Evidence Report

Chapter 1. Introduction

Obesity has been defined as excess body fat relative to lean body mass,[1] and in humans is the result of interactions of the environment with multiple genes. While humans are well-adapted to starvation, they are poorly adapted to over-nutrition. In fact, only for the past 100 years have humans have had a continuous surplus of food. The modern high-fat, high-calorie diet combined with physical inactivity has resulted in an epidemic of obesity and overweight.

The age-adjusted prevalence of obesity was 30.5 percent in 1999-2000.[2] While a precise estimate of the change in the prevalence of obesity over time is difficult because of changing definitions, nearly all clinical authorities agree that obesity is reaching epidemic proportions.[2-13] Obesity is currently defined as a body mass index (BMI) of 30 or greater: BMI is obtained by dividing body weight (in kilograms) by the height (in meters) squared. Those individuals whose BMI falls between 25 and 29.9 are termed "overweight." According to the most recent results of the National Health and Nutrition Examination Survey (NHANES), 15.5 percent of adolescents are currently overweight[14] and are displaying increasing rates of obesity-related chronic diseases not previously seen in children,[6] such as Type II diabetes. Moreover, efforts to stem this increase have failed thus far: Attempts to meet the body weight goal of the Healthy People 2000 Initiative[7] – to reduce the prevalence of overweight among adults to less than 20 percent of the population – did not succeed.

The United States is not alone in facing rising rates of obesity. In Canada, between 1985 and 1998, the overall prevalence of obesity increased in adults from 5.6 percent to 14.8 percent, and from 1981 to 1996, it tripled in children.[8, 9] The World Health Organization reports that there are more than 300 million obese people in the world, and the rising rate of obesity is no longer solely a problem of industrialized countries but is rapidly appearing in developing countries as well.[10, 11]

The health consequences of obesity include some of the most common chronic diseases in our society. Obesity is an independent risk factor for heart disease,[15] the most common killer disease in most developed countries. Type II diabetes, hypertension and stroke, hyperlipidemia, osteoarthritis, and sleep apnea are all more common in obese individuals.[16-18] A recent prospective study involving 900,000 U.S. adults reported that increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites.[19] Adult weight gain is associated with increased risk of breast cancer in postmenopausal women.[20] Weight loss of 5 to 10 percent can be associated with marked reductions in the risk of these chronic diseases [21]. In the Diabetes Prevention Program, a weight loss of about 5 to 6 percent among persons with a BMI of 34 kg/m^2, along with increased physical activity, resulted in a 58 percent reduction in the incidence of diabetes.[22]

In response to the increase in obesity, treatments for obesity have become both more numerous and more commonly used. This Evidence Report was commissioned to review the evidence on pharmacologic and surgical treatments of obesity in adults, adolescents, and children.

Prescription Weight Loss Medications

Drugs prescribed for weight loss can be divided into two categories, based on their putative mechanisms of action: appetite suppressants and lipase inhibitors. Appetite suppressants can be

further subdivided, based on the neurotransmitters on which they are believed to exert their effects.

Appetite Suppressants

Medications have been prescribed for their ability to suppress appetite for over half a century. The first prescription appetite suppressants were the sympathomimetic amphetamine derivatives, so described because they exert their effects by stimulating the sympathetic nervous system. Some of the newer appetite suppressants exert their effects by mimicking the sympathetic nervous system.

Sibutramine is a combined norepinephrine and serotonin reuptake inhibitor. Its putative effect on weight loss is attributed to appetite suppression and increased thermogenesis, secondary to stimulation of brown adipose tissue. Sibutramine was approved for use in conjunction with a low calorie diet as an aid to weight loss in 1998.[23]

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that was originally approved to treat depression. The original manufacturer submitted an New Drug Application for use of fluoxetine as a weight loss drug in the early 1990s; however, approval was not given, and the application was eventually withdrawn.[24]

Sertraline, like fluoxetine, is a SSRI. In the early 1990s, it was noted that sertraline administered to laboratory animals resulted in weight loss.[25,26]

Phentermine is a sympathomimetic amine of the β-phenethylamine family. It was approved for use by the FDA in 1959 as a short term aid to weight loss in conjunction with a low calorie diet and exercise. Unlike use of sibutramine, use of phentermine leads to the development of tolerance.[27]

Diethylpropion, like phentermine, is a sympathomimetic agent prescribed for short-term weight loss when used in conjunction with diet and exercise. Diethylpropion is similar in chemical structure to bupropion, which is approved as an antidepressant and as a smoking cessation aid and has also been tested as a weight loss aid.[28]

Zonisamide was approved by the FDA in 2000 for the treatment of partial (focal) seizures in adults with epilepsy, in conjunction with other anticonvulsants. Although the precise mechanism of action is unknown, it may exert its effects by acting as a sodium or calcium channel blocker. Because one of zonisamide's side effects is appetite suppression, its use as a weight loss drug has been tested.[29]

Topiramate is also an anticonvulsant, approved in the mid 1990s for the treatment of refractory seizures in conjunction with other anticonvulsants. In the process of testing topiramate for treatment of mood disorders, it was discovered that the agent might mitigate the weight gain often observed with antidepressant treatment[30], and a dose-ranging study established it does so in a dose-dependent manner.[31,32]

Lipase Inhibitors

Lipase inhibitors putatively aid weight loss by reversibly binding to the active center of the enzyme lipase, preventing the digestion and absorption of some dietary fats. Orlistat was approved in the late 1990s and is currently the only lipase inhibitor approved for weight loss. Orlistat inhibits approximately 30 percent of fat absorption, including the absorption of fat-soluble vitamins.[33]

Bariatric Surgical Procedures

A variety of surgical procedures have been used to induce weight loss for obese patients. These procedures result in weight loss via of one of two mechanisms: mechanically restricting the size of the stomach or bypassing a portion of the intestines; however, several procedures exert their effects by both mechanisms. Restricting the size of the stomach limits the quantity of food a patient can consume at a single meal. Malabsorptive (bypass) procedures decrease the proportion of nutrients that are absorbed from a meal. Details of selected bariatric procedures (i.e., those performed frequently now and in the past) are provided below.

Restrictive Procedures

Gastric banding. Gastric banding achieves weight loss by creating gastric restriction. The uppermost portion of the stomach is encircled by a band to create a gastric pouch with a capacity of approximately 15 to 30 cc. The band consists of an inflatable doughnut-shaped balloon whose diameter can be adjusted in the clinic by adding or removing saline via a reservoir port that is positioned beneath the skin. When the procedure was introduced, the bands were of a fixed size. However, the bands used today are adjustable, which allows the size of the gastric outlet to be modified as needed, depending on the rate of a patient's weight loss. Gastric banding does not produce malabsorption. Currently, almost all of the banding procedures are performed laparoscopically. While it is technically possible to remove the band (e.g., for failed weight loss or complications), doing so will expose the patient to potential risks associated with a second operation and, of course, will necessitate identifying an alternative method for weight loss.

Vertical Banded Gastroplasty (VBG) and other gastroplasty procedures. VBG uses the strategy of mechanical restriction to cause weight loss. The upper part of the stomach is stapled to create a narrow gastric inlet or pouch that remains connected with the remainder of the stomach. In addition, a non-adjustable band is placed around this new inlet in an attempt to prevent future enlargement of the stoma. As a result, patients experience a sense of fullness after eating small meals. Weight loss from this procedure results entirely from eating less: There is no component of malabsorption. VBG was one of the more common surgical procedures for weight loss in the late 1980s and early 19990s but has been superseded since 1995 by adjustable band procedures and procedures that combine mechanical restriction with bypass (see below).

Variations of gastroplasty procedures include horizontal gastroplasty and gastric partitioning without a band. These procedures are no longer performed because they had a high failure rate; thus, they are only of historic interest.

Bypass Procedures

Jejunoileal bypass. Jejunoileal bypass was one of the earliest procedures performed for weight loss. This procedure connected the proximal small intestine to a segment of distal small intestine (located a short distance upstream from the ileocecal junction), which bypassed the majority of the absorptive capacity of the small intestine. Although this procedure produced significant weight loss, patients developed complications such as severe malnutrition, chronic diarrhea, and liver failure. Thus, the procedure was abandoned about 25 years ago and is generally of only historical interest.

Combination Procedures

Roux-en-Y Gastric Bypass (RYGB). RYGB achieves weight loss through a combination of gastric restriction and malabsorption. Reduction of the stomach to a small gastric pouch (30 cc) results in feelings of satiety following even small meals. In addition, because this small pouch is connected to a segment of the jejunum (which is downstream), thus bypassing the duodenum and very proximal small intestine, absorptive function is reduced. The resultant "dumping" of sugar may also aid weight loss via the production of some unpleasant gastrointestinal symptoms following ingestion of high-density carbohydrate-containing foods. Typical symptoms include abdominal pain, cramping, and diarrhea.

The RYGB procedure has been performed regularly since the early 1980s; it was first performed laparoscopically in the early 1990s. RYGB is one of the most common types of weight loss procedures in current use, with almost 50,000 cases performed in 2001.

Biliopancreatic diversion (BPD). BPD, like RYGB, combines both the restrictive and malabsorptive strategies of obtaining weight loss. The stomach is partially resected, but the remaining capacity is generous compared to that achieved with the RYGB. As such, patients eat relatively normal-sized meals and do not need to restrict intake severely. Because the most proximal areas of the small intestine (i.e., the duodenum and jejunum) are bypassed, substantial malabsorption occurs. Although this procedure is not as commonly performed as either banding procedures or RYGB, the approach is strongly favored by some bariatric surgery specialists. The partial biliopancreatic diversion with duodenal switch is a variant of the BPD procedure that, until recently, was performed mostly in Italy and only rarely performed in the United States. Recently, a number of centers in the United States and Canada have begun to perform this procedure, which involves resection of the greater curvature of the stomach, preservation of the pyloric sphincter, and transection of the duodenum above the ampulla of Vater with a duodeno-ileal anastomosis and a lower ileo-ileal anastomosis.