Internal Medicine Grand Rounds
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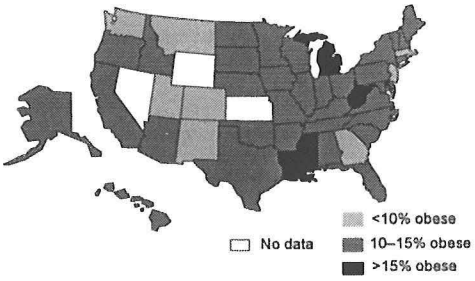
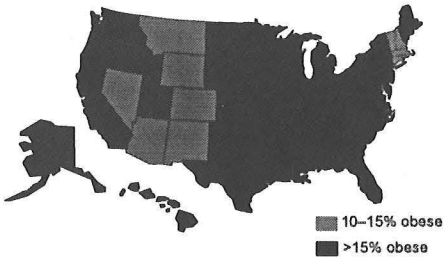
EFFECTIVE TREATMENTS FOR OBESITY

Prevalence of Obesity, 1991



Mokdad AH, et al. *JAMA*. 1999;282:1519–1522.

Prevalence of Obesity, 1998



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Abstract

Recently released 1999 statistics show that 27% of the American population met the BMI criteria for obesity; an additional 34% of Americans met the criteria for overweight. As health care professionals, we must prepare for the long-term medical consequences of excess body weight. Besides treating the medical consequences of obesity, every physician should develop their clinical strategies to prevent further weight gain and to promote weight loss in suitable patients.

Background

Excess body weight is an impressive health risk. The first quantitative effort to link excess body weight to mortality was a cooperative effort of 26 US life insurance companies, who combined actuarial data from 4.9 million persons without heart disease, cancer or diabetes.[1] The Build and Blood Pressure Study found a graded effect between excess body weight and all-cause mortality. Individuals with the lowest mortality were 5 – 10 lbs. thinner than average.

The first efforts to educate the public regarding healthy weights were spearheaded by the Metropolitan Life Insurance company. In 1959 and 1983, healthy body weight tables were released for men and women according to height and frame size. Using the tables, each patient could identify a target healthy weight for them.

The recent promotion of BMI criteria for over weight and obesity have simplified the physicians assessment of excess body weight. BMI expresses the continuous range of relative body weight – weight in kg divided by height in meter squared-- (kg/m^2). Although body weight is the sum of heterogeneous body components, BMI is highly correlated with fat mass (r 2 = 0.9);[2] regional body fat distribution[3] adds additional risk in persons whose BMI < 35 kg/m^2. The NIH Obesity Evidenced Based report has recommended that obesity be defined by BMI criteria; the risks for the medical complications of obesity are defined by BMI plus waist circumference.[4] Waist circumference is measured midway between the lowest rib and the iliac crest; acceptable waist circumference is < 40" (102 cm) in a man and < 35" (88 cm) in a woman.[5]

Table 1
Classification of Risk for Metabolic Complications of Obesity

Waist Circumference	BMI Category (kg/m^2)				
	18.5-24.9	Overweight 25.9-29.9	Obesity Grade I 30.9-34.9	Obesity Grade II 35.0-39.9	Obesity Grade III ≥ 40.0
<40" for men <35" for women	--	Increased	High	Very high	Extremely high
>40" for men >35" for women	Increased	High	Very high	Very high	Extremely high

Etiology of Excess Body Weight. Obesity is a direct consequence of the first law of thermodynamics. Energy that is not consumed must be stored. Obese persons become obese because of a cumulative excess in energy intake that exceeds their energy requirements.

Obesity is not associated with a specific personality or psychiatric profile. Obese persons do not have higher prevalence of psychopathology, including depression, obsessive-compulsive disorders, and low self esteem.[6] However, obese persons seeking treatment for their obesity are more likely than the general population to have psychiatric symptomatology, including depression and low self esteem.[7]

The growing prevalence of obesity is probably the natural consequence of changes in our environment. Food is plentiful and most Americans are sufficiently prosperous to purchase more than adequate food to meet their metabolic demands. Unfortunately, metabolic demands have declined as computer technology plus prosperity has eliminated many of the day to day routine physical activities that burn energy. Leisure time, once devoted to outdoor activities, is now more commonly spent watching television or playing on the computer. An imbalance of energy ensues if dietary intake is not reduced appropriately to meet reduced demands.

Appetite and its regulation have been a major research focus in the etiology of obesity. Expression of appetite is chemically coded in the hypothalamus by distinct circuitry.[8] Orexigenic signals of neuropeptide Y, galanin, edogeneous opioid peptides, melanin-concentrating hormone, glutamate and gama-aminobutyric acid promote eating behavior. Anorexigenic signals, including an entire family of CRH related peptides, neurotensin, glucagon peptide-1, melanocortin and agoutiprotein and cocaine, promote cessation of eating behaviors. Each signal has its specific cellular receptors, occurring in high concentration in the paraventricular nucleus but present in other areas of the brain. No single peptide is the gatekeeper to turning on appetite; what is apparent is an entire network of signals, their frequency and amplitude, are responsible for triggering behaviors.

The network of appetite signals accounts for the behavioral observations that appetite and food consumption patterns are dynamic, and readily influenced by biological, environmental, and psychological events.[9] Human eating behaviors are easily modified by internal clues such as habitual intake, memories of food-related activities, and anticipation of consumption. External clues such as the appearance of food, aroma, anticipated palatability, and the number of food choices modify the perception of appetite as well as the behaviors of eating.[10] Psychosomatic consequences of eating, such as reduction in anxiety, can exert additional influences on behavior.[11] Our understanding of eating behaviors is akin to that of memory; although memory and appetite are chemically encoded, every individual has their own unique circuitry underlying their eating behaviors. Similar to memory, this circuitry can be modified over time.

A major breakthrough in the physiology of appetite regulation came with the discovery of leptin, a hormone synthesized by adipocytes. Leptin secretion increases as adipocytes enlarge, and decreases during fasting. Identification of leptin receptors in the hypothalamus provided an intriguing biochemical explanation for the ability of an animal to tightly regulate body weight within a fairly narrow set point range.[12] The leptin signal may serve as an anorexin by its ability to alter secretion of orexins and anorexins. Obese persons have appropriately elevated leptin levels, but whether this is an epiphenomena of obesity or a clue to the pathologic cause of obesity remains unclear.

The importance of each of these anorexigenic and orexigenic signals and their receptors has been highlighted by the identification of rare families with specific genetic defects associated with childhood obesity.[13] Mutations in leptin, leptin receptor, prohormone convertase 1 (PC1), pro-opiomelanocortin (POMC), melancortin 4-receptor (MC4-R), and peroxisome proliferator-activated receptor (PPAR) gamma2 genes have been described in patients with severe obesity.

Health Consequences. Most of the deleterious effects of obesity are direct consequences of excess body weight. Osteoarthritis is more common in overweight persons.[14] The prevalence of hypertension, dyslipidemia with high total cholesterol, high triglycerides and low HDL cholesterol levels, and diabetes increase with increasing BMI.[4] This places obese patients at high risk for the development of coronary disease. Besides ischemic coronary disease, overweight and obesity are independent risk factors for the development of congestive heart failure.[15] Excessive body weight predicts the severity of sleep apnea; most patients with sleep apnea have a BMI > 30 kg/m^2.[16] Patients with excess body weight are at risk for gallstones[17] and liver disease including fatty liver and non-alcoholic hepatosteatosis.[18,19] Colonic polyps and colon cancer are more prevalent in obese persons.

Women, in particular, have significant hormonal consequences from excess body weight. Polycystic ovarian disease,[20] hirsuitism, infertility and higher obstetric complications ensue.[21] Weight gain in adult women increases the risk for breast cancer,[22] presumably because of the conversion of adrenal androgens to estrone by peripheral fat cells. It is speculated that the high levels of unopposed estrogens explain the increased risk for endometrial cancer.[23]

Approach to the Patient

Dietary History. There are no consistent eating behaviors underlying obesity.[24] Patients may not readily reveal their food intake. Some patients report a stellar low calorie diet that should easily result in weight loss but hasn't. The physician must shift the interview to ask about the "bad days" when either extra meals, large meals, or binge eating provides sufficient calories to obliterate the caloric deficit achieved on a good day. The chronological recording of intake and physical activity can identify triggering events that derail dietary intentions . Questions regarding binge eating behavior (Table 2) should be asked of all obese persons seeking treatment.

Table 2
Binge Eating Questions

Have you ever felt out of control about your eating?
Have you ever eaten more than being comfortably full? So much that it hurts?
Have you ever started eating and couldn't stop? Did the food satisfy your cravings or were you still hungry?
Do you ever feel guilty about eating?
Are you ever embarrassed by how much you ate?
Do you ever vomit or take laxatives after you eat too much?

The prevalence of binge eating coincides with the magnitude of excess body weight. In one series, 10% of women with a BMI 25-28 kg/m^2 reported binge eating compared to 40% of women with a BMI 31-42 kg/m^2.[25]

Physical Activity History. Obese persons require more calories to perform routine physical activity than lean persons.[26] In some patients, low energy expenditure associated with spontaneous physical activity contributes to lifetime weight gain.[27]

Physical Examination. Secondary causes of obesity are rare and physical examination can identify persons who need further workup. Cushing's syndrome presents with central obesity and proportionally thin extremities. The presence of supraclavicular fat and thin skin with bruises are indicative of cortisol excess. Hypothyroidism leading to myxedema can be detected by doughy dry skin, deep voice, delayed reflexes, and elevated TSH. Hypothalamic tumors may present with visual field defects and headaches.

Dietary Therapy

The physician can estimate caloric requirements to maintain body weight.[28,29]

Table 3
Predict Caloric Requirements

Men = [900 + 4.5 x (wt in lb)] x activity factor

Women= [800 + 3.2 x (wt in lb)] x activity factor

Where activity factor low = 1.2 (e.g., sedentary job),moderate = 1.4, high = 1.6 (e.g., manual labor; daily exercise program)

A weekly deficit of 3700 kcal will produce on average a one pound loss of weight. Simplistically speaking, restriction of calories should cure every obese person. The effectiveness of diet follows a simple, straight line[30] where the magnitude of weight loss is directly proportional to the severity and duration of the caloric restriction. Two

different approaches – very low calorie diets or low calorie diets – can be taken. Behavior modification improves long term success of dietary therapy.

Very-Low Calorie Diets. Very low calorie diets provide 500-750 kcals/d, often in a liquid formula. Their macronutrient composition is designed to provide the minimum number of calories from protein to avoid severe negative nitrogen balance and the minimum number of calories from carbohydrate to avoid severe ketosis. Weight loss is dramatic and predictable. Although the short term success of these diets is phenomenal, in the long term these diets provide no greater weight loss at one year than natural food, low calorie diets.[31] More than 70% of patients who lost weight on these diets regain at least half of this weight within two years of stopping the diet.[32] The use of very low calorie diets is limited to patients who require immediate weight loss (e.g., obstructive sleep apnea), with the caveat that they are only a "stopgap" measure that precedes a long term dietary/behavior solution.[33]

Low Calorie Diets. Low calorie diets, in contrast, provide 1,000-1,500 kcal/d. The macronutrient content of these diets can be quite varied, but at least 20% of calories from fat is recommended.[34] Although the weight loss is slower than in very-low-calorie diets, the incidence of gallstones is lower.[35] The long term success rate may be better because the diet teaches the patient to make food choices. Several free NIH Websites provide excellent materials regarding healthy diets. The web site http://www.nhlbisupport.com/chd1/lifestyles.htm discusses a Step I diet that is balanced in nutrients; more specific information regarding weight loosing diets is found at http://www.nhlbi.nih.gov followed by a click on "Aim for a Healthy Weight" will provide the patient a BMI calculator and a flexible low calorie menu planner that uses the American Dietetic Exchanges.

Exercise. Exercise is an underutilized adjunct to dietary restriction. In a metaanalysis evaluating the benefits of exercise training, the addition of an exercise regimen did not enhance total weight loss, but did reduce the percent loss of fat free mass.[36] This means that for every kg of weight lost, exercisers lose a greater amount of fat than non-exercisers.

Exercise is an impressive predictor of weight maintenance following weight loss. In an interview study comparing women who were formally obese to normal weight women and obese women who lost weight by dieting but regained, 90% of women who maintained their reduced weights reported regular exercise.[37] A 2 – 3 year followup of very-low-calorie diet program participants, documenting the expected weight regain (initial loss of 27.2 kg; followup loss diminished to 11.3 kg.), showed that exercise predicted individual success. Those reporting an exercise program burning > 1,000 kcal/wk maintained an average weight loss of 17.5 kg compared to those reporting no exercise, whose average weight loss was 5.6 kg.[38] Information regarding physical activity can be found on the web site: www.surgeongeneral.gov/ophs/pcpfs.htm . The amount of exercise needed to facilitate weight maintenance is not excessive. For example, walking 3 miles per day, at a leisurely pace, should burn 2,000 kcal/wk.

Drug Therapy

Drug therapy for obesity has undergone major changes in the past 10 years. Three drugs have been removed from the market and two new drugs have been released.

Two of the three agents removed from the market, fenfluramine and dexfenfluramine, were schedule IV drugs used as the FEN part of the Phen-FEN combination. The fenfluramines reduced appetite by selectively blocking reuptake of serotonin in hypothalamic neurons; serotonin secretion was also simulated. Both drugs were associated with the rare development of primary pulmonary hypertension; however, they were voluntarily taken off the market because of anecdotal associations with valvular heart disease.[39]

The third drug taken off the market, phenylpropanolamine, was an over-the-counter diet aid that reduced appetite by acting on adrenergic receptors in the paraventricular nucleaus. Phenylpropanolamine had the potential to raise blood pressure; a recent large population study implicated phenylpropanolamine in hemorrhagic stroke in young women. Currently, in the United States, pharmacotherapy is essentially restricted to three drugs: phentermine, sibutramine, and orlistat (Table 4).

Phentermine. Phentermine hydrochloride and phentermine resin have been used extensively since the 1970's as appetite suppressants. Daily dose is typically 8 to 37.5 mg of phentermine hydrochloride or 15 to 30 mg of phentermine resin; tablets are taken first thing in the morning because of their stimulatory effect. The majority of the weight loss occurs in the first 20 weeks of therapy; withdrawing drug leads to weight regain. Intermittent phentermine can be as effective as daily phentermine.[40]

Sibutramine. Sibutramine inhibits the reuptake of both serotonin and norepinephrine. Daily dose is typically 5- 20 mg. It can increase blood pressure and blood pressure should be monitored during the first few months of therapy. As with phentermine, the majority of the weight loss (2-12 kg above placebo) is in the first few months of therapy; continuation of sibutramine prevents the weight regain expected from stopping the drug.[41]

Orlistat. Orlistat is a selective inhibitor of pancreatic lipase, resulting in malabsorption of 1/3 dietary fat. Orlistat is taken as a 120 mg tablet, with each meal. The malabsorbed fat does not cause the flatulence and diarrhea associated with carbohydrate malabsorption. When fat intake is restricted to 30% of calories, the unabsorbed fat can be emulsified in the stool. If fat intake is excessive, an oil leak can occur several days after the dietary discretion. Orlistat has been shown to reduce body weight on average 2-6 kg; as with any drug therapy for obesity, some patients are able to achieve ideal body weight.[42] Continuation of drug blunts weight regain.

Table 4
FDA Approved Drugs for Obesity

	Phentermine		Sibutramine	Orlistat
Site of Action	CNS		CNS	Gut
Mechanism of Action	Stimulates norepinephrine release		Inhibits reuptake of both serotonin and norepinephrine	Lipase inhibitor
RCCT efficacy	2-8 kg greater than placebo		2-12 kg greater than placebo	2-6 kg greater than placebo
Safety	In use since the 1970's		In use since late 1990's	In use since late 1990's ; little if any systemic absorption
Major adverse events	Nervousness, irritability, headache, dry mouth, nausea, constipation, dizziness, insomnia, depression, bladder spasm		Increase in blood pressure and heart rate is seen with significant increases in occasional patients; dry mouth, insomnia, constipation, headache	Nausea; Oily spotting can occur 12-48 h after high-fat meal (<30% calories from fat diet avoids this potential adverse event); Vitamin E and beta-carotene absorption are reduced (daily multivitamin taken between meals is recommended)
Absolute contraindications	Patients taking MAO inhibitors		Patients taking MAO inhibitors; patient taking serotonergic drugs such as sumatriptan succinate, dihydroergot-amine, dextromethorphan, meperidine, pentazocine, fentanyl, lithium, and tryptophan.	Patients with bile acid deficiencies
Relative contraindications	Patients with sicca syndrome, arrhythmias, panic attacks or hallucinations may have exacerbation of symptoms		Hypertension; use cautiously and monitor BP. Patients with coronary or cerebral atherosclerosis, CHF should be monitored for ill effects from changes in BP and HR; narrow angle glaucoma and seizure disorder patients should be monitored for worsening disease. Use in patients taking SSRI's unproven. Metabolized by p450($3A_4$)	Patients with calcium oxalate nephrolithiasis may increase risk for stone because of increased oxalate excretion; patients taking cyclosporin may have reduction in cyclosporin levels; more frequent monitoring and separation of dosing by 2 hrs is recommended
Sub-Preparations	hydrochloride	resin	--	--
DEA Schedule	Schedule IV	Schedule IV	Schedule IV	Not scheduled
Trade name	Fastin® Ionamin-Phentrol® Adipex-P® Obermine®	Ionamin®	Meridia®	Xenical®
Generic Available	Yes	Yes	No	No
Doses	8, 15, 18.75, 30, 37.5 mg	15, 30 mg	5, 10, 15 mg	120 mg

Investigational Drugs. Human recombinant leptin has been administered to normal weight and obese.[43] Those randomized to the highest dose in the trial (0.3 mg/kg/d) achieved lower caloric intakes and lost more weight compared to placebo, with net weight reduction of 6 kg over 20 weeks. The magnitude of weight loss is remarkably consistent with that achieved by the appetite suppressant drugs currently on the market (Table 12). Whether or not higher dosages of leptin will confer greater weight loss awaits results of additional clinical trials.

Goals of Diet/Drug Therapy

Weight loss goals should include the amount of weight to be lost and the time frame required for the weight loss. Many obese patients have unrealistic goals for both their target weight and the time it will take to reach that weight. Oftentimes, unrealistic expectations are the cause of diet failures.[44] The NIH evidenced based panel has identified a 10% reduction in body weight as an achievable and sustainable goal. The striking benefit of even this small amount of weight loss on cardiovascular risk factors is outline in Table 5.[4]

Table 5
Benefits of Modest Weight Loss on Cardiovascular Risk Factors

Risk Factor	5-10 Lbs Weight Loss	≥20 Lbs Weight Loss	Long-term Benefits
Blood Pressure	Reduction in systolic pressure by 4-8 mm Hg; diastolic pressure by 4-6 mm Hg	Improvements in blood pressure can be equivalent to drug therapy	Incidence of hypertension reduced 20-50%; Patients taken off medication less likely to return to medication if weight loss maintained
Lipids	Reductions of 4-20 mg/dL total cholesterol, and 20-60 mg/dL triglycerides	May allow dose reduction of lipid lowering drugs May allow patients with mixed dyslipidemia to use monotherapy	Blunts the expected rise of cholesterol (30-50 mg/dL) with age Doubles cholesterol lowering benefits expected from dietary composition changes alone
Lipoproteins	Reductions of 5-20 mg/dL LDL Increases of 1-6 mg/dL HDL	HDL/TG benefits are striking --- no drug improves HDL to this extent	HDL is a risk factor at any age; benefits of staying lean are experienced even among older persons
Insulin Resistance	18-30% reduction in fasting insulin levels	Improvements seen in glucose tolerance testing	Over a six year period, individuals who lost weight and kept it off had 1/3 the incidence of diabetes than people who kept weight
Diabetes	HbA1c can be reduced 0.8– 2.2%	Dosages of hypoglycemic drugs markedly reduced	Long term glucose control has been linked to reductions in renal and retinal disease

Bariatric Surgery

Bariatric surgery creates an anatomic barrier preventing overconsumption and accumulation of excess calories by either restricting the gastric reservoir or by inducing malabsorption. Since these two approaches are complimentary, they are frequently combined in a single operative procedure. An NIH consensus conference on the surgical treatment of obesity recommended consideration of surgery in patients with a BMI ≥ 40 without medical complications, or BMI ≥ 35 if a severe comorbidity was present.[45] Two aggressive surgical therapies, jejunoileal bypass and biliopancreatic bypass have fallen out of favor because of high rates of metabolic complications. Gastric restriction and gastric bypass are the main procedures employed in the United States today.

Gastric restriction. Gastric restriction can be achieved by several different surgical approaches. Vertical stapled gastroplasty with a banded outlet creates a small capacity pouch that then empties into the remaining stomach. The surgery requires stapling several centimeters down the anterior stomach parallel to its hepatic border. The pouch is completed by inserting a 0.9 cm diameter band at the bottom. The pouch capacity is only 15-20 ml; it empties into the remaining stomach. Overtime, excessive intake can distend and ultimately stretch the pouch.

In patients where stretching is a potential long-term concern, an adjustable gastric banding operation can be performed. In this operation, a gastric band is placed several centimeters beneath the esophageal-gastric junction, again creating a pouch. The inflatable gastric band is attached to a subcutaneous port that can be inflated/deflated to achieve the desired results. Complications of the adjustable gastric banding include 5% band migrations/erosions, and a 5% incidence of GERD. [46] laproscopic adjustable esophagogastric banding may reduce the incidence of postoperative GERD.[47]

Gastric bypass. The first gastric bypass surgeries for obesity were modeled after gastric resections performed for patients with recurrent ulcers or with intestinal cancers. A Roux-en-Y anastomosis was performed, with varying amounts of intestinal surface being bypassed. Gastric bypass is the most common surgical procedure performed today for obesity. This surgery combines the techniques of gastric restriction with a lesser amount of intestinal bypass. A gastric pouch is created, in a similar manner to that performed in vertical stapled gastroplasty. This pouch is severed from the stomach and connected to the jejunum 50 cm from the ligament of Treitz using a Roux-en-Y connection. In contrast to routine gastroplasty, Roux-en-Y gastric bypass can be an effective therapy for symptomatic GERD.[48]

Complications from Bariatric surgery. The most immediate reported side effect of gastric restrictive or gastric bypass surgery is vomiting and regurgitation. Patients can generally control this symptom by consuming smaller meals and taking more time to consume each meal; rarely vomiting is due to a stoma stricture that can be

endoscopically dilated. Nearly 70% of patients following gastric bypass, experience dumping, which occurs after ingestion of high-caloric, high-fat, soft foods. Patients who undergo gastroplasty do not suffer from dumping because the pylorus is left intact. Dietary counseling can limit the severity of the dumping syndrome. Reported side effects and complications of gastric bypass surgery, are listed in Table 6.[49]

Table 6
Side Effects/Complications of Gastric Bypass Surgery

Side Effects		Complications	
Dumping	70%	B12 deficiency	25%
Dairy intolerance	50%	Abdominal pain	15%
Constipation	40%	Vomiting	15%
Headache	40%	Diarrhea	15%
Hair loss	33%	Incisional hernia	15%
Depression	15%	Anemia	15%
		Arrhythmia	10%
		Non-B12 Vitamin Deficiency	10%

Prognosis. The success rate of bariatric surgery is difficult to glean from the literature, since most series contain patients with wide variations in the severity of their obesity, varying rates of loss of followup, and the lack of a standard method for reporting body weights and magnitude of weight loss. Long-term weight loss of 25-40% of preoperative weight is typically achieved.[179] Using the disappearance of comorbidities as an endpoint, 80% of patients receiving gastric bypass surgery improve.[50] When the encouraging, preliminary data from a major Swedish surgical trial are released, the role of surgery in the management of morbid obesity may increase.[51]

Complications of Weight Loss From Diet/Drugs/Surgery

Gallstones. Weight loss from dieting or bariatric surgery further increases the risk of gallstones.[52] The incidence of new gallstones has been estimated at 12% during very low calorie dieting and 38% after successful gastric bypass surgery.[53] Both initial BMI and absolute rate of weight loss are significant predictors.[54] The mechanism is due to an increase in the cholesterol saturation index,[55] and reductions in gallbladder motility.[56] Some surgeons perform a cholecystectomy at the time of gastric bypass surgery to avoid perioperative complications due to gallstone disease.[57]

Greater caloric restriction, providing faster weight loss, increases the rate of gallstone formation. In a meta-analysis of studies of weight loss in which the rate of gallstone formation was tracked by ultrasound, the prevalence of new gallstones increased from 0.5% to 3.0% per week when the magnitude of weight loss increased from 1.5 to 3.0 kg per week.[58] Very low calorie or very low fat diets reduce gallbladder motility and increase the risk for gallstone formation. In a study comparing two different low calorie diets, half of the patients randomized to the 5% of calories from fat diet developed

gallstones compared to none of the subjects randomized to the 20% of calories from fat diet.[59]

Ursodeoxycholic acid has been used successfully to reduce the risks of gallstone formation associated with weight loss. In a randomized trial of 29 gallstone-free patients undergoing bariatric surgery, 1,000 mg/d ursodeoxycholic acid significantly prevented gallstone formation compared to placebo (0/10 vs 6/14).[60] The clinical significance is far greater in that 2 of the 6 placebo patients who developed gallstones required cholecystectomy. In fact, a cost-savings has been estimated if ursodeoxycholic acid was provided for every obese patient who was expected to undergo rapid weight reduction.[61] Aspirin, 1,300 mg/d[62] and ibuprofen, 1,600 mg/d[63] have also been shown to reduce the incidence of gallstone formation in patients undergoing weight reduction.

Hepatitis. Large and rapid weight loss has been shown to increase the prevalence of inflammatory hepatitis. One case report describes the development of occult cirrhosis in a patient whose preoperative liver biopsy was normal.[64] Two series of patients who had liver biopsies pre and post weight reduction have been reported.

In a study of patients undergoing gastroplasty, [65] pre and 2 yr postoperative liver biopsies were performed in 69 patients. Following surgery, the mean BMI in this cohort fell from 43.9 kg/m^{2}to BMI 31.7 kg/m^2. Although the prevalence of steatosis fell from 83% to 38%, the prevalence of steatohepatitis increased from 14% to 26%. Most of the cases were mild in severity. At the time of surgery, none of the patients had cirrhosis by biopsy; a single patient had fibrosis which was unchanged on repeat biopsy.

The increase in prevalence of hepatitis is not due to surgical therapy. In a study of 41 patients who had liver biopsies prior to the initiation of a very-low-calorie diet and repeat liver biopsy at the time of an elective gastroplasty 4-20 months later, [66] a similar picture emerged. Following dietary therapy, the mean BMI fell from 43.3 to 32.9 kg/m^2. Although the prevalence of steatosis fell from 90% to 29%, the prevalence of steatohepatitis increased from 15% to 34%. On the initial biopsy, no patients had evidence for fibrosis or cirrhosis; on repeat biopsy, fibrosis was present in five cases – two that had portal inflammation on initial biopsy, and three that had only fatty change on initial biopsy. The presence of new fibrosis was significantly associated with a higher degree of fatty change on initial biopsy, a greater reduction of fatty change on repeat biopsy, and weight loss faster than 4 lbs/wk.

Prognosis

Obesity is a chronic, remitting and relapsing condition. It cannot be cured but can be modified by consistent changes in eating behaviors and physical activity. Although many obese patients complain that they have "ruined their metabolism" by intermittent attempts to lose weight using diets or drugs, basal metabolic rates of women who had repeatedly gained and lost weight were no different than similar weight women who had

never dieted.[67] Although previous estimates suggested that only 5-10% of patients who participate in a clinical weight reduction program can maintain their new weight for at least three years,[68] advances in the behavioral management of patients now suggest that 19% of patients can maintain long-term weight loss.[69] Drug therapy and surgical therapy may be indicated in patients with significant comorbidities, since both modalities have been shown to improve risk factors. Data supporting long-term drug therapy are limited to results from trials two years in duration. Data from surgical therapy suggest that 25-40% of preoperative weight is typically achieved and maintained.[49] Using the disappearance of comorbidities as an endpoint, 80% of patients receiving gastric bypass surgery improve.[70] When the encouraging, preliminary data from a major Swedish surgical trial are released, the role of surgery in the management of morbid obesity may increase.[71] Although the risk for gallstone formation can be eliminated during rapid weight loss, the risk for hepatitis, and its clinical significance, remains uncertain.

Physicians should at a minimum ask patients to stop their weight gain trajectory. Some patients will be successful in the long-term keeping off weight lost by dieting.

References

[1] Anonymous. Build and Blood Pressure Study. Volumes 1 and 2, Society of Actuaries, Chicago IL, 1959.
[2] Heymsfield SB, Aaumgartner RN, Ross R. Evaluation of total and regional body composition. In: Handbook of Obesity. Eds GA Bray, C Bouchard, WPT James, Marcel Dekker, New York, 1998 pp 41-78.
[3] Kissebah AH, Krakower GR Regional adiposity and morbidity. Physiological Reviews, 1994; 74: 761-811.
[4] NHLBI Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults – The evidence report. Obesity Research, 6 suppl2, 51S – 209S.
[5] World Health Organization: Measuring obesity: classification and description of anthropometric data. Copenhagen: WHO, 1989.
[6] Wadden TA, Stunkard AJ Psychopathology and obesity. Ann NY Acad Sci, 1987; 499: 55-65.
[7] Williamson DA, O'Neil PM Behavioral and psychological correlates of obesity. In: Handbook of Obesity. Eds GA Bray, C Bouchard, WPT James, Marcel Dekker, New York, 1998 pp 129-142.
[8] Kalra SP, Dube MG, Pu S et al Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocr Rev 1999; 20 (1): 68-100.
[9] Rogers PJ Eating habits and appetite control: a psychobiological perspective. Proc Nutr Soc 1999; 58 (1): 59-67.
[10] Rogers PJ, Blundell JE Psychobiological bases of food choice. Brit Nutr Found Nutri Bull 1990; 15, supplement 1, 31-40.
[11] Robbins TW, Fray PJ Stress-induced eating: fact, fiction or misunderstanding? Appetite, 1: 1980; pp 103-133
[12] York DA Peripheral and central mechanisms regulating food intake and macronutrient selection. Obes Surg 1999; 9 (5): 471-479.
[13] Chen D, Garg A Monogenic disorders of obesity and body fat distribution. J Lipid Res 1999; 40 (10): 1735-1746.
[14] Hochberg MC, Lethbridge-Cejku M, Scott WW Jr. et al The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: Data from the Baltimore Longitudinal Study of Aging. J Rheumatol, 1995; 22: 488-493.
[15] DiBianco R The changing syndrome of heart failure: An annotated review as we approach the 21st century. J Hypertens 1994; 12 Suppl 1, S73-S87.
[16] Young T, Palta M, Dempsey J. et al The occurrence of sleep-disordered breathing among middle –aged adults. N Engl J Med, 1993; 328: 1230-1235.
[17] Khare M, Evrhart JE, Maurer KR Association of ethnicity and body mass index (BMI) with gallstone disease in the United States. Am J Epidemiol 1995; 141: S69.
[18] Braillon A, Capron JP, Hervé M, et al Liver in obesity. Gut, 1985; 26: 133-139.
[19] Clain D, Lefkowitch J Fatty liver disease in morbid obesity. Gastroenterology clinics of north America, 1987, 16: 239-252.
[20] Dunaif A. Polycystic Ovary Syndrome. Boston: Blackwell Scientific Publications; 1992.
[21] Johnson SR, Kolberg BH, Varner MN et al Maternal obesity and pregnancy. Surg Gynecol Obstet 1987; 164: 431-437.

[22] Huang Z, Hankinson SE, Colditz GA et al. Dual effects of weight and weight gain on breast cancer risk. JAMA, 1997; 278: 1407-1411.
[23] Schottenfeld D, Fraumenia JF Cancer Epidemiology and Prevention. New York: Oxford University Press, 1996.
[24] Spitzer L, Rodin J Human eating behavior: A critical review of studies in normal weight and overweight individuals. Appetite, 1981; 2: 293-329.
[25] Spitzer RL, Devlin M, Walsh BT et al Binge eating disorder: A multisite field trial of the diagnostic criteria. In J Eating Disor 1992; 11: 191-203.
[26] Welle S, Forbes GB, Statt M et al Energy expenditure under free-living conditions in normal weight and overweight women. Am J Clin Nut, 1992; 55: 14-21.
[27] Zurlo F, Ferraro R, Fontvieille AM et al Spontaneous physical activity and obesity: Cross-section and longitudinal studies in Pima Indians. Am J Physiol 1992; 263; E296-E300.
[28] Owen OE, Holup JL, D'Alessio DA et al: A reappraisal of the caloric requirements of men. Am J Clin Nutr, 1987; 46: 875-885.
[29] Owen OE, Kavle E, Owen RS et al A reappraisal of caloric requirements in healthy women. Am J Clini Nutr, 1986; 44: 1-19.
[30] Wadden TA, Stunkard AJ, Brownell KD Very low calorie diets: Their efficacy, safety, and future. Ann Intern Med 1983; 99: 675-684.
[31] Wadden TA, Foster GD, Letizia KA One-year behavioral treatment of obesity: Comparison of moderate and severed caloric restriction and the effects of weight maintenance therapy. J Consult Clin Psychol, 1994; 62: 165-171.
[32] Wing RR, Blair E, Marcus M et al Year-long weight loss treatment for obese patients with Type II diabetes: Does including an intermittent very-low-calorie diet improve outcome? Am J Med, 1994; 97: 354-362.
[33] National Task Force on the prevention and treatment of obesity. Very low caloric diets. JAMA 1993; 270: 967-974.
[34] Festi D, Colecchia A, Orsini M et al Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well). In J Obes Relat Metab Disord, 1998;; 22: 592-600.
[35] Weinsier RL, Wilson LJ, Lee J Medically safe rate of weight loss for the treatment of obesity: A guideline based on risk of gallstone formation. Am J Med, 1995; 98: 115.
[36] Ballor DL, Poehlman ET Exercise training enhances fat-free mass preservation during diet-induced weight loss: a meta-analytical finding. Int J Obes 1994; 18:35-40.
[37] Kayman S, Bruvoild W, Stern JD Maintenance and relapse after weight loss in women: behavioral aspects. Am J Clin Nutr, 1990; 52: 800-807.
[38] Hartman WM, Stroud M, Sweet DM et al Long-term maintenance of weight loss following supplemented fasting. In J Eating Disor, 1993; 14: 87-93.
[39] Poston WS, Foreyt JP Scientific and legal issues in fenfluramine/dexfenfluramine litigation. Tex Med, 2000; 96: 48-56.
[40] Stell JM, Munro JF, Duncan LJP A comparative trial of different regimens of fenfluramine and phentermine in obesity. The Practitioner, 1973; 211: 232-236.
[41] James WPT, Astrup A, Finer N et al Effect of sibutramine on weight maintenance after weight loss: a randomized trial. Lancet 2000; 356: 2119-2125.
[42] Lindgarde F The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. J Intern Med 2000; 248(3): 245-254.
[43] Heymsfield SB, Greenberg AS, Fujioka K et al Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 1999; 282 (16): 1568-1575.
[44] Bennett GA Expectations in the treatment of obesity. Brit J Clin Psychology, 1986; 25: 311-312.
[45] National Institutes of Health Consensus Development Conference. Gastrointestinal surgery for severe obesity Am J Clin Nutr 1992; 55 (suppl) 487S-619S.
[46] Forsell P, Hallerback B, Glise H et al complications following Swedish adjustable gastric banding: A long-term followup. Obes Surg, 1999; 9: 11-16.
[47] Niville E, Vankeirsbilck J, Dams A et al laproscopic adjustable esophagogastric banding: A preliminary experience. Obes Surg, 1998; 8: 39-43.
[48] Smith SC, Edwards CB, Goodman GN Symptomatic and clinical improvement in morbidly obese patients with gastroesophageal reflux disease following Roux-en-Y gastric by[ass. Obes Surg, 1997; 7: 479-484.
[49] Kral JG Surgical Treatment of Obesity. In: Handbook of Obesity. Eds GA Bray, C Bouchard, WPT James, Marcel Dekker, New York, 1998 pp 977-993.
[50] Pories WJ, Swanson MS, MacDonald KG et al Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995; 222: 339-352.
[51] Sjostrom CD, Lissner L, Wedel H, et al Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. Obes Res 1999; 7 (5): 477-484
[52] Ko CW, Lee SP Obesity and Gallbladder Disease. In: Handbook of Obesity. Eds GA Bray, C Bouchard, WPT James, Marcel Dekker, New York, 1998 pp 709-724.
[53] Everhart JE Contributions of obesity and weight loss to gallstone disease. Ann Intern Med, 1993; 119: 1029.

[54] Yang H, Peterson GM, Roth MP et al Risk factors for gallstone formation during rapid loss of weight. Dig Dis Sci, 1992; 37: 912-918.
[55] Shiffman ML, Sugerman HJ, Kellum JM et all changes in gallbladder bile composition following gallstone formation and weight reduction. Gastroenterology 1992; 103: 214-221.
[56] Stone BG, Ansel HJ, Peterson FJ, et al. Gallbladder emptying stimuli in obese and normal-weight subjects. Hepatology, 1992; 15: 795-798.
[57] Calhoun R, Willbanks O Coexistence of gallbladder diseases and morbid obesity. Am J Surg, 1987; 154: 655-658.
58 Weinsier RL, Wilson LJ, Lee J Medically safe rate of weight loss for the treatment of obesity: A guideline based on risk of gallstone formation. Am J Med, 1995; 98: 115.
59 Festi D, Colecchia A, Orsini M et al Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well). In J Obes Relat Metab Disord, 1998; 22: 592-600.
60 Worobetz LJ, Inglis FG, Shaffer EA The effect of ursodeoxycholic acid therapy on gallstone formation in the morbidly obese during rapid weight loss. Am J Gastroenterology 1993; 88: 1705-1710.
61 Shoheiber O, Biskupiak, Nash DB Estimation of the cost savings resulting from the use of ursodiol for the prevention of gallstones in obese patients undergoing rapid weight reduction. In J Obes Relat Metab Disord 1997; 21: 1038-1045.
62 Broomfield PH, Chopra R, Sheinbaum RC et al Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 1988; 319: 1567-1572.
63 Marks JW, Bonorris GG, Schoenfield LJ Effects of ursodiol or ibuprofen on contraction of gallbladder and bile among obese patients during weight loss. Dig Dis Sci 1996; 41: 242-249.
64 Drenick EJ, Simmons F, Murphy J Effect on hepatic morphology of treatment of obesity by fasting, reducing diets, and small bowel bypass. N Engl J Med, 1970; 282: 829.
[65] Luyckx F, Desaive C, Thiry A et al. Liver abnormalities in severely obese subjects: Effects of drastic weight loss after gastroplasty. Int J Obes 1998; 22: 222-226.
[66] Andersen T, Gluud C, Franzmann M et al. Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatology, 1991; 12: 224-229.
[67] Wadden TA Bartlett S, Letizia KA et al A relationship of dieting history to resting metabolic rate, body composition, eating behavior, and subsequent weight loss. Am J Clin Nut, 1992; 56S1: 203S-208S.
[68] Woolly SC, Garner DM Dietary treatment of obesity are ineffective Br Med J, 1994; 309: 655-656.
[69] Ayyad C, Andersen T A comprehensive literature study of long term efficacy of dietary treatment of obesity. Int J Obes 1994; 18 (suppl C): 78.
[70] Pories WJ, Swanson MS, MacDonald KG et al Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995; 222: 339-352.
[71] Sjostrom CD, Lissner L, Wedel H, et al Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. Obes Res 1999; 7: 477-484