material (eg, phytobezoar) obstructing the stoma.

Endoscopic dilation by a variety of methods is safe and effective for treating stomal stenosis, and this reduces the need for revisional surgery.

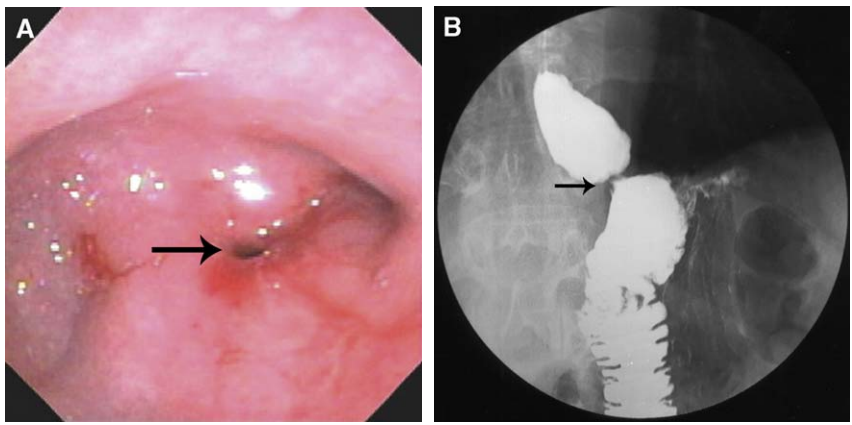

Fig. 10. (*A*) Endoscopic appearance of significant stomal stenosis after gastric bypass, resulting in a pinpoint stoma *(arrow)*. (*B*) Radiographic appearance of stomal stenosis after gastric bypass *(arrow)*.

Staple line dehiscence

Staple line dehiscence with gastrogastric fistula following RYGBP can be heralded by weight gain and may contribute to marginal ulcer formation. The incidence of staple line dehiscence following gastric bypass appears to be highly dependent on surgical technique, with rates over 20% when the pouch and bypassed stomach are stapled in continuity, compared with 1% when the segments are transected completely [32]. Dehiscences are frequently small and easily overlooked, and they may have an endoscopic appearance similar to that of a diverticulum (Fig. 11A). Barium studies are helpful in identifying small dehiscences (Fig. 11B). In contrast, large dehiscences are identified easily and may permit passage of the endoscope into the bypassed stomach and duodenum (Fig. 11C).

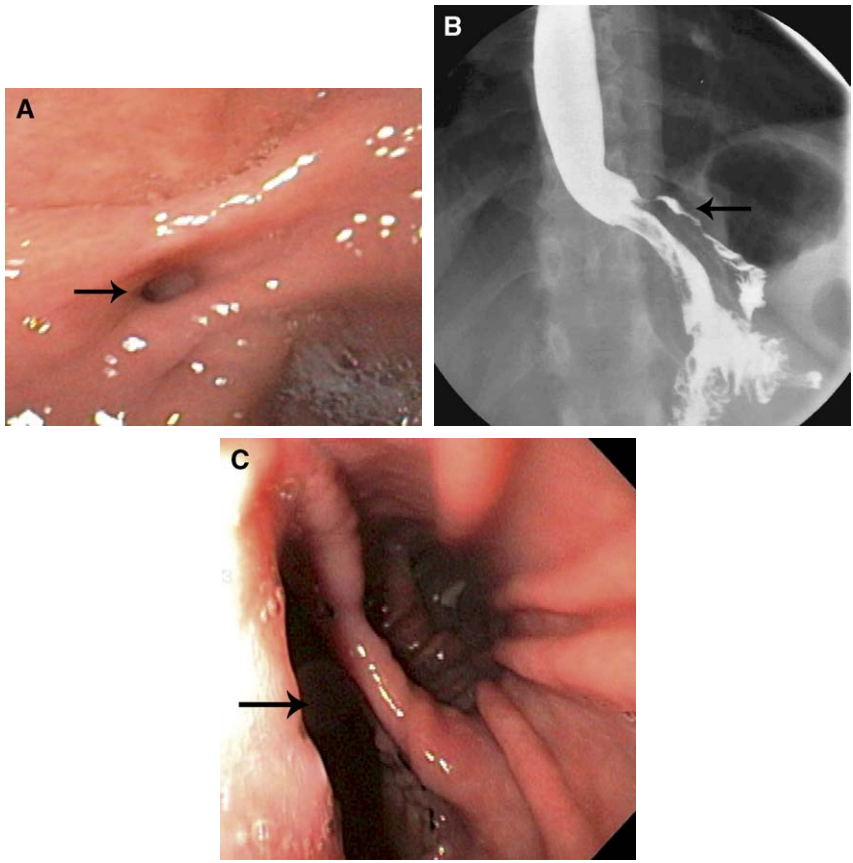

Fig. 11. (*A*) Endoscopic appearance of a small staple line dehiscence after gastric bypass *(arrow)*. (*B*) Radiographic appearance of staple line dehiscence with gastrogastric fistula *(arrow)*. (*C*) Endoscopic appearance of a large staple line dehiscence *(arrow)*, allowing easy access to the bypassed stomach.

Band erosion

Band erosion is a relatively uncommon complication of VBG and LASGB, occurring in approximately 1% to 2% of VBG patients and 1% to 11% of LASGB patients [44–46]. In VBG patients, band erosion may cause pain, but more often presents with weight gain and reduced restriction to food intake. Because of the tubing used for band insufflation, band erosion is a potentially serious complication after LASGB (Fig. 12), and this can result in pain, vomiting, bleeding, intra-abdominal abscess, or fistula formation [47]. As in VBG patients, sudden weight gain can occur with band erosion after LASGB; in many cases, the first sign of erosion is infection at the access port site by means of the connecting tube [45]. Therefore, erosion should be excluded at the first sign of port infection. Endoscopic removal of an eroded band can be performed [48], but surgical removal generally is recommended, as patients ultimately will require a repeat bariatric operation.

Therapeutic endoscopy in the bariatric surgical patient

Endoscopic dilation of stomal stenosis

Endoscopic dilation of stomal stenosis after bariatric surgery is safe, effective, and durable. It can be performed successfully by several methods, including balloon dilation, passage of dilators over a guide wire (Eder-Puestow, Savary-Guilliard), and endoscopic electrosurgical incision [34,39–42,49–55]. The optimal technique for dilation of stomal stenoses remains to be determined, but the authors prefer to use through-the-scope (TTS)

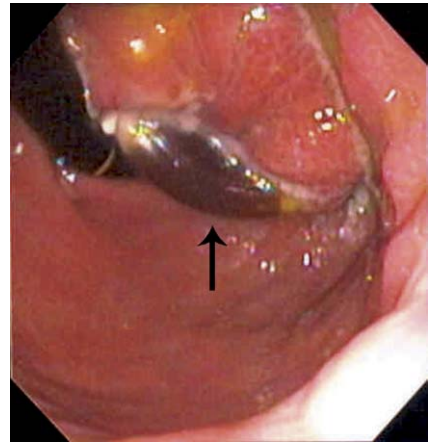

Fig. 12. Endoscopic appearance of band erosion after gastric banding. (*Courtesy of* Christine Ren, MD, New York).

balloon catheters whenever possible. The goal stomal diameter after dilation is 10 to 12 mm, up to a maximum of approximately 15 mm (45F) [47]. In a recent series using TTS balloons, nearly 60% of patients had complete symptomatic resolution after a single dilation session with a 15 mm balloon, suggesting that this size should be used initially [39]. Significant stenoses should be dilated gradually over several sessions using progressively larger balloons to reduce the risk of perforation. The incidence of perforation was 3% in a recent study in which the mean initial and final balloon size was 13 mm and 16 mm, respectively [55]. Overaggressive dilation should be avoided, not only to reduce the perforation risk, but also because of the concern that dumping symptoms and weight regain may occur as a result. Although there are reports of successful dilation to 18 to 20 mm without resulting in reoperation for weight regain [39,50], the authors recommend performing serial dilations up to a maximum of 15 mm using TTS balloons. Endoscopists should exercise caution when passing TTS balloon catheters through a tightly strictured stoma, recognizing that there is a short blind loop of jejunum beyond the gastrojejunostomy. A guide wire should be used when the TTS balloon catheter cannot be advanced with ease.

Endoscopic therapy for acute gastrointestinal bleeding

The management of acute GI bleeding in the early postoperative period is often challenging because of the inaccessibility of the excluded stomach and the jejunojejunostomy and the risks associated with early postoperative endoscopy. Some have advised against using therapeutic endoscopy in this setting, given the risk of perforation at the surgical anastomoses [16]. There are isolated reports of safe and effective therapeutic endoscopy for managing early GI bleeding after RYGBP [56,57]. Early reoperation with intraoperative endoscopy (or laparoscopy-assisted enteroscopy), however, is considered the preferred management approach in patients who fail conservative therapy [16,58].

Late GI bleeding commonly is caused by a marginal ulcer, which can be managed endoscopically using standard hemostatic interventions such as injection, thermal, and mechanical therapy.

Endoscopic management of staple line dehiscence, gastric fistulas, and dilated stomas

Staple line dehiscence complicating RYGBP and VBG generally requires surgical revision, and experience with endoscopic closure is limited. Local injection of sodium morrhuate surrounding the area of dehiscence was not effective in a small series of VBG patients [59]. A more promising, but technically difficult technique employs a combination of endoscopic suturing, hemoclip application, and argon plasma coagulation. In a preliminary study, Thompson et al achieved complete staple line closure in six

of eight RYGBP patients using this method, resulting in symptom improvement and cessation of weight gain [60]. Additional experience and clinical trials with long-term follow up are necessary before endoscopic closure of staple line dehiscence can be recommended routinely.

Successful closure of gastrocutaneous fistulas after bariatric surgery (VBG and BPD) using endoscopic fibrin sealant injection has been reported [61]. It is not known whether this technique can treat staple line dehiscence with gastrogastric fistula successfully. In the authors' experience with several patients, the use of fibrin sealant in combination with argon plasma coagulation and hemoclips did not result in long-term gastrogastric fistula closure.

An excessively dilated stoma resulting in weight gain after gastric bypass can be managed endoscopically with sodium morrhuate injection in four quadrants surrounding the stoma. In a small series published in abstract form, this technique resulted in a decrease in stomal size (to 12 mm or less) and resumption of weight loss in five of eight (63%) gastric bypass patients [59].

Endoscopic retrograde cholangiopancreatography

Performing endoscopic retrograde cholangiopancreatography (ERCP) in RYGBP patients is an arduous task, but it can be accomplished by several methods [62]. Using an enteroscope or pediatric colonoscope, Elton et al reported an 84% success rate in patients who had undergone a long-limb surgical bypass, including three RYGBP patients [63]. The investigators noted several disadvantages with this technique, however, including the lack of ERCP accessories compatible with the enteroscope, the lack of an elevator, and the limitations of forward-viewing endoscopes in performing biliopancreatic therapy. Wright et al described successful ERCP in 6 of 11 (55%) RYGBP patients by implementing maneuvers such as advancing the duodenoscope over a stiff guide wire previously placed into the bypassed stomach with a forward-viewing endoscope, or pulling up the duodenoscope by means of a wire-guided biliary balloon anchored at the pylorus [64]. The main reason for failure was inability to advance the duodenoscope through the biliopancreatic limb to the region of the papilla.

An alternative technique involves establishing percutaneous access to the bypassed stomach by means of a surgical gastrostomy, through which the duodenoscope is passed [64–66]. The advantages of this method include rapid, reliable access to the duodenum and visualization of the papilla in the usual anatomic orientation for ERCP.

Summary

Endoscopy in the bariatric surgical patient presents a new challenge for gastroenterologists, one that will be encountered with increasing frequency as the performance of bariatric surgery increases. To ensure a safe, successful,

and useful endoscopy, it is important to be familiar with the expected postsurgical anatomy and endoscopic appearance after the various bariatric operations and common complications that can arise.

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