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Editor

Bariatric Endoscopy

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Preface

This textbook on bariatric endoscopy is the work of a multidisciplinary group of experts, and is intended to serve as a comprehensive guide to the endoscopic management of obese and bariatric patients. Epidemiology, pharmacological, surgical treatment of obesity, surgical anatomy, postoperative complications, and endoscopic methods are covered in-depth. Thus, clinical gastroenterologists, gastroenterologists in training, and surgeons with a special interest in bariatric surgery may find this book of importance.

The issues presented in this text have particular relevance in our obesogenic society. Over one-third of the adult population in the United States suffers from obesity, and it is now apparent that this epidemic is progressively becoming global in scale. Behavioral modification, dietary programs, and medical therapies have thus far yielded meager long-term outcomes. Bariatric surgery, however, has provided an effective alternative for achieving durable weight loss in many patients with morbid obesity, and there are currently several types of surgery being employed for weight loss and the treatment of obesity associated comorbid illness.

It is estimated that over 220,000 bariatric procedures are performed annually in the United States. The most common is Roux-en-Y gastric bypass; others include sleeve gastrectomy, adjustable gastric band, duodenal switch, biliopancreatic diversion, among others. Each of these surgeries may also have important variations, and are in turn associated with unique gastrointestinal complications. For example, one version of the Roux-en-Y gastric bypass includes placement of a Silastic ring at the gastrojejunal anastomosis which can erode the overlying mucosa and cause severe pain necessitating endoscopic removal. Additionally, some surgeons create longer Roux limbs that may render ERCP unfeasible even with longer equipment. It is important to be familiar with local surgical practice and to review operative reports prior to scheduling endoscopic procedures. This will result in better procedural planning, more accurate choice of sedation and equipment, and better outcomes.

As technology has improved the endoscopist has become increasingly effective at managing a variety of surgical complications. These include basic ulcer and stricture management, as well as more complex scenarios, such as the use of stents and bioprosthetics to treat postoperative leaks and endoscopic suturing for the management of weight gain. Nonetheless, even what appears to be a routine and familiar complication has notable differences in the bariatric patient. For example, in the management of stomal ulceration,

biopsies of the gastric pouch and breath tests may not be adequate to exclude *Helicobacter pylori*. Additionally, removal of foreign material, such as suture or staples, may be needed for ulcer healing to occur. Similarly, excessive dilation of anastomotic stenosis may result in weight gain, an adverse outcome not encountered in other populations. Some endoscopic techniques utilized to manage these complications may be more aggressive than those seen in traditional endoscopic practice; however, they are significantly less invasive than surgical alternatives and should be employed when appropriate.

Numerous devices are also currently being developed for the endoscopic treatment of obesity. These include a variety of devices that work via different mechanisms of action, including implantable sleeves, balloons, neuromodulatory devices, gastric restriction devices, staplers, and suturing platforms. The favorable risk profile of these emerging therapies may offer new points of intervention for obese patients. Potential procedure categories include: *Early-Intervention Procedures* to treat obesity that is not yet severe enough to meet criteria for traditional surgery; *Primary Obesity Procedures* that may provide durable weight-loss similar to conventional bariatric surgeries; *Metabolic Procedures* that focus on obesity related co-morbid disease; *Bridge Procedures* that provide short-term weight-loss to reduce operative risk associated with morbid obesity; and *Revision Procedures* that repair failed gastric bypass.

Current management strategies do not appear to be adequately addressing the worsening obesity epidemic, and it is now clear that a full spectrum of multidisciplinary care is needed. The best approach will involve noninvasive methods of diet, exercise, and education, medications, minimally invasive endoscopic techniques, and traditional surgery. Additionally, endoscopy will continue to have a primary role in the management of surgical complications as these technologies evolve into broader applications.

I am deeply grateful to each contributor for their efforts, and I am confident that this work will help endoscopists and patients achieve better outcomes.

Boston, MA, USA Christopher C. Thompson

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The Epidemiology of Obesity

1

Kervin Arroyo and Daniel M. Herron

Introduction

Obesity is one of the most rapidly emerging health problems in the United States as well as throughout the world. The World Health Organization (WHO) [1] estimates that worldwide, more than one billion people are overweight, and 300 million are classified as obese. Additionally, the prevalence of overweight and obese young people is increasing rapidly in both the industrialized and developing world, constituting a global epidemic [2]. This prevalence indicates that the obesity epidemic will persist, since the risk of obesity in adulthood is at least twice as high for obese children as for children of normal weight [3]. The resultant public health impact is worrisome: a recent estimate [4] projects that obesity in the United States will account for more than 16% of all healthcare expenditures by 2030.

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Definition and Measurement of Obesity in Adults

No single definition of obesity is universally accepted. The WHO [5] broadly defines obesity as "abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired." This broad definition, however, is difficult to use in practice as the terms "abnormal or excessive" are vague and ill-defined.

In past decades, many investigators utilized the concept of "ideal body weight," comparing an individual's weight to standardized values, such as those in the Metropolitan Life Insurance tables [6]. These tables were compiled in 1959 and revised in 1983 based on the mortality rates of insurance policy holders in different weight categories. This system was somewhat confusing and prone to misuse, as it required individuals to be classified according to "frame size." Additionally, it did not actually indicate an "ideal" weight for a given height, but rather suggested a range of "desirable weights" for small, medium, and large frames. Although widely used in the past few decades, the concept of frame size was arbitrary and has resulted in this system falling out of favor with most current investigators.

Presently, obesity is most widely measured via the body mass index (BMI). BMI is calculated as weight divided by the square of the height and given in units of kg/m^2. Although not a perfect indicator of obesity (muscular athletes may have an elevated BMI without excessive body fat), BMI

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Table 1.1 The international classification of adult underweight, overweight, and obesity according to BMI

	BMI (kg/m^2)	
Classification	Principal cut-off points	Additional cut-off points
Normal range	18.50–24.99	18.50–22.99
		23.00–24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00–29.99	25.00–27.49
		27.50–29.99
Obese	≥30.00	≥30.00
Obese class I	30.00–34.99	30.00–32.49
		32.50–34.99
Obese class II	35.00–39.99	35.00–37.49
		37.50–39.99
Obese class III	≥40.00	≥40.00

Source: Adapted from WHO (1995, 2000, 2004) (WHO and consultation in obesity)

is reliable, objective, and easily calculated. For this reason, the use of BMI has become widely accepted by investigators and clinicians and has been formally recommended by the WHO [7].

A BMI between 18.5 and 24.9 kg/m^2 is generally considered normal. Patients with a BMI between 25 and 29.9 kg/m^2 are considered overweight, and those with a BMI greater than or equal to 30 kg/m^2 are considered to be obese [8]. Obesity is further subclassified into class I, class II, and class III obesity as indicated in Table 1.1. Patients with a BMI greater than 40 kg/m^2 (class III obesity) are considered to be "morbidly obese," and those with a BMI greater than 50 kg/m^2 are classified as "super-obese." The term "super-super obese" is less commonly used to describe a BMI above 60 kg/m^2. Due to concerns of the pejorative nature of the term "morbid obesity," less objectionable but technically equivalent terms such as "severe obesity" and "clinically significant obesity" are increasingly used (Table 1.1) [9].

Types of Obesity: Central Versus Peripheral

While BMI is a very useful indicator of obesity, the distribution of body fat, either peripheral or central, is also of substantial clinical importance. In peripheral or gynecoid obesity, fat deposits are located in subcutaneous tissues in the lower body, mainly in the hips and thighs. Individuals with central-type obesity, also referred to as android or visceral adiposity, have the majority of their fat located in the abdominal area in both subcutaneous and visceral locations.

Measurement of waist circumference has been shown to correlate well with the amount of visceral adipose tissue [10]. A waist circumference more than 88 cm for women and more than 102 cm for men is indicative of substantially elevated cardiovascular risk and need for medical intervention [11]. While the waist-to-hip ratio (WHR) is used preferentially by some investigators [12], data exist to suggest that waist circumference alone is better correlated with visceral adipose tissue, especially in women. Waist circumference provides a gross approximation of abdominal adipose tissue, while WHR indicates the relative accumulation of abdominal fat [13].

Differentiation between the different types of fat distribution has clinical relevance, as visceral central adiposity is associated with a greater risk of metabolic and cardiovascular disorders, including insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, and coronary heart disease [14, 15].

Prevalence of Obesity in US Adults

The prevalence of obesity is typically determined from broad-based surveys or population studies. Two major sources of data in the United States are the National Health and Nutrition Examination Survey

Table 1.2 Age-adjusted[a] prevalence of the overweight, obese, and extremely obese among US adults, age 20 years and over

	NHANES III 1988–1994 $n=16,679$	NHANES 1999–2000 $n=4,117$	NHANES 2001–2002 $n=4,413$	NHANES[b] 2003–2004 $n=4,431$	NHANES[b] 2005–2006 $n=4,356$
Overweight ($25.0 \le BMI < 30.0$)	33.1	34.0	35.1	34.1	32.7
Obese ($BMI \ge 30.0$)	22.9	30.5	30.6	32.2	34.3
Extremely obese ($BMI \ge 40.0$)	2.9	4.7	5.1	4.8	5.9

[a] Age-adjusted by the direct method to the year 2000 US Bureau of the Census estimates using the age groups 20–39, 40–59, and 60 years and over

[b] Crude estimates (not age-adjusted) for 2005–2006 are 32.6% with a $25 \le BMI < 30$, 34.7% with a $BMI \ge 30$, and 6% with a $BMI \ge 40$

(NHANES), conducted by the Centers for Disease Control and Prevention (CDC), and the Behavioral Risk Factor Surveillance Survey (BRFSS).

NHANES [16] is a series of studies designed to assess the health and nutrition status of both adults and children throughout the United States. The program was initiated on an intermittent basis in the 1960s and became a continuous study in 1999, evaluating a representative sample of approximately 5,000 individuals. Study participants are evaluated with an extensive questionnaire that includes demographic, socioeconomic, dietary, and health-related questions, as well as a thorough physical exam and laboratory studies.

BRFSS [17] is a much larger survey, evaluating more than 350,000 adults throughout the United States and affiliated territories. Unlike the NHANES, it is limited to a phone survey, focusing on health-related behaviors and healthcare access, particularly as they relate to chronic disease and injury. While advantageous because of its large size, the BRFSS necessarily relies upon self-reported weight (commonly underestimated) and height (commonly overestimated) and thus likely underreports the prevalence of obesity.

NHANES provides some striking statistics regarding the prevalence of obesity in the United States. The 2001–2004 study [18] revealed that 133.6 million adults were either overweight or obese. This constitutes 66%, or roughly two-thirds, of the US population. The most recent NHANES 2-year cycle was completed in 2008 and included 8,082 subjects, 71% of whom were both interviewed and examined. This study [19] showed an overall prevalence of obesity of 32.2% in men and 35.5% in women. The prevalence of both the overweight and obese increased slightly from 2004 to 68.0%.

Comparing data from different NHANES study periods provides valuable information regarding population trends in obesity. From the 1976–1980 study to the 1988–1994 study, obesity prevalence increased by 8.9% for women and 7.9% for men. Between that time and the 1999–2000 study, obesity rates continued to increase, by 8.1% for women and 7.1% for men [19]. The most recent study period available suggests that this increase may be leveling off. The increase from 1999–2000 to 2007–2008 was 2.1% for women (nonsignificant) and 4.7% points for men [19].

Obesity trends are shown in Table 1.2. From 1988 to 2006, the overall prevalence of obesity (BMI greater than 30) increased from 22.9 to 34.2%, an increase of nearly 12% over a period of 18 years. The prevalence of class III obesity (BMI greater than 40), which generally qualifies a patient for bariatric surgery, increased during the same period from 2.9 to 5.9% [19].

Worldwide obesity data are similarly concerning, although the prevalence is generally not as high as that in the United States. In 2005, according to the WHO [1, 5], approximately 1.6 billion adults (age higher than 15) were overweight and at least 400 million were obese. Projections suggest that by 2015, approximately 2.3 billion adults may be overweight (BMI greater than 25) and more than 700 million obese (BMI greater than 30) [1, 5, 7].

Table 1.3 What does the BMI-for-age percentile mean?

BMI-for-age percentile	
Below the 5th percentile	Underweight
Between the 5th and 85th percentile	Healthy weight
Between the 85th and 95th percentile	Risk of overweight
Above the 95th percentile	Overweight

Source: National Institute of Heath

Measurement of Overweight and Obesity in Children and Adolescents

Multiple approaches have been used in the past to describe and report overweight and obesity rates in children. These systems have been deemed necessary since children are still growing in both height and weight, and boys and girls mature at different rates. The CDC [20] uses growth charts based on national surveys that indicate weight for age and BMI for age. Data sources for these charts include the National Health Examination Surveys (NHES) I and II, and the NHANES I, II, and III. These data were obtained over a substantial time span, starting in 1963 (NHES I) and extending through 1994 (NHANES III). Such charts are primarily used clinically to measure growth.

Commonly used references for childhood obesity are the 85th and 95th percentiles of BMI for ages 6–19 based on data from the NHANES I (1971–1974). Use of these values has been endorsed by a WHO expert committee in 1995 [21]. Gender-specific BMI above the 95th percentile is considered to represent excessive weight (Table 1.3). BMI at 14 years of age has been shown by Laitinen et al. [22] to be an important predictor of adult obesity.

Prevalence of Obesity in US Children and Adolescents

The most recent NHANES data available for children and adolescents is the 2007–2008 study. Earlier studies had categorized heavy children and adolescents into two groups: "at risk of being overweight or obese" (BMI for age between the 85th and 95th percentile) and "overweight" (BMI for age at the 95th percentile or higher). The 2007–2008 study used the simplified nomenclature of "overweight" and "obese" to describe children between the 85th and 95th percentile BMI for age and above the 95th percentile, respectively.

For children aged 2–19 years, 31.7% had a BMI above the 85th percentile and 16.9% were above the 95th percentile [23]. BMI above the 97th percentile was noted in 11.9% overall. Age ranges were broken down into 2–5 years, 6–11 years, and 12–19 years. The incidence of BMI above the 85th percentile was 21.2% for the youngest group, 35.5% for the middle group, and 34.2% for the oldest group. The incidence of BMI above the 95th percentile was 10.4% for the youngest group, 19.6% for the middle group, and 18.1% for the oldest group. Overall, no statistically significant differences by gender were noted at any of the three BMI cutoff points of 85, 95, and 97%.

From 1976 to 2006, the obesity prevalence tripled in children 6–10 years old [23]. However, this trend may have leveled off in recent years. Data regarding prevalence of high BMI for age were compared from the 1999–2000 NHANES through the 2007–2008 studies [23, 24]. No statistically significant trend for BMI above the 85th or 95th percentile was noted for 6- to 19-year-olds during this time period, although a slight increasing trend was identified for those above the 97th percentile.

Some correlation is noted between childhood obesity and low socioeconomic status. In 2009, the CDC [25] reported that the incidence of obesity in children of low-income families was higher than that in the general population: 14.6% vs. 12.4%, respectively.

Longitudinal trends in the adolescent population were reported in a 2009 study. The National Longitudinal Study of Adolescent Health [26] followed more than 20,000 US teenagers in grades 7–12 through their early 30s. Obesity, defined as BMI above the 95th percentile on the 2000 CDC growth charts, was found in 13.3% of adolescents in 1996. This increased to 36.1%

overall by 2008. Substantial differences were noted among different subpopulations, with the highest obesity prevalence found in non-Hispanic black females (54.8%).

Prevalence of Obesity Around the World

The obesity epidemic observed in the United States is echoed in many countries around the world. As in the USA, the prevalence of obesity in Europe has tripled since 1980 [27]. As of 2007, the worldwide prevalence of overweight people ranges from 32 to 79% in men and from 28 to 78% in women as per WHO estimates [1]. Worldwide, an estimated 1.7 billion adults are overweight and 310 million are obese [28]. Overall, class III obesity (BMI greater than 40) afflicts 4.7% of the world's population.

Worldwide, the highest prevalences of obesity are found in Albania, Bosnia, and the UK; the lowest rates are noted in Turkmenistan and Uzbekistan [29]. Obesity levels are relatively low in China (with a prevalence under 5%) and high in Samoa (with a prevalence of 75%) [29]. In England, from 1993 to 2004, the prevalence of obesity in men increased from 13.6 to 24% and in women from 16.9 to 24.4% [30]. A total of 9.3 million people were obese in England in 2004.

In 2008, Kelly et al. estimated the prevalence of overweight people in the world in 2005 at 23.2% overall, 22.4% in women and 24% in men. The prevalence of obesity was 9.8% overall, 7.7% for men and 11.9% for women. These estimates suggest that obesity afflicts approximately 396 million people worldwide [31]. The WHO global database calculates the prevalence of overweight people (BMI greater than 25) and the prevalence of obesity (BMI greater than 30) [32].

The WHO data [29] suggests that significant gender differences in obesity exist in about one-third of countries studied—the prevalence of obesity was noted to be higher in men than in women in 14 of the 36 evaluated countries. Disparity also exists in the pediatric obesity rates—about 22 million children under the age of five are overweight. In Europe, the highest prevalences of overweight school-age children were found in Portugal (32% in children 7–9 years), Spain (31% in children 2–9 years), and Italy (27% in children 6–11 years) [29]. Throughout the world, an estimated 10% of all children are overweight [28].

Obesity-Related Comorbid Conditions

Obesity is associated with an increase in both morbidity and mortality [33]. Obesity is strongly correlated with cardiovascular disease through its exacerbating effects on hypertension, dyslipidemia, congestive heart disease, heart failure, and myocardial steatosis. The term "metabolic syndrome" is commonly used to refer to a group of risk factors associated with obesity. Metabolic risk factors include central obesity, elevated triglycerides, decreased high-density lipoproteins (HDL), hypertension, and hyperglycemia. Metabolic syndrome is considered to be present if three of these five findings are present [34, 35].

T2DM has been strongly linked with obesity. Approximately 80% of T2DM patients are obese [29]. T2DM is one of the most common diseases in the United States as well. As reported in the Nurse Health study [36], there is a strong correlation between diabetes mellitus and a high BMI. Insulin resistance is the main component of T2DM and is strongly related to intra-abdominal fat.

Hypertension is the most common chronic disease in society. The risk of an obese patient suffering from hypertension is five times higher than that of a normal-weight individual. Approximately 60% of cases of hypertension are considered to be related to obesity [33]. More than 100,000 cases of congestive heart disease are attributed to obesity [37]. There has been a correlation between BMI during childhood and the risk of coronary artery disease in adulthood [38]. The age-adjusted prevalence of blood pressure increases as the BMI increases [39].

Morbid obesity has been strongly correlated with a constellation of other negative effects on health including sleep apnea, gastroesophageal reflux disease, cholelithiasis, osteoarthritis,

venous thrombosis, gout, nonalcoholic steatohepatitis, endocrine changes (such as polycystic ovarian syndrome), kidney disease, skin changes, and decreased quality of life.

Mortality Associated with Obesity

Many studies have attempted to estimate the impact of obesity on overall mortality rates. According to the CDC, approximately 112,000 deaths related to obesity occur annually in the United States. In a widely publicized 2004 study, Mokdad et al. [40] utilized a thorough review of epidemiologic studies along with CDC data to calculate that 365,000 annual deaths in the USA were attributable to poor diet and physical inactivity. Several other studies link a person with BMI greater than 30 kg/m^2 to a 5–30% increased overall mortality rate compared to a person with normal BMI [41, 42].

The weight range associated with the lowest mortality may not necessarily be the one traditionally considered to be "normal," i.e., 18–25 kg/m^2. Rather, several studies suggest that mortality is minimal with overweight subjects with BMI of 25–30 kg/m^2. Other studies suggest that excess mortality associated with greater BMI decreases with age [43, 44].

Cost and Public Health Implications

The problem of overweight and obese people constitutes one of the greatest public health challenges of modern times. The substantial increase in obesity since the 1970s has been attributed to multiple underlying causes, with poor diet and inadequate physical activity as the primary bases. As the prevalence of obesity has increased over the past three decades, so has the cost of treating obesity and its associated comorbidities.

According to NIH data, $51.6 billion was expended in direct medical costs of obesity in 1995. Health costs for the obese increased to $78.5 billion by 1998. More recent estimates were provided by the WHO [45], which estimated expenditures of $118 billion in 2006 and $147 billion in 2008. Finkelstein reported that annual monies spent to treat the overweight and obese represented 9.1% of US healthcare expenditures, or $92.6 billion, in 2002.

In addition to the direct costs of treating obesity and its related comorbid conditions, indirect costs such as lost productivity contribute substantially to the negative impact of obesity on the US economy. A 1994 study estimated the total cost of workdays lost at $39.3 million and restricted activity days at $239 million. Colditz's 2005 study [46] suggested that US healthcare charges due to physical inactivity, the overweight, and obese represented about 27% of national healthcare charges.

Not surprisingly, several studies [47] have shown a correlation between obesity and the time expended at physician office visits. If the trend of obesity continues, by 2030 the USA would spend $860 billion to $956 billion in healthcare costs related to obesity, roughly 16–18% of total US healthcare cost [4].

Projected Trends in Future Outlook for Obesity

Because the causes of obesity are multifactorial and poorly understood, predicting future trends in obesity presents a substantial challenge. Overall, the prevalence of obesity in the USA and throughout the world has roughly tripled over the past three decades. In a 2007 study, Bibbins-Domingo et al. [37] estimated future US obesity rates on the basis of adolescent obesity rates in 2000. Using historical trends of how many obese adolescents become obese adults, the authors projected that by 2020, 30–37% of male 35-year-olds and 34–44% of females will be obese. Projected obesity rates for England are similarly concerning: 35–41% of men and 31–36% of women are predicted to be obese in 2012 [35]. These projections suggest that lower socioeconomic status (SES) may be correlated with this increase, with a projected obesity prevalence of 34% in lower SES subjects vs. 27.4% in the higher SES group [35].

Continuing US population studies performed by the CDC confirm that obesity has been

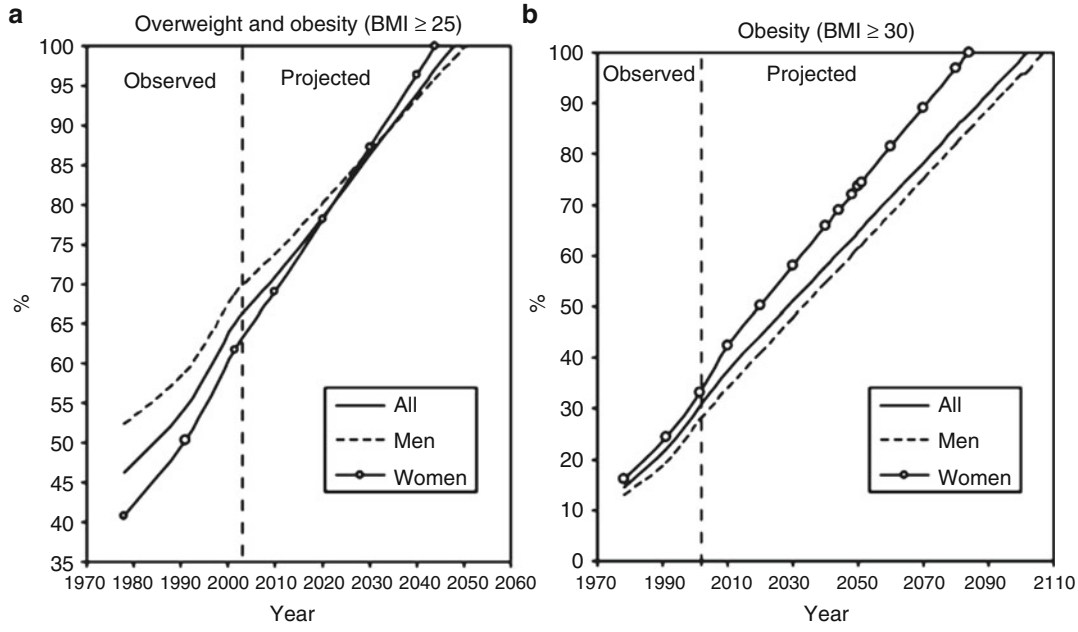

Fig. 1.1 Prevalence of obesity and overweight among US adults: observed during 1976–2004 and projected. (**a**) Observed and projected incidence of overweight or obesity (BMI >= 25). (**b**) Observed and projected incidence of obesity (BMI >=30) (Adapted from Wang 2323–30) Youfa Wang, May A. Beydoun, Lan Liang, Benjamin Caballero and Shiriki K. Kumanyika. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity 2008;16: 2323–30

increasing dramatically; only one state, Colorado, boasted a prevalence of obesity less than 20% in 2008. Although all states are being affected by increasing obesity rates, the Midwest and Southeast regions appear to be hardest hit, with six states suffering an obesity rate more than 30% as of 2008 [25]. The Long-Term Policy Research Center [48] in the state of Kentucky estimates that by 2015 the statewide prevalence of obesity will be 36%.

In 2008, Wang [4] published a study based on NHANES data from 1970 through 2004. The authors predicted that by 2030, 86% of adults will be overweight and 51% obese (Fig. 1.1). They projected that the mean BMI will increase from 27.9 kg/m^2 in 2004 to 31.2 kg/m^2 in 2030. A study by Kelly et al. [31] predicted that by 2030, 1.35 billion people worldwide will be overweight and 573 million will be obese.

Some of this alarm may need to be tempered, as some data suggest that obesity trends may be flattening out, at least for children and adolescents. In a 2010 study by Ogden, the most recent NHANES data (2007–2008) was compared to data from 1999 to 2000. No statistically significant trends in BMI were noted for 6- to 19-year-olds during this period.

Is there anything to be done to slow down the worldwide epidemic of obesity? The simplest and least expensive intervention is lifestyle modification, including more exercise and a less sedentary lifestyle. According to the CDC, at least 40% of adults in the United States do not participate in any leisure-time physical activity. Dietary changes, aimed at keeping an appropriate energy balance, are an integral part of the CDC's recommended therapeutic lifestyle changes (TLC), where the goal is to achieve decreased low-density lipoproteins (LDL), increased HDL, decreased triglycerides, decreased blood pressure, decreased glucose, and deceased weight [49].

However, once severe obesity is present, dietary and behavioral approaches are minimally effective in producing clinically significant and sustained

weight loss. While bariatric surgery has been shown to be effective in treating class III obesity on a long-term basis, logistics, cost, and fear of complications prevent its use on a population-wide basis. At present, we await the results of ongoing research studies focusing on molecular, genetic, behavioral, environmental, clinical, and epidemiologic bases of obesity. Only through better understanding of the underlying physiologic causes will an enduring solution be found.

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Pathophysiology of Obesity

2

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Introduction

The conventional wisdom is that changes in body weight follow the law of thermodynamics: if caloric intake is greater than caloric output, weight gain will occur. However, regulation of body weight is in fact a complex integration of genetic, behavioral, environmental, and physiologic factors, many of which have yet to be fully understood.

While obesity has been recognized for thousands of years, the idea that body weight is determined by a complex interaction between internal regulatory systems and the environment first received scientific attention in the mid-twentieth century. Animal studies [1–4] indicated that disruption of the ventro-medial hypothalamus produced obesity and hyperphagia, while ablation of the lateral hypothalamus resulted in aphagia, adipsia, and dramatic weight loss, suggesting that these areas were critical to the maintenance of energy balance. Subsequently, a series of parabiosis experiments [5, 6] performed between ob/ob and db/db mice (mice genetically altered to be obese) suggested that circulating factors might play a role in determining adiposity. The discovery of the leptin gene in 1994 and its receptor led to a paradigm shift in the understanding of obesity and the nature of the fat cell [7, 8].

Despite day-to-day variations in caloric intake and expenditure, the regulation of body weight is precisely controlled over long periods of time. To achieve this objective, the body possesses a wide and complex network of neuroendocrine signals originating in the gastrointestinal system, the central nervous system, and adipose tissue, among other sources to regulate both short- and long-term balances between energy intake and energy expenditure. Short-term energy balance is mainly regulated by gastrointestinal (GI) hormones such as cholecystokinin (CCK), ghrelin, and peptide YY, which are secreted on a meal-to-meal basis. On the other hand, long-term energy balance is regulated by adiposity signals such as leptin and insulin, released in circulation in amounts proportion to total body fat storage [9]. Signals reflecting energy balance are processed centrally. A disruption of this tightly regulated mechanism gives rise to obesity and type 2 diabetes mellitus (T2DM), which are strongly linked epidemiologically and experimentally.

Adipose Tissue: An Endocrine Organ

Adipose tissue is now widely recognized not only as a fat storage depot but also as an endocrine organ capable of secreting a large number of adipocytokines. Leptin, a product of the ob gene, is a 167-amino-acid-peptide hormone secreted by

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adipocytes [7, 8]. Leptin signaling is required for normal energy balance; lack of leptin or leptin receptors leads to severe hyperphagia and obesity [10, 11]. In the case of leptin mutations in both ob/ob mice and in rare human patients, leptin administration leads to a marked resolution of the syndromes [12–14]. However, in the vast majority of obese individuals commonly seen in clinical practice, leptin levels are elevated corresponding to the increased fat stores, and peripheral administration of leptin has little effect on appetite. This apparent leptin resistance may result from a decrease in the ability of circulating leptin to enter interstitial fluids of the brain or reduced leptin receptor signaling transduction in the hypothalamus and other CNS targets [15].

Leptin targets specific neurons in the brain; the best characterized are the neuropeptide Y (NPY), agouti-related peptide (AGRP) neurons and the pro-opiomelanocortin (POMC) neurons [16, 17]. Leptin directly inhibits the activity of orexigenic (appetite-inducing) NPY/AGRP neurons. Thus in conditions of low circulating leptin (such as in a food deficit), NPY and AGRP expression are increased. Conversely, in the fed state, when leptin levels are high, the anorexigenic POMC neurons are activated.

Leptin plays an important role in glucose and fat metabolism. It enhances peripheral insulin action when administered by central infusion [18]. It also plays an important role in preventing triglyceride accumulation outside of adipose tissue [19]. Leptin is thought to act indirectly on muscles and the liver to prevent triglyceride accumulation by phosphorylation and activation of a critical energy sensor, AMP-activated protein kinase (AMPK), leading to increased fatty acid oxidation [20]. Leptin resistance in obesity promotes lipid storage in tissues other than adipose tissue.

Adiponectin

Adiponectin is an anti-inflammatory cytokine synthesized exclusively by adipocytes, which increase tissue sensitivity to insulin. Animal studies [21–24] have shown that a deficiency of adiponectin is important in the pathogenesis of insulin resistance, and adiponectin levels have been shown to positively correlate with insulin sensitivity in both animals and humans. Plasma adiponectin levels in humans are decreased in both obesity and type 2 diabetes [25, 26].

Conversely, it has been shown that lifestyle changes leading to a 5–7% reduction in body weight by a combination of caloric restriction and increased physical activity for at least 6 months result in a significant increase in plasma adiponectin level in obese, type 2 diabetic patients with insulin resistance [27]. Similar results [28–30] have been reported after weight loss following bariatric surgery. Increased adiponectin levels may protect against later development of type 2 diabetes, whereas decreased adiponectin levels may predispose to development of diabetes independent of obesity [31].

Resistin

Resistin is a peptide mostly secreted by central fat and has been reported to correlate closely to hepatic insulin resistance [32]. Studies [33, 34] have demonstrated that circulating resistin levels are elevated in patients with type 2 diabetes and obesity.

Excess adiposity is also associated with increased expression of multiple inflammatory markers in fat tissue. These include interleukin-1, interleukin-6, TNF, and plasminogen activator-1, among others. These factors play a role in the insulin resistance associated with obesity.

Hypothalamic Factors

The number of hypothalamic peptides known to be involved in body weight regulation has increased dramatically over the past decade. Peptides that act as orexigenic signals (ones that stimulate appetite) include NPY, AGRP, melanin-concentrating hormone (MCH), galanin, β-endorphin, dynorphin, and enkephalin. Peptides that act as anorexigenic signals (ones that inhibit appetite) include α-melanocyte-stimulating hormone

(αMSH), cocaine, amphetamine responsive transcript (CART), corticotrophin-releasing hormone, urocortin, neurotensin, and neuromedin. The POMC is the parent molecule of several peptides concerned with weight regulation. This includes the endogenous orexigenic opioid peptides as well as α-melanocyte (αMSH), which have the opposite effect. The action of α-melanocyte (αMSH) is mediated through the melanocortin family of receptors, five of which have been identified. α-melanocyte (αMSH) activation of the MC-4 receptor and possibly the MC-3 receptor inhibits eating behavior and increases energy expenditure as deduced from antagonist and gene knockout experiments [35]. Disruption of the MC-4 receptor in rodents leads to hyperphagia and obesity [36]. MC-4 receptor mutations have been identified in humans, especially in children with early-onset obesity and a strong family history of obesity. It is currently estimated that 5% of people with severe familial early-onset obesity have abnormal MC-4 mutations [37]. Obesity has also been associated with mutations in the POMC gene, which encodes multiple transcripts. Disruption of this gene leads to deficiency of both adrenocorticotropic hormone (ACTH) and α-melanocyte (αMSH), producing a clinical syndrome of obesity and adrenal insufficiency [38, 39].

The GI Tract: An Endocrine Organ

The gut is the largest endocrine organ of the body. The past 20 years have witnessed the discovery of several novel gut peptide hormones. It is now evident that in addition to their vital role in the regulation of gastrointestinal function, a number of gut peptides play crucial roles in the control of appetite, the regulation of energy balance, insulin secretion, and glucose homeostasis.

Gut Hormones

Cholecystokinin

CCK was the first gut hormone reported more than 30 years ago to suppress appetite [40]. The importance of CCK in regulation of appetite and food intake was established with the use of selective antagonists in animal studies [41]. While CCK reduced meal intake by nearly one-half, a selective antagonist completely reversed this suppression. The CCK receptors are widely expressed in the brain, pancreas, and the vagal afferent and efferent neurons. Abdominal or gastric vagotomy has been shown to eliminate the satiety effect of CCK [42].

Ghrelin

Ghrelin is produced in the fundus of the stomach [43]. It was identified as the endogenous ligand for the receptor responsible for growth hormone secretion. Subsequently, it was found in rodents that ghrelin is a potent stimulus for eating and produces adiposity [44]. Ghrelin is transported to the brain, where it stimulates NPY/AGRP neurons in the arcuate nucleus of the hypothalamus. Although infusion of ghrelin in humans induces hunger and increases feeding, endogenous levels are low in obese individuals and increase with weight loss [45, 46]. Plasma ghrelin concentration has an inverse relationship with body weight in humans.

The rise in ghrelin level is not seen following gastric bypass surgery, which may help to explain the success of the procedure in mediating and sustaining weight loss in obese individuals [47, 48].

Peptide YY

Peptide YY (PYY) is synthesized and secreted throughout the intestine. PYY release is stimulated by food intake, particularly by fatty meals. PYY acts on both the brain and the intestine. It increases fluid absorption in the intestine and delays gastric emptying [49]. In the brain, the "3–36" form of PYY has significant effects on appetite. Intravenous administration in humans reduces caloric intake and increases satiety [50]. However, intracerebroventricular (ICV) injection of PYY clearly increases feeding, possibly by targeting a different receptor subset [51].

PYY levels are low in morbidly obese patients and are reported to increase after weight loss secondary to gastric bypass surgery [52].

Glucagon-Like Peptide-1

Glucagon-like peptide-1 (GLP-1) is produced by processing the preproglucagon gene in response to food intake by the L cells of the small intestine and neurons within the nucleus tractus solitarius (NTS) of the brainstem [53]. GLP-1 levels rise after a meal and reduce on fasting [54]. It is now recognized that GLP-1 and other incretin peptides such as gastric inhibitory peptide (GIP) are responsible for the incremental release of insulin that occurs after oral administration of glucose relative to that after an equivalent amount of glucose is administered intravenously. GLP-1 lowers blood glucose by increasing glucose-mediated insulin release, delaying gastric emptying and inhibiting glucagon release. ICV administration of GLP-1 significantly decreases food and water intake [55]. Some reports indicate that GLP-1 is reduced in obese subjects, and that the anorectic effect of GLP-1 is preserved in obesity [56, 57].

GLP-1 analogues have now been shown in clinical practice to be very effective antidiabetic agents with the additional benefit of weight loss. Increased levels of GLP-1 have been consistently reported in several animal and human studies [58, 59] following Roux-en-Y gastric bypass surgery. The gastrointestinal hormonal changes occur even before significant weight loss takes place, which may account for the early improvement or resolution of diabetes following gastric bypass surgery.

Oxyntomodulin

Oxyntomodulin is also a cleavage product of preproglucagon and is secreted along with GLP-1 and PYY following ingestion of a meal. Its secretion is proportional to the amount of calories ingested [60]. Peripheral administration of oxyntomodulin to rodents and humans reduces food intake [61].

Role of the Gut in Obesity and Diabetes

The gastrointestinal tract is not commonly considered in discussions of the etiology of insulin resistance, obesity, and type 2 diabetes. Attention is usually focused on the liver, muscle, adipose tissue, and pancreatic β cells, which are the major peripheral organs and tissues involved in the control of whole-body energy homeostasis. However, there are a number of reasons why the gastrointestinal tract should be included in these considerations.

The gastrointestinal tract is the first organ to come into contact with the nutrient load of a meal, and as an endocrine organ, it transmits this information via hormonal secretion and direct neural signaling to peripheral tissues (including the brain), thereby modulating the control of metabolism. As a consequence, the gastrointestinal tract has a major role in the integration of nutrients with metabolic responses, and changes in its anatomy can predictably have profound effects in the control of metabolism.

In fact, the remarkable efficacy of bariatric surgery in inducing profound and long-lasting weight loss cannot be explained simply by a reduction of energy intake and/or absorption. A growing body of evidence indeed supports a role for neuroendocrine mechanisms in the control of energy balance, increased satiety, and reduced body weight after bariatric operations.

Furthermore, the evidence that surgical manipulations of the intestine has direct influence on T2DM independent of weight loss is consistent with the hypothesis that the gastrointestinal tract has a physiological role in glucose homeostasis and might also have a role in abnormalities in glucose homeostasis, such as insulin resistance and T2DM [62].

Dysfunction of the gastrointestinal tract could provide a potential explanation for the link between excess nutrition and the development of insulin resistance and T2DM. The passage of excess nutrients in general or an increase in the passage of specific nutrients through the gastrointestinal tract could trigger intestinal neuroendocrine dysfunction, possibly owing to