Update on Obesity

Daniel H. Bessesen

Division of Endocrinology, Denver Health Medical Center and Division of Endocrinology Metabolism and Diabetes, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado 80045

Endocrinologists have unique skills in evaluating and caring for patients with metabolic diseases. As such, they have a special role to play within the organizations in which they work as leaders in the approach to managing obese patients. Recent epidemiological data demonstrate that the prevalence of obesity is beginning to plateau. However, the rate of severe obesity in adults and the prevalence of overweight among children continue to grow, suggesting that in the future there will be an increasing burden of obesity-related illnesses. A number of recent studies have identified a number of novel mechanisms that predispose to obesity including several newly identified genes, the role of intestinal microflora, and even social networks. The selection of treatment for obese patients remains a complex issue. Recent studies demonstrate that a range of dietary approaches including the Atkins diet can provide modest weight loss, although the key feature appears to be adherence in the dietary strategy. High levels of physical activity appear to be necessary to maintain a reduced state, although modest increases in activity improve fitness. Although the new understanding of biology of weight regulation has provided a wide range of potential drug targets, available pharmacotherapy options remain limited although a number of potential targets show promise. Recent data provides the most enthusiasm for surgical treatment of obesity. Several recent studies demonstrate a reduction in mortality and dramatic benefits in diabetes in obese patients treated surgically. Questions remain as to the best surgical approach and the cost effectiveness. Research advances in obesity continue to move at a rapid pace and raise hopes for more effective management strategies in the future. **(*J Clin Endocrinol Metab* 93: 2027–2034, 2008)**

Obesity is a degree of excess weight that is associated with adverse health consequences. In adults, overweight and obesity are defined using the body mass index (BMI), which is the ratio of weight in kilograms divided by the height in meters squared. Overweight is defined as a BMI between 25.0 and 29.9 kg/m^2, and obesity is defined as a BMI higher than 30.0 kg/m^2 (1). In children, the term overweight has been preferred because of the potential for stigmatization associated with the term obesity. In the United States, criteria for overweight in childhood are based on the 2000 Centers for Disease Control BMI-for-age growth charts with values at or above the 95th percentile categorized as overweight (2). Research on obesity spans a broad range of disciplines from molecular biology to epidemiology. Progress has been made over the last year on many fronts. In this paper, I will highlight a few recent developments on the epidemiology of obesity, the health effects of excess weight, recent advances in our understanding of the causes of obesity, and new aspects of treatment including diet, physical activity, pharmacotherapy, and surgery.

Epidemiology of Obesity

Although it is clear to all that obesity remains a serious public health problem, a number of new studies provide insights into the current magnitude of the problem and associated health complications. Within the United States, there are two sources of data on the prevalence of obesity (www.cdc.gov/nccdphp/dnpa/obesity/trend/index.htm). The first is the Behavioral Risk Factor Surveillance Survey. This nationally representative sample provides state-by-state data on the prevalence of obesity yearly. However, the Behavioral Risk Factor Surveillance Survey data come from self-reports and, given the known inaccuracies of self-reported height and weight, likely result in an underestimate of the actual prevalence of obesity. The other data set is the

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2008-0520 Received March 4, 2008. Accepted April 15, 2008.

Abbreviations: BMI, Body mass index; CHD, coronary heart disease; NHANES, National Health and Nutrition Examination Surveys; PYY, peptide YY.

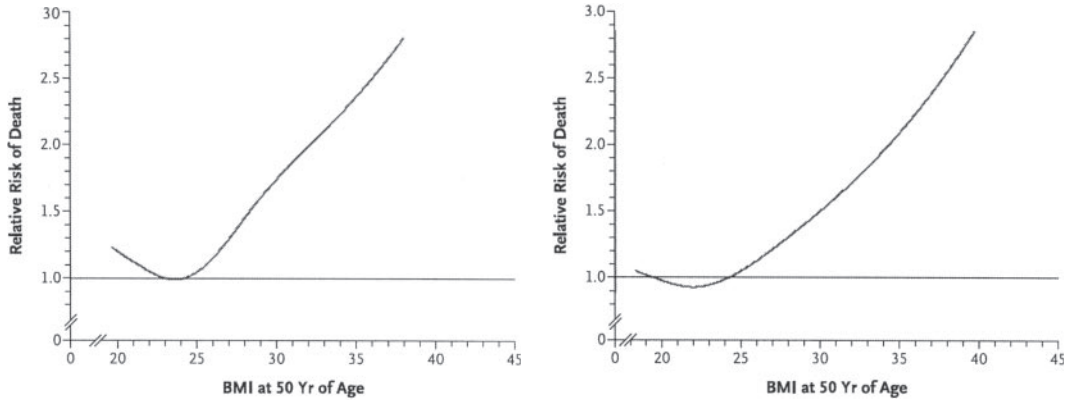
National Health and Nutrition Examination Surveys (NHANES) conducted by the Centers for Disease Control (3). This ongoing study uses directly measured heights and weights in a much smaller sample to describe the prevalence of obesity in the United States. The most recent data from this ongoing study released in November of 2007 demonstrates that over the last several years there has been a plateau in the prevalence in obesity in the United States, with over 72 million adults having a BMI greater than 30 kg/m^2. This represents 33.3% of men and 35.3% of women. In the 2003–2004 period, the prevalence was 31.1% in men and 33.2% in women, not significantly different from the more recent numbers. This plateau in the prevalence of obesity suggests that either public health efforts to control the problem are beginning to have effects or that the subset of the population that is susceptible to obesity has already manifested the phenotype.

What is happening to the problem of obesity in other countries? The World Health Organization monitors the prevalence of obesity around the world. Although prevalence rates vary dramatically from country to country, the World Health Organization estimates that over 1.7 billion people around the globe are overweight and 310 million are obese. The problem of obesity is growing in many developing countries (http://www.who.int/topics/obesity/en/). Rates of obesity have tripled in the last 20 yr in the developing world with 10% of the world's children currently overweight or obese. The Middle East, Pacific Islands, Southeast Asia, and China are facing the greatest challenges (4). These dramatic increases in the prevalence of obesity raise serious concerns about a future characterized by increasing rates of diabetes and other obesity-associated disorders around the globe.

Although obesity is clearly associated with an increased risk for diabetes, coronary heart disease (CHD), degenerative joint disease, and a number of cancers, there has been controversy over the relationship between BMI and mortality. This controversy has made some feel that concern over the risks of obesity is overstated. Data from NHANES comparing the relationship between BMI and mortality in cohorts from the 1960–1970s to the 1990–2000s suggested that increased mortality rates seen with BMIs of 25–30 kg/m^2 in the early cohorts were not seen in later cohorts (5). The author's ideas for explaining these findings included the notion that overweight and obese individuals receive more aggressive treatment for diabetes, hypertension, hyperlipidemia, and other metabolic disorders now than they did in previous generations reducing their mortality (6).

A new study by Adams and co-workers published in 2006 addresses the relationship between mortality and weight more definitively than previous studies (7). This study reported 10-yr mortality rates in more than 500,000 Americans who were 50–71 yr old at the time of enrollment in the National Institutes of Health-American Association of Retired Persons (NIH-AARP) cohort. Because of the large sample size, this study included a direct analysis of individuals who were nonsmokers and had no preexisting illness. These factors are known to affect the relationship between mortality and weight and have been controlled for statistically in most previous studies. The results of this study depicted in Fig. 1, A (men) and B (women), demonstrate a 20–40% increase in mortality in both men and women who were overweight in midlife, and a 2- to 3-fold increased risk of mortality among obese individuals. These results provide strong support for the idea that even modest increases in weight may reduce lifespan. They also suggest that there will be substantial costs associated with the obesity epidemic as the population ages.

How will increasing levels of obesity in children affect disease prevalence in the future when these individuals are adults? This question was addressed by Bibbins-Domingo *et al.* (8) in a study in 2007. They estimated the prevalence of obesity in 35-yr-olds in the year 2020 based on the prevalence of adolescent overweight in 2000 and then modeling subsequent weight gain and disease risk. They predict that in 2020, the prevalence of obesity among 35-yr-olds will be 30–37% in men and 34–44% in women. As a consequence, they project that the prevalence of CHD will increase by 5–16% with more then 100,000 excess cases of CHD attributable to obesity. Similarly concerning results were reported by Baker *et al.* (9). This study from Denmark



Men who had never smoked (n=54,925; 18,417 deaths)

Women who had never smoked (n=56,156; 2867 deaths)

FIG. 1. Relative risk of death as a function of BMI at age 50 for men (A) and women (B). The data have been adjusted for age, race or ethnic group, education, alcohol consumption, and physical activity. [Reproduced with permission from K. F. Adams *et al.*: N Engl J Med 355:763 (7). ©Massachusetts Medical Society.]

looked at the prevalence of CHD in a cohort of over 14,000 adult men and women who had childhood BMI data available from measurements taken when these individuals were 7–13 yr of age. This large study with a long period of direct follow-up demonstrated a positive linear association between BMI in childhood and the risk of CHD in adulthood as well as age of onset and risk (Fig. 2). These two studies highlight the serious impact that the growing prevalence of childhood obesity in the United States and around the world will have on adverse health events and costs of care in the future and suggest continuing efforts to prevent weight gain in children are justified.

In addition to producing illness, obesity can reduce functional capacity. A recent paper by Alley examined the relationship between obesity and disability in the period of 1998–2004 (10). This study used NHANES data to examine how changes in the weight of the population affected the prevalence of disability defined as impaired activities of daily living and/or functional impairment. This study found that over this time period, the prevalence of disability among obese individuals grew relative to that seen in normal-weight individuals. In the later time period extending to 2004, 42.2% of obese individuals reported some degree of functional impairment compared with 26.6% in normal-weight individuals. For impairment of activities of daily living the numbers were 5.5% in obese compared with 3.5% in normal weight individuals. This study highlights the increasing social costs associated with the growing prevalence of obesity, in particular serious obesity.

In the area of epidemiology of obesity, the good news is that rates of obesity in the United States appear to be reaching a plateau. The bad news is that the prevalence of obesity continues to grow around the world, and increasing evidence supports the notion that obesity is associated with morbidity, disability, and increased rates of mortality.

New Insights into the Causes of Weight Gain

Although there is concern over the public health challenges posed by the problem of obesity, hope for the development of new treatments grows out of progress that is being made in our understanding of the systems that regulate body weight and the genes that are associated with weight gain. The most compelling recent data of genetic linkage comes from the FTO (fat mass and obesity-associated) gene. A number of variant alleles in the first intron of FTO have been shown in several independent genome-wide association studies to be strongly and significantly associated with obesity-related traits (11). Individuals who are homozygous for the high-risk alleles weigh roughly 3 kg more than those individuals homozygous for the low-risk allele (12–14). Homozygosity appears to occur in roughly 16% of several populations that have been studied. The product of this gene appears to be an enzyme that is likely involved in demethylation of single-stranded DNA in hypothalamic nuclei involved in regulating energy balance (15). Farooqi and co-workers (16) have been looking for alterations in the leptin receptor (LEPR) gene in individuals with severe early-onset obesity, especially those who were the product of consanguineous families. They found that 3% of 300 of these subjects had missense or nonsense mutations of the LEPR. Although this rate of gene abnormalities is substantially higher than the prevalence of mutations of the leptin gene, it still accounts for an extremely small number of cases of obesity. Herbert and co-workers performed a dense whole-genome scan of DNA samples obtained from subjects enrolled in the Framingham Heart Study and a number of other large cohort studies looking for gene loci that were associated with obesity. They identified a common gene variant near the INSIG2 (insulin-induced gene 2) that was present in roughly 10% of their cohorts and was associated with roughly 2 kg of excess weight compared with those individuals with low-risk alleles (17). Although the mechanism by which this high-risk allele increases the risk for

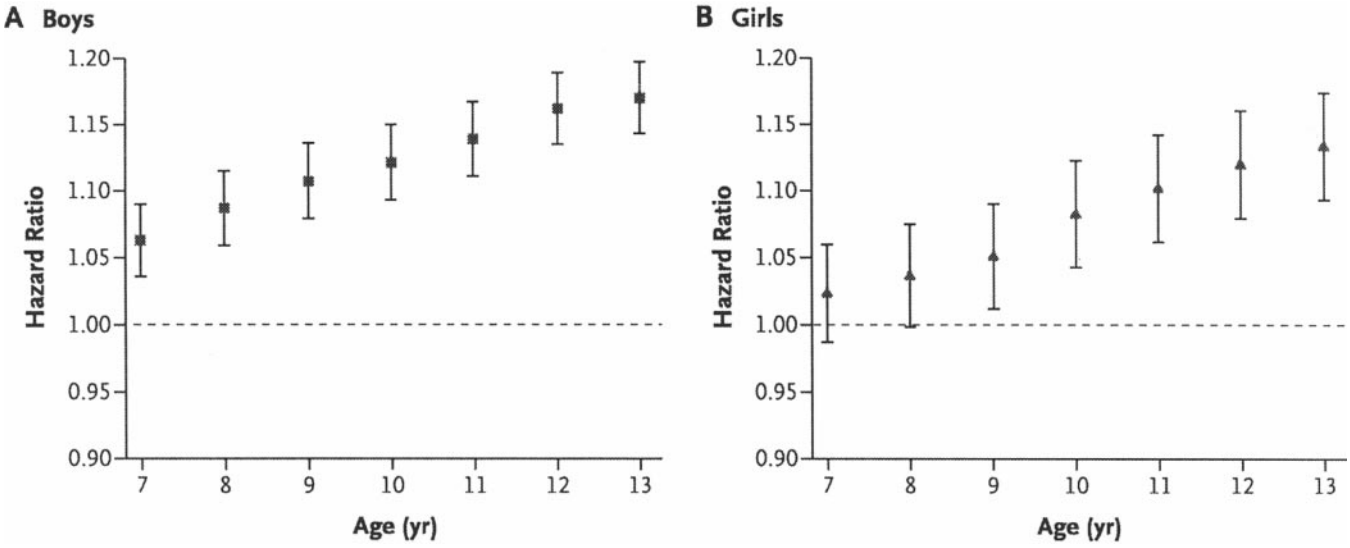


FIG. 2. The risk of coronary artery disease in adulthood as a function of BMI in childhood. The figure depicts the increase in risk for a CHD event (fatal or nonfatal) associated with a 1 U increase in BMI z-score at each age from 7–13 yr. Data are from 139,857 boys (A) and 136,978 girls (B). [Reproduced with permission from J. L. Baker *et al.*: N Engl J Med 357:2329 (9). ©Massachusetts Medical Society.]

obesity is not known, evidence from animal models suggests that it may promote abnormalities in triglyceride metabolism. This brief review of recently identified genes that appear to be associated with weight gain highlights a number of features about this line of research. First, the amount of weight gain associated with these genes, although statistically significant, is fairly small, suggesting either that the environment plays a substantial role it the current epidemic of obesity or that we are yet to find the genes that are most important. Alternatively it may be that many genes, each with relatively small effects, come together in an individual to produce clinically significant weight gain. In any event, it seems likely that it will be some time before these advances in the genetics translate into advances in the clinical care of most obese individuals.

Although it is attractive to try to attach pathogenic importance to one gene, it is increasingly clear that systems and networks of systems ultimately conspire to promote or protect against weight gain. A dramatic example of this view comes from an innovative study by Christakis and Fowler (18) on the role of social networks in the spread of obesity. This study drew on information obtained from individuals enrolled in the Framingham Heart Study who were asked to identify their friends in an effort to facilitate long-term follow-up and retention in that study. The investigators used these data on over 12,000 interconnected individuals followed for more than 30 yr to examine the effects of relationships on weight gain. They found that a person's risk of becoming obese over the period of follow-up increased by 57% if one of their friends became obese. The effect was present but of smaller magnitude if the social contact was a sibling or spouse. By highlighting the importance of significant interpersonal relationships in human behavior, this study potentially has implications not only for understanding the pathogenesis of weight gain but also the prevention and treatment of this condition.

In another novel line of research, Gordon and colleagues unexpectedly found that intestinal bacteria appear to have an important effect on body weight. Two recent papers in mice (19) and human subjects (20) extend their work in this interesting area. They found that the intestinal flora of obese mice and human subjects are enriched in firmicutes species and relatively deficient in bacteroidetes. They further found that transplantation of intestinal flora from obese mice to lean mice promoted weight gain. In obese humans who lost weight, intestinal flora began to look more like that of lean individuals, raising questions as to whether these changes are primary or secondary to some aspect of the diet or energy balance. These intriguing studies also open the possibility of novel therapeutic approaches.

Diet Therapy

Overweight and obese individuals have four choices: accept their weight where it is, change their diet and physical activity behaviors, use a weight loss medication, or have weight loss surgery. These options go from low risk/low effectiveness to greater risk/greater effectiveness. The foundation of any weight loss strategy is the diet and physical activity behaviors of the individual. But what advice should a physician give patients in these areas? What is the best diet and how much physical activity is needed to produce weight loss and maintain the reduced state? Several recent studies provide insights into these important questions.

The A-Z study conducted by Gardner and colleagues (21) directly compared the effectiveness of the Atkins (low carbohydrate), Ornish (high carbohydrate, low fat), LEARN (behavior modification approach), and Zone (high protein, moderate fat) diets in a randomized 1-yr trial in 311 overweight or obese premenopausal women. Unlike many weight loss studies where 35–45% of subjects drop out in the first year (22–24), subject retention in this study was 75–88% in each group. Although all groups lost weight, the weight loss produced by the Atkins diet (5.5%) was significantly greater than the other groups. The strengths of this study are its size and the high retention rates. One weakness of this study is the lack of data on adherence rates. This is particularly relevant in that a similar previous study by Dansinger testing the relative effectiveness of several popular diet approaches demonstrated that the most important factor associated with weight loss on one of these programs was the ability of the individual to adhere to the prescribed diet (25).

One problem seen in virtually all studies of dietary therapy for obesity is weight regain after the period of weight loss (26–29). There is a growing belief that specific approaches to weight maintenance need to be developed and that these may be different from approaches used for producing weight loss. A study by Wilfley *et al.* (30) published in 2007 addressed this important issue in a group of 204 healthy overweight children. After a period of weight loss, children were randomly assigned to a control condition of usual care, a maintenance condition that emphasized behavioral skills, or a maintenance condition that emphasized social support including strategies for dealing with teasing. This 2-yr treatment study demonstrated that both maintenance strategies were superior to the control condition in sustaining weight loss. Children with higher levels of social functioning randomized to the social facilitation arm did the best. This study emphasizes the value of controlled trials examining specific hypothesis-based weight-maintenance strategies.

In summary, dietary modifications that reduce energy intake remain central to any weight loss strategy. Experimental data now support the use of a range of dietary strategies including low-carbohydrate, low-fat, and high protein diets. It appears that the central question now is not what the best diet is, but rather how we can help people adhere to a dietary program for the long term. In addition, data are still lacking as to the health benefits of dietary therapy using hard endpoints such as cardiovascular morbidity and mortality.

Exercise

How about physical activity recommendations? In the last few years, progress has been made in a number of related areas. A study by Church *et al.* (31) examined the dose-response relationship between exercise and fitness. This study randomized 464 sedentary obese/overweight postmenopausal women to three levels of exercise and measured a number of health-related endpoints. The low-dose group exercised 72 min/wk, whereas the high-dose group exercised 191 min/wk. This study showed a

linear dose response with measurable improvements in fitness even at the lowest treatment dose. This study supports the recommendation that even modest increases in physical activity can produce measurable benefits, but as one might suspect, more exercise had greater effects. The study is limited in that it does not provide information about the long-term risks (musculoskeletal or sudden death) of higher doses of exercise in less healthy women or men, and as is true with dietary therapy, important questions remain about the benefits of exercise on hard endpoints such as CVD risk, although new information indirectly addresses this latter issue. In the latest of a series of studies of the relationship between fitness, obesity, and all-cause mortality, Blair and co-workers (32) examined data from a prospective study of over 2600 adults 60 yr of age or older followed for a mean of 12 yr. This analysis demonstrated that the increased risk of overall mortality seen in individuals with increased waist circumference was abolished if these abdominally obese individuals were fit. Higher levels of fitness were inversely associated with all-cause mortality in both normal-weight and obese individuals after correcting for a number of potential confounding variables. In fact, within the high-fitness-level group, increased BMI did not confer any added mortality risk. These data are consistent with previous studies in younger individuals (33–35), and they support the recommendation that older people remain physically active independent of any effects on weight. Many physicians promote increased physical activity levels by prescribing pedometers and step goals. A recent metaanalysis of this approach by Bravata *et al.* (36) provides support for continuing this practice.

Drug Therapy of Obesity

Over the last several years, there has continued to be dramatic advances in our understanding of the mechanisms that regulate body weight. Morton *et al.* (37) have written an excellent review of this area of research. Although patients and physicians alike are hopeful that these advances in basic science will translate into new therapeutics, progress in the pharmacotherapy of obesity has been slow. The greatest excitement had been generated by a new class of medications that block the cannabinoid 1 receptor (CB-1R). The endocannabinoid system is a fascinating neurotransmitter system that is widely distributed in the brain and peripheral tissues. The first drug in this class to reach the Food and Drug Administration (FDA) was rimonabant (Sanofi Aventis). A recent metaanalysis by Christensen *et al.* (38) summarizes the existing clinical data on this compound, which is currently approved, prescribed, and used in many countries around the world. This analysis described the findings in a total of 4105 participants of published clinical trials. These trials demonstrated that rimonabant produced a statistically significant 5% weight reduction compared with placebo. However, there were a number of adverse side effects of this medication, the most concerning being an increased prevalence of depressed mood and anxiety in individuals receiving medication compared with placebo. Summaries of the discussions that took place at the FDA in June of 2007 including the data presented on adverse neurological events, depression, suicidal ideation, attempted suicides, seizure risks, and the potential for central nervous system toxicity can be viewed at http://www.fda.gov/OHRMS/DOCKETS/AC/07/slides/2007-4306s1-00-index.htm. After this hearing, the FDA acknowledged the documented ability of rimonabant to produce weight loss and improve markers of metabolic health. However, the FDA did not approve rimonabant due to concerns over potential psychological side effects. This decision has apparently not slowed development of other drugs in this class including taranabant (Merck), which will likely be the next to come before the FDA this year as well as other related compounds under development at Pfizer, Lilly, and Solvay/Bristol Meyers Squibb. Further studies are being conducted, and rimonabant will likely be reviewed by the FDA in a few years once this new data become available.

There are a number of novel targets for pharmacotherapy that have been identified or have come into greater promise during 2006–2008. A group from Japan used a subtraction cloning strategy to identify a new satiety molecule that they named nesfatin (NUCB2) that is expressed in hypothalamic nuclei involved in feeding and reduces food intake in a dose-dependent manner when injected intracerebroventricularly into the brain of rats (39). It reduces body weight when injected daily for a period of 10 d. In contrast, injection of a neutralizing antibody is associated with increased food intake. Another molecule that is undergoing intense scrutiny is peptide YY (PYY). PYY 3–36 has been shown to modulate neural activity in brain systems involved in food intake in a manner that reduces spontaneous food intake (40). Studies have demonstrated that this molecule can increase satiety, reduce hunger, and reduce food intake in humans when given iv or sc (41). Recent data using intranasal administration have produced mixed results (42). However, studies continue, and there remains hope that this molecule or a related molecule that acts on its cognate receptor may have utility in weight management. There have, however, been some bumps in the road for some new agents. Perhaps the most striking of these was a neuropeptide Y Y1 and Y5 receptor antagonist that was being developed by Merck (MK0557). This drug was tested in a 1-yr trial involving more than 1600 overweight and obese subjects but failed to show clinically meaningful weight loss (43). Although there was initially great enthusiasm for leptin as a weight loss medication, this molecule, which appears to play a fundamental role in body weight regulation in animals, has failed to find a niche in human weight therapy. Although one could be discouraged by this lack of progress in the drug treatment of obesity, there remains tremendous interest on the part of basic researchers funded by the National Institutes of Health and other federal organizations as well as pharmaceutical companies in developing weight loss medications and tremendous opportunities that have grown out of new scientific developments on the regulation of body weight.

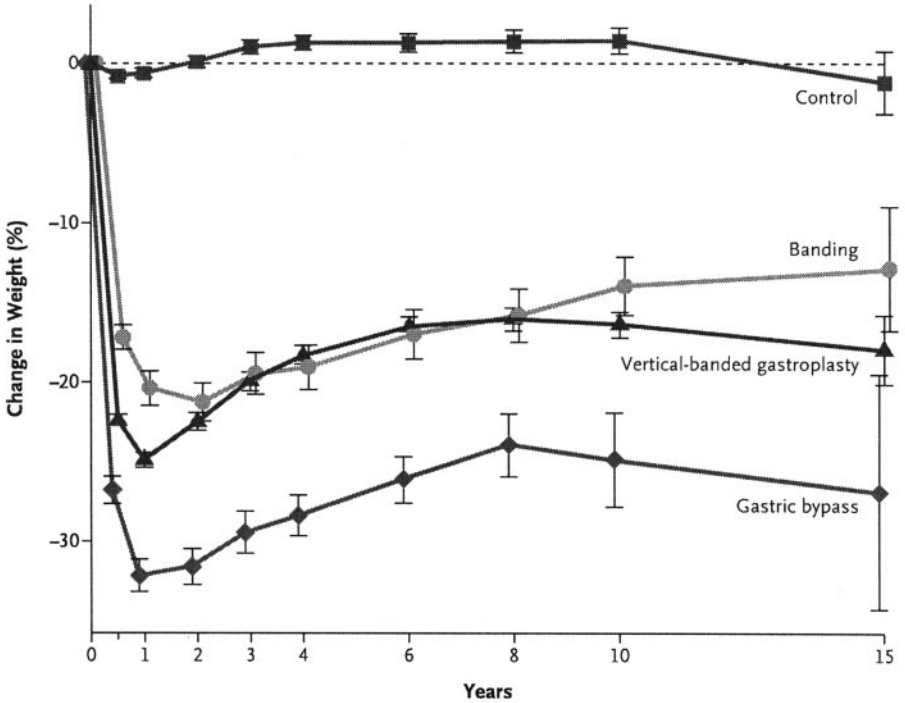
It seems likely that a substantial increase in the use of medications to help patients lose weight would ultimately depend on developing medications that promote a degree of weight loss that is attractive to both patients and physicians. It also seems that this degree of effectiveness will more likely be achieved through the use of combinations of treatments. This is an area that has attracted growing interest over the last several years. Combination therapy could mean coadministration of medications that act through different mechanisms, adding weight loss medications to an aggressive behavior modification approach, or prescribing weight loss medications along with newer less aggressive

surgical approaches that have lower risk than gastric bypass but also less effectiveness. Several companies have begun studies of combination drug formulations including Qnexa, a proprietary combination of phentermine and topiramate, (Vivus Inc.) and Contrave (naltrexone and buprobion) and Empatic (a sustained-release combination of zonisamide and bupropion) both being developed by Orexigen Therapeutics Inc. Amylin Pharmaceuticals also has an active preclinical program in combination pharmacotherapy combining as many as three medications (pramlintide, PYY3–36, and leptin) in an effort to maximize weight loss.

In summary, although there is hope that pharmacotherapy will eventually improve the treatment outlook for obese patients, currently available agents deliver a degree of weight loss that has not been very attractive to patients or insurers, and a number of obstacles have impeded progress in the development of newer more effective medicines. It is hoped that by combining medications that act through different mechanisms or combining medications with other weight loss strategies, a higher degree of weight loss will be achieved with less toxicity. If this can be achieved, perhaps there will be more enthusiasm on the part of clinicians for embracing weight loss treatments.

Surgical Therapy

Perhaps the greatest excitement in obesity treatment has come from increasing evidence of the effectiveness of surgical approaches. Many patients are not satisfied with the degree of weight loss they achieve with behavior modification or drug therapy. Surgical therapies currently offer the greatest likelihood of the highest degree of weight loss. However, questions have persisted about whether bariatric surgery has long-term beneficial effects on mortality. Two papers published in the *New England Journal of Medicine* in 2007 directly addressed this issue. The first is the long-term follow-up of the Swedish Obesity Study (SOS) (44). This study was a prospective controlled trial of more than 4000 individuals, half of whom had weight loss surgery and half of whom had medical therapy. Many of the patients in the surgical arm had an older gastric restriction procedure that is not used any more because it had lower levels of efficacy and greater risk than currently used approaches. The degree of weight loss produced by surgery compared with nonsurgical treatment is depicted in Fig. 3. For the first time and despite the limitation of the types of surgery done, the long-term follow-up from this well done study demonstrates almost a 30% reduction in mortality in surgically treated patients compared with those treated medically (Fig. 4). Although an expected decrease in mortality due to diabetes was seen, the more dramatic effect was seen in the reduction in death rates due to cardiovascular disease and especially cancer. Although it has long been known that obesity is associated with increased rates of certain cancers, this study provides compelling evidence that weight loss decreases the risk of cancer associated with obesity. Data on the specific types of cancer that subjects in each arm of the trial developed were not



No. Examined									
Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

FIG. 3. The mean percent weight change as a function of time after bariatric surgery. The results are depicted for the 15 yr after surgery as a function of the type of surgery performed. [Reproduced with permission from L. Sjostrom *et al.*: N Engl J Med 357:741 (44). ©Massachusetts Medical Society.]

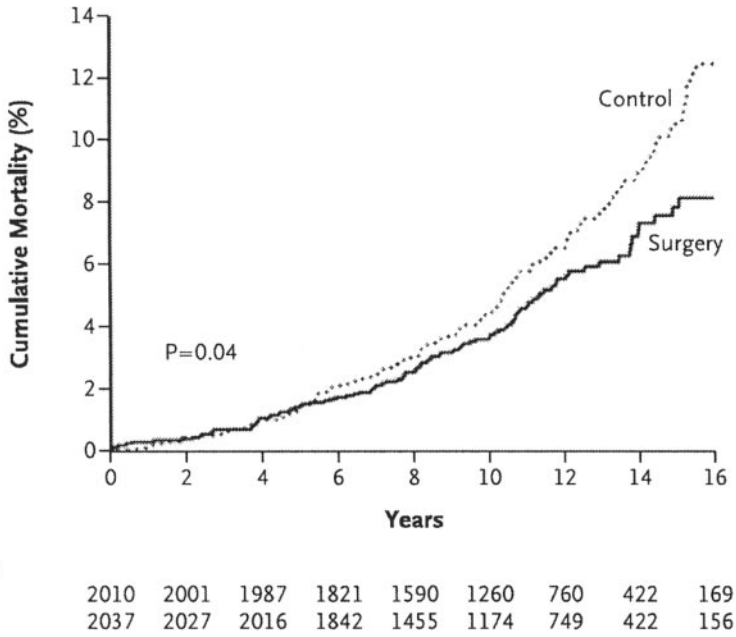


FIG. 4. Adjusted cumulative mortality of subjects who had bariatric surgery compared with controls. [Reproduced with permission from L. Sjostrom *et al.*: N Engl J Med 357:741 (44). ©Massachusetts Medical Society.]

presented in this paper. A second study by Adams *et al.* (45) examined this same issue using a retrospective cohort design. This study reported mortality rates in 9949 patients who had undergone bypass surgery and were compared with a control group identified through driver's license records. With a follow-up of 7.1 yr, all-cause mortality in those individuals who had undergone weight loss surgery was 40% less than that seen in the control group. As was found in the SOS study, there was a 92% reduction in mortality due to diabetes and a 60% reduction in mortality due to cancer. Because mortality due to cancer was a greater fraction of the overall death rate, the benefits in reduction of cancer rates prove to be the more important health benefit in this study as well. No data were presented on the specific types of cancer in the two cohorts. Surprisingly, rates of death caused by accidents and suicide were 58% higher in the surgery group compared with the control group. Although the magnitude of this difference was small enough that the overall mortality after gastric bypass surgery was significantly reduced, this increase in accidents and suicide should not be dismissed and merits further study. In summary, although they are not randomized controlled trials, these two studies provide strong evidence that gastric bypass surgery and even gastric restriction surgery has beneficial affects on mortality.

Another recent study examined the potential benefits of laparoscopic banding procedures on diabetes control (46). In this study by Dixon *et al.* (46) from Victoria, Australia, a group of 60 obese patients with recently diagnosed type 2 diabetes and a BMI of 30–40 kg/m^2 were treated in an unblinded randomized controlled trial between 2002 and 2006. Half the group received conventional diabetes therapy focusing on weight loss by lifestyle change, whereas the intervention group received a laparoscopic adjustable gastric banding along with their usual care. Remission of type 2 diabetes defined as a fasting glucose less then 106 mg/dl and glycosylated hemoglobin less than 6.2% while taking no medications occurred in 73% of the surgical group but only 13% of the conventionally treated group. The surgically treated patients lost an average of 20.7% of their baseline weight, whereas the conventionally treated group lost only 1.7% at 2 yr of follow-up. Remission of type 2 diabetes was directly related to the degree of weight lost. There was no evidence of any special benefit of the banding procedure *per se* on glucose homeostasis. The surgical results at this site are outstanding, and as a result, questions could be raised about how generally this study can be applied. However, this was a well done study that directly compared standard medical therapy to surgical therapy and demonstrated a dramatic advantage of surgical therapy in the management of diabetes. Whether this approach will be cost effective remains to be shown, although cost data were collected by this group, and future publications should address this important issue.

Summary and Conclusions

Obesity is one of the most common health problems in the United States and around the world, and it underlies many of the most common illnesses seen in medical practice. Because of their special expertise in the management of metabolic diseases that require extensive self-care, endocrinologists have an opportunity to not only provide excellent care for their patients with weight problems but to also provide leadership in the their local practice sites and communities as well as regionally in how best to address the serious public health problem of obesity. New research developments raise the hope that more effective treatments are on the horizon for this challenging clinical condition.

Acknowledgments

Address all correspondence and requests for reprints to: Daniel H. Bessesen, M.D., Division of Endocrinology, Denver Health Medical Center and Division of Endocrinology Metabolism and Diabetes, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado 80045. E-mail: daniel.bessesen@uchsc.edu.

References

1. 1998 Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. National Institutes of Health. Obes Res [Erratum (1998) 6:464] 6(Suppl 2):51S–209S
2. **Chinn S** 2006 Definitions of childhood obesity: current practice. Eur J Clin Nutr 60:1189–1194
3. **Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM** 2006 Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 295:1549–1555

4. **Hossain P, Kawar B, El NM** 2007 Obesity and diabetes in the developing world: a growing challenge. N Engl J Med 356:213–215
5. **Flegal KM, Graubard BI, Williamson DF, Gail MH** 2005 Excess deaths associated with underweight, overweight, and obesity. JAMA 293:1861–1867
6. **Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM, Narayan KM, Williamson DF** 2005 Secular trends in cardiovascular disease risk factors according to body mass index in US adults. JAMA 293:1868–1874
7. **Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF** 2006 Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 355:763–778
8. **Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L** 2007 Adolescent overweight and future adult coronary heart disease. N Engl J Med 357:2371–2379
9. **Baker JL, Olsen LW, Sorensen TI** 2007 Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med 357:2329–2337
10. **Alley DE, Chang VW** 2007 The changing relationship of obesity and disability, 1988–2004. JAMA 298:2020–2027
11. **Loos RJ, Bouchard C** 2008 FTO: the first gene contributing to common forms of human obesity. Obes Rev 9: 246–250
12. **Do R, Bailey SD, Desbiens K, Belisle A, Montpetit A, Bouchard C, Perusse L, Vohl MC, Engert JC** 2008 Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec Family Study. Diabetes 57:1147–1150
13. **Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, Ebrahim S, Shields B, Zeggini E, Weedon MN, Lindgren CM, Lango H, Melzer D, Ferrucci L, Paolisso G, Neville MJ, Karpe F, Palmer CN, Morris AD, Elliott P, Jarvelin MR, Smith GD, McCarthy MI, Hattersley AT, Frayling TM** 2008 Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected, given its effect on BMI. Diabetes 57:1419-1426
14. **Hotta K, Nakata Y, Matsuo T, Kamohara S, Kotani K, Komatsu R, Itoh N, Mineo I, Wada J, Masuzaki H, Yoneda M, Nakajima A, Miyazaki S, Tokunaga K, Kawamoto M, Funahashi T, Hamaguchi K, Yamada K, Hanafusa T, Oikawa S, Yoshimatsu H, Nakao K, Sakata T, Matsuzawa Y, Tanaka K, Kamatani N, Nakamura Y** 1 April 2008 Variations in the *FTO* gene are associated with severe obesity in the Japanese. J Hum Genet 10.1007/s10038-008-0283-1
15. **Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ** 2007 The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 318:1469–1472
16. **Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I, Dattani MT, Ercan O, Myhre AG, Retterstol L, Stanhope R, Edge JA, McKenzie S, Lessan N, Ghodsi M, De Rosa V, Perna F, Fontana S, Barroso I, Undlien DE, O'Rahilly S** 2007 Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med 356:237–247
17. **Herbert A, Gerry NP, McQueen MB, Heid IM, Pfeufer A, Illig T, Wichmann HE, Meitinger T, Hunter D, Hu FB, Colditz G, Hinney A, Hebebrand J, Koberwitz K, Zhu X, Cooper R, Ardlie K, Lyon H, Hirschhorn JN, Laird NM, Lenburg ME, Lange C, Christman MF** 2006 A common genetic variant is associated with adult and childhood obesity. Science 312:279–283
18. **Christakis NA, Fowler JH** 2007 The spread of obesity in a large social network over 32 years. N Engl J Med 357:370–379
19. **Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI** 2006 An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444:1027–1031
20. **Ley RE, Turnbaugh PJ, Klein S, Gordon JI** 2006 Microbial ecology: human gut microbes associated with obesity. Nature 444:1022–1023
21. **Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC** 2007 Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA [Erratum (2007) 298:178] 297:969–977
22. **Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J** 2006 Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 295:761–775
23. **Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S** 2003 A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 348:2082–2090
24. **Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF** 2004 The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 140:778–785
25. **Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ** 2005 Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 293:43–53
26. **Wadden TA, Butryn ML** 2003 Behavioral treatment of obesity. Endocrinol Metab Clin North Am 32:981–1003, x
27. **Stunkard A, Laren-hume M** 1959 The results of treatment for obesity: a review of the literature and report of a series. AMA Arch Intern Med 103:79–85
28. **Mark AL** 2006 Dietary therapy for obesity is a failure and pharmacotherapy is the future: a point of view. Clin Exp Pharmacol Physiol 33:857–862
29. **Kramer FM, Jeffery RW, Forster JL, Snell MK** 1989 Long-term follow-up of behavioral treatment for obesity: patterns of weight regain among men and women. Int J Obes 13:123–136
30. **Wilfley DE, Stein RI, Saelens BE, Mockus DS, Matt GE, Hayden-Wade HA, Welch RR, Schechtman KB, Thompson PA, Epstein LH** 2007 Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. JAMA 298:1661–1673
31. **Church TS, Earnest CP, Skinner JS, Blair SN** 2007 Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA 297:2081–2091
32. **Sui X, Lamonte MJ, Laditka JN, Hardin JW, Chase N, Hooker SP, Blair SN** 2007 Cardiorespiratory fitness and adiposity as mortality predictors in older adults. JAMA 298:2507–2516
33. **Church TS, LaMonte MJ, Barlow CE, Blair SN** 2005 Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med 165:2114–2120
34. **Gibbons LW, Mitchell TL, Wei M, Blair SN, Cooper KH** 2000 Maximal exercise test as a predictor of risk for mortality from coronary heart disease in asymptomatic men. Am J Cardiol 86:53–58
35. **Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger Jr RS, Blair SN** 1999 Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 282:1547–1553
36. **Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, Stave CD, Olkin I, Sirard JR** 2007 Using pedometers to increase physical activity and improve health: a systematic review. JAMA 298:2296–2304
37. **Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW** 2006 Central nervous system control of food intake and body weight. Nature 443:289–295
38. **Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A** 2007 Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet 370:1706–1713
39. **Oh I, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K, Eguchi H, Yamamoto M, Imaki T, Hashimoto K, Tsuchiya T, Monden T, Horiguchi K, Yamada M, Mori M** 2006 Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature 443:709–712
40. **Batterham RL, ffytche DH, Rosenthal JM, Zelaya FO, Barker GJ, Withers DJ, Williams SC** 2007 PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature 450:106–109
41. **Sloth B, Davidsen L, Holst JJ, Flint A, Astrup A** 2007 Effect of subcutaneous injections of PYY1–36 and PYY3–36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. Am J Physiol Endocrinol Metab 293:E604–E609
42. **Gantz I, Erondu N, Mallick M, Musser B, Krishna R, Tanaka WK, Snyder K, Stevens C, Stroh MA, Zhu H, Wagner JA, MacNeil DJ, Heymsfield SB, Amatruda JM** 2007 Efficacy and safety of intranasal peptide YY3–36 for weight reduction in obese adults. J Clin Endocrinol Metab 92:1754–1757
43. **Erondu N, Addy C, Lu K, Mallick M, Musser B, Gantz I, Proietto J, Astrup A, Toubro S, Rissannen AM, Tonstad S, Haynes WG, Gottesdiener KM, Kaufman KD, Amatruda JM, Heymsfield SB** 2007 NPY5R antagonism does not augment the weight loss efficacy of orlistat or sibutramine. Obesity (Silver Spring) 15:2027–2042
44. **Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lonroth H, Naslund I, Olbers T, Stenlof K, Torgerson J, Agren G, Carlsson LM** 2007 Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 357:741–752
45. **Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC** 2007 Long-term mortality after gastric bypass surgery. N Engl J Med 357:753–761
46. **Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M** 2008 Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA 299: 316–323