ADULT OBESITY
DIAGNOSIS, ETIOLOGY AND MANAGEMENT

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REZUMAT

Obezitatea este o problemă medicală, socială și economică de mare importanță. Prevalența sa este în creștere, mai ales datorită factorilor de mediu care stimulează creșterea aportului alimentar și reducerea consumului energetic. Patogeneza obezității este neclară, dar cercetările recente au pus în evidență căile neurologice cu rol în controlul alimentației. Tratamentul obezității este dificil, cu rezultate nesatisfăcătoare și necesită aderență și multă motivație din partea pacientului, de aceea sunt necesare măsuri eficiente de prevenție. Tratamentul chirurgical a produs, până în prezent, cele mai bune rezultate.

Cuvinte cheie: obezitate, epidemie, indice de masă corporală, scădere ponderală, dietă, tratament chirurgical

ABSTRACT

Obesity is a medical, social and economical issue of paramount importance. Its prevalence is increasing mainly because of environmental factors that promote high food intake and decreased energy expenditure. Pathogenesis of obesity is unclear in many aspects, but new insights in neurological pathways that control feeding are now unveiled. Treatment is difficult, with poor results and demand extended adherence and motivation on behalf of the patient, therefore effective preventive measures are warranted. The most effective so far in treating obesity has been the surgical treatment.

Key Words: obesity, pandemics, body mass index, weight loss, diet, surgery

Learning objectives: This CME is based on internationally accepted obesity guidelines and aims to provide the reader:
- Tools to diagnose and evaluate the degree of weight excess and the risk of associated diseases;
- Recent information on epidemiology of obesity;
- Etiological and pathogenetical outline;
- Main treatment modalities currently available.

INTRODUCTION

Obesity is one of the hot topics within the medical community around the globe. A Medline search using as keywords "obesity" and "overweight" retrieved a number of over 48,000 articles and reviews published between 1996 and 2006.

The importance of obesity derives from the rising incidence and prevalence figures, the direct association with chronic conditions and with reduction in life-expectancy, as well as from the high economic costs (up to 6% of all health care costs in developed countries).[1] Obesity is part of the the so-called "New World Syndrome", a group of non-communicable diseases that is frequently observed in affluent and underdeveloped countries alike: obesity, type 2 diabetes mellitus, hypertension, and cardiovascular diseases. This cluster of diseases is now known as the metabolic syndrome.[2] All these have determined the researchers to label obesity as the disease of the 21st century.[3]

As a recognition of its importance, action plans to tackle obesity have been devised at national and international level. In 2005, European Community released a green paper on Promoting Healthy Diets and Physical Activity, while in the USA, Centers for Disease Control and Prevention have designed The Nutrition and Physical Activity Program to Prevent Obesity and Other Chronic Diseases.[4,5]

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DEFINITION, ASSESSMENT AND CLASSIFICATION

Definition

Obesity is defined as an increase in body weight 30% above the normal value for age, sex and height, on the account of fat tissue, resulting in a body mass index of 30 kg/m^2 or more.[6-8]

Assessment

Although sophisticated methods exist that can measure the extent and distribution of excess fat (densitometry, plethismography, dual X-ray absorptiometry, computed tomography and magnetic resonance imaging), they are expensive and rarely available in clinical practice.[6]

Weighing is the first step in assessing obesity. Excess weight results from comparison of measured weight against the ideal weight. The latter is either derived from available weight tables (such as Metropolitan Life Tables), or computed using various equations, some of which are presented in Table 1.[9,10]

Table 1. Equations for ideal body weight.

Formula	Men	Women
Broca Index	H - 100, ± 10%	H - 100, ± 15%
Metropolitan Life Insurance Company	50 + 0.75 x (H-150)/4 + (A-20)	The formula for men is multiplied with 0.9
Lorentz	(H-100) - (H-150)/4	(H-100) - (H-150)/2

H= height (in cm), A= age (years)

Currently, the most used tool for diagnosis and classification of obesity is the body mass index (BMI), also known as Quetelet index. BMI is more accurate in assessing weight excess than measurement of weight alone, is readily available and is reproducible. BMI is computed by dividing weight (in kilograms) to square height (expressed in m).[11] Despite the fact BMI is only a crude measurement, it reflects closely the amount of body fat in most of the subjects.[2] It must be kept in mind that BMI is less accurate in case of edema, high muscle mass or muscle wasting (e.g., older subjects have less muscle than younger ones, thus for a given BMI, their fat mass is higher).[8] Furthermore, at a given BMI, body fat content differs with ethnicity and gender (higher in Caucasians, and in women).[2]

The distribution of body fat is evaluated by measurement of anthropometric indices: waist-to-hip ratio, abdominal index (the waist-to-height index), and waist circumference.

Waist-to-hip ratio is obtained by dividing the waist circumference to hip circumference. A ratio > 0.9 in women and > 1.0 in men is considered abnormal showing an increase in abdominal fat.[12]

Waist circumference has somewhat replaced waist-to-hip ratio in assessing the extent of intra-abdominal fat. Measurement of waist circumference is performed at the level of the top of iliac crests with subject in standing position, at normal respiration, with the measuring tape tight but not compressing the skin and held parallel to the floor.[13] Intra-abdominal fat accumulation, indicated by a waist circumference above 102 cm in men and above 88 cm in women) in subjects with a BMI between 25 and 34.9 kg/m^2 is associated with an increased overall mortality and a high risk for obesity-associated conditions such as type 2 diabetes, dyslipidemia, high blood pressure and coronary heart disease.[14-17] However, waist circumference brings no supplementary information regarding health risks in subjects with BMI ≥ 35 kg/m^2.[2,11] Waist circumference may be a better estimate of body fat in older subjects, who have a lower fat-free mass and in whom BMI underestimates the obesity-related risk, and in some ethnic groups genetically predisposed to unfavorable distribution of fat despite normal body weight.[18]

The cut-off values for acceptable waist circumference were lowered to 80 cm for women and 94 cm for men, based on epidemiological studies that demonstrated that risk increased at a lower threshold, and these values were adopted in 2005 by the International Diabetes Federation in the newly revised criteria for the definition of metabolic syndrome. These new criteria also acknowledged the need to use different threshold values, depending on the ethnicity (i.e., the above mentioned are valid for Caucasians, and are lower in Indian and Asians).[18]

In a recently published study, body fat was measured using plethismography and was compared to BMI and waist circumference regarding the correlations with the metabolic risk factors (triglycerides, cholesterol, HDL-cholesterol, uric acid, systolic blood pressure, insulin resistance by homeostasis model assessment (HOMA-IR) and C-reactive protein). Direct assessment of fat mass showed no practical advantage over BMI or waist circumference, as the correlation with metabolic risk factors was weaker for the former. Moreover, the differences found between BMI (as an indication of general adiposity) and waist circumference (as a measure of central adiposity) in predicting obesity-related metabolic risk were small, indicating a similar value of the methods.[19]

Existing clinical practice guidelines recommend both BMI and waist circumference as assessment tools of excess weight.

Classification

Obesity can be classified on different grounds: severity of weight excess (expressed as BMI), etiology, and clinical.[9]

Table 2 presents weight status classification depending on BMI, as well as the risk for associated diseases (type 2 diabetes, hypertension, cardiovascular disease) relative to waist circumference. This classification is the primary tool in the evaluation of obesity and associated risk and has been universally accepted.[2]

Table 2. Weight status classification.[2]

	BMI (kg/m^2)	Disease risk relative to normal weight and waist circumference	
		Men: ≤ 102 cm Women: ≤ 88 cm	Men: ≥ 102 cm Women: ≥ 88 cm
Underweight	<18.5	-	-
Normal	18.5-24.9	-	-
Overweight (preobese)	25-29.9	Increased	High
Obesity	> 30		
-Grade I	30-34.5	High	Very high
-Grade II	35-39.9	Very high	Very high
-Grade III (extreme, morbid)	≥ 40	Extremely high	Extremely high

Etiological criteria divide obesity into primary, and secondary to other diseases (endocrine- Cushing syndrome, myxedema, hypothalamic diseases) or to the use of some drugs (insulin, sulfonylureas, antiepileptic drugs, antidepressants, corticosteroids). Primary obesity comprises the majority of cases and is usually diagnosed after causes for secondary obesity are ruled out.[9,13]

Clinical classification is done based on fat tissue distribution:[9]

- Android obesity, or apple-shaped: trunkal fat disposition (waist-to-hip ratio > 0.9 in women and > 1.0 in men), carries a higher risk for cardiovascular diseases.

- Gynoid obesity, or pear-shaped: excess fat is predominantly distributed around hips and thighs, has a lower risk for associated diseases. Waist-to-hip ratio is < 0.9 in women and < 1.0 in men.

- Particular forms: generalized obesity from some genetic syndromes (e.g., Prader Willi), partial or localized obesity (paralipodystrophies, Dercum disease).

EPIDEMIOLOGY

Adult obesity rates and prevalence are increasing worldwide at an alarming pace. Epidemiological reports from Europe, North America, Africa, Asia all demonstrate that in the past 40-50 years prevalence of overweight and obesity has sky-rocketed, regardless of age, gender, occupation, and social status.[1,20-22]

Conservative estimations of WHO show that currently one billion people on the globe have a BMI ≥ 25 kg/m^2, with 300 million from them having a BMI equal or greater than 30 kg/m^2, i.e. are obese. In the past 30 years rates have doubled in some developed countries, and the trend is similar in the developing nations.[1] Currently, it is generally accepted that we are facing a true obesity pandemic. The obesity pandemic started in the world's rich nations (USA, Western Europe) and then it overtook the world's underdeveloped countries especially in their urban areas.[23]

Obesity prevalence and trends are best documented in the USA, by National Centers for Health Statistics (NCHS), that conducted six consecutive population-based health surveys between 1974 and 2004, called National Health and Nutrition Examination Surveys (NHANES). Between NHANES II (1978-1980) and NHANES 2003-2004, the percentage of people with a BMI ≥ 25 kg/m^2 increased with 50%, while obesity rates doubled. (Table 3)[20]

Latest data show no differences in gender-specific prevalence, but important variations are seen with ethnicity: obesity is more prevalent in African Americans and Mexican Americans, and less frequent in Asian Americans.[24]

World Health Organization (WHO) reports show similar trends in Europe. Between 25 and 75% of adult population have a BMI ≥ 25 kg/m^2, with figures higher than 50% in many countries. Obesity affects up to 20% of men and up to 30% of women, with Eastern countries rapidly catching up their Western counterparts.[21]

In Romania, WHO data show that 37.7% of men and 40.5% of women have a BMI equal or greater than 25 kg/m^2, with 9.1% of men and 19.1% of women falling in the obese group.[21,25]

Table 3. Age-adjusted prevalence of overweight and obesity in adults (20-74 years) in USA (modified from Ref. 20).

	NHANES II (1976-1980)	NHANES III (1988-1994)	NHANES 1999-2000	NHANES 2001-2002	NHANES 2003-2004
Overweight (BMI 25 kg/m^2 - 30 kg/m^2) (%)	32.0	32.7	33.6	34.4	33.3
Obesity (BMI ≥30 kg/m^2) (%)	15.0	23.2	30.9	31.3	32.9
BMI < 25 kg/m^2 (%)	53.0	45.	35.5.	34.3	33.8

Overweight is also frequent in Australia (67% of adult males and 52% of adult females were overweight or obese in 1999-2000) and Oceania (between 36 and 76%). Prevalence data is fragmented and scarce for the rest of the world, with lower rates found in sub-Saharian Africa, India, China and Japan.[2,22] Most importantly, even in low-prevalence countries, temporal trends are ascending, such as happened in China, where the combined prevalence of overweight and obesity increased from 14.6 to 21.8%, in the past decade.[26]

In children and adolescents, overweight (defined as a BMI $\geq$ 95th percentile for age and height) has also increased with an alarming speed. In USA, the figures tripled in the past 30 years (from 6.5% to 18.8% in the 6-11 years old and from 5% to 17.4% in the 12-19 years old).[20,24] Similar trends are reported for the European region, with highest rates found in Greece, Portugal, United Kingdom and Malta.[27] This will have dramatic effects in the future, as overweight children turn into young obese adults, with a higher risk for developing type 2 diabetes and early cardiovascular disease.[21]

OBESITY ASSOCIATED HEALTH RISK

The relationship between excess weight, disease and mortality has been recognized since ancient times but has been documented only recently, based on the long-term epidemiological studies, such as Framingham Study and US Nurses Health Study.[28,29]

Mortality

Obesity is associated with an increased overall mortality, parallel to the magnitude of BMI.[6] (Fig. 1) Data from Framingham Study in the United States showed that a BMI $\geq$ 30 kg/m^2 at the age of 40 reduces life expectancy in non-smoking males and females by 5.8 and 7.1 years, respectively. Life-expectancy is reduced with 13 years for both sexes if obesity is associated with smoking.[30] Excess mortality in the obese is accounted for by the increased cardiovascular and cancer mortality.[31]

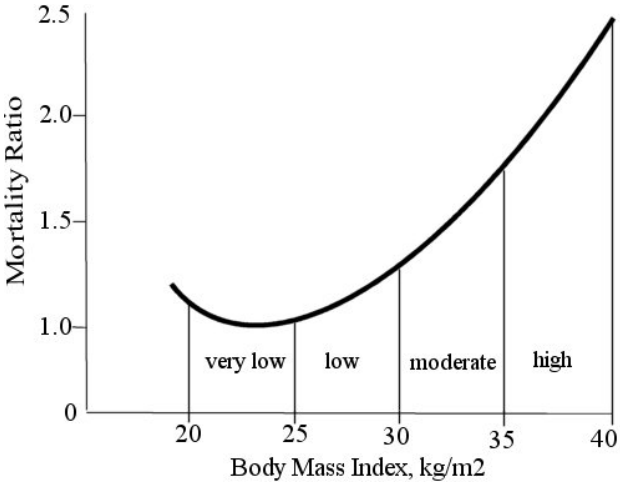

Figure 1. The correlation between the BMI and overall mortality.[6]

Morbidity

Increased body fat is accompanied by profound changes in physiological and metabolic functions, directly dependant on the degree of weight excess and on its distribution. Obesity is associated with numerous conditions, which can occur either as the consequence of metabolic impairment induced by obesity or as the direct effect of excess body weight.[22] The most important associations are presented in Table 4. Proportion of disease prevalence that can be attributed to obesity is 61% for type 2 diabetes, 34% for uterine cancer, 30% for gallbladder disease, 24% for osteoarthritis, and 17% for hypertension and coronary heart disease.[13]

Table 4. Diseases associated with obesity (adapted from Ref.22).

Relative risk for the diseases compared to non-obese individuals	Consequence of metabolic impairment	Consequence of excess weight
> 3 (highly increased)	Insulin resistance	Sleep apnea
	Type 2 diabetes mellitus	Pickwick syndrome
	Hypertension	Asthma
	Dyslipidemia (increased triglycerides, decreased HDL cholesterol, increased LDL cholesterol)	Depression
	Non-alcoholic fatty liver disease	
2-3 (moderately increased)	Coronary heart disease	Osteoarthritis
	Stroke	Hernia
	Congestive heart failure	Psychological problems
	Hyperuricemia	
1-2 (slightly increased)	Cancer (breast, endometrial, colon)	Varicose veins
	Impaired fertility	Musculoskeletal problems (back pain)
	Polycystic ovaries	Stress incontinence
	Acanthosis nigricans	Edema, cellulitis

The cardiovascular risk associated with obesity is either a direct effect of excess weight on the heart, or an indirect consequence, through influencing other risk factors, such as diabetes, hypertension and lipids.[31] In fact, these diseases (associated with metabolic impairment) are largely mediated by insulin resistance. Insulin resistance is defined as the requirement of an abnormally large amount of insulin for a normal biologic response that leads to a compensatory increase in insulin secretion and hyperinsulinemia.[9]

Insulin resistance is the key pathologic feature underlying the metabolic syndrome. Labeled as "sindrome X" or CHAOS syndrome (**c**oronary heart disease, **h**ypertension, **a**bdominal **o**besity and **s**troke), this entity encompasses a cluster of clinical and metabolic abnormalities: abdominal obesity, altered glucose metabolism, arterial hypertension, dyslipidemia, prothrombotic state, chronic subclinical inflamation and endothelial dysfunction.[32] The latest diagnostic criteria for metabolic syndrome are those adopted by IDF in 2005. (Table 5)

Table 5. 2005 IDF Criteria for definition and diagnosis of metabolic syndrome.[18]

Abdominal obesity (waist circumference > 94 cm in men and > 80 cm in women) plus any two of the following:

- Elevated triglyceride levels, ≥ 1.7 mmol/L (≥ 150 mg/dL) or receiving specific treatment for this lipid abnormality
- Reduced HDL-cholesterol, < 1.03 mmol/L (< 40 mg/dL) in men or < 1.29 mmol/L (< 50 mg/dL) in women, or receiving specific treatment for this lipid abnormality
- Raised BP, systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, or receiving treatment for previously diagnosed hypertension
- Raised fasting plasma glucose levels, ≥ 5.6 mmol/L (≥ 100 mg/dL), or previously diagnosed with type 2 diabetes.

ETIOPATHOGENESIS

Etiology of obesity

There is general agreement on the fact that the etiology of obesity is represented by various factors (social, behavioral, physiological, metabolic, cellular, and molecular) that interact in complex ways and lead to a positive energy balance.[2,11,22] However, the obesity epidemics is primarily the consequence of the environmental and behavioral changes, as the prevalence increased in a too short period of time that cannot account for significant genetic alterations.

Environment

The modern, industrialized environment (the so-called obesogenic environment) is a major determinant of overweight and obesity, primarily by influencing food intake and physical activity.[2,11,22]

Modern diet has undergone significant changes regarding both quality and quantity, and dietary patterns.

Firstly, food is available in large amounts, is easily reachable and is inexpensive. Diet is calorie dense due to intake of high-fat, high-carbohydrate, highly-processed aliments. The food is made more palatable by addition of sugar, fat and other taste enhancers.

High calorie consumption is stimulated by aggressive food marketing in mass media, supermarkets and restaurants and by the increased portion size, that offer more value for money.[11] The consumption of caloric beverages also contributes significantly. The typical meal sold in fast-food restaurants such as MacDonald's serves as the prototype for the changes in the diet of the modern subject. (Table 6)

Table 6. Calorie content of a fast-food meal.

	Quantity	Calories /serving	Carbs (g)	Fat (g)	Protein (g)
French fries, medium	100g	305	38	16	3
Hamburger	100 g	250	32	8	12
Coke	400 g	176	44	-	-
Ice cream	150 g	270	50	5	5
Total		~ 1000 cal	~ 150 g	~ 30 g	20 g

A recent study on dietary intake of overweight or obese subjects in comparison with normal weight individuals showed that the former had a higher intake of fat, less complex carbohydrate and fiber than normal weight controls. Number of fruit portions eaten daily was negatively related to percent of body fat.[33]

The chemical pollutants of the environment are the novel putative obesogenic factors as they can alter the normal control mechanisms of fat accumulation and energy expenditure. Wide-spread xenobiotic chemicals such as environmental estrogens and organotins have been documented to perturb the adipogenic mechanisms and to stimulate the lipogenesis.[34]

Dietary patterns have also changed. The number of meals and snacks has increased, people are eating more meals outside the home and they rely more heavily on convenience food that is highly processed.

Decreased physical activity is also the direct consequence of technology progress. The obligatory activity has been reduced by mechanization. Many

people are caught in sedentary daily routines consisting of sitting at work, sitting in traffic, and sitting in front of a television or a computer monitor for most of their waking hours.[2,22]

Genetic factors

Twin and adoption studies showed that genetic factors are responsible for 30 to 50% of the variation in body weight between individuals and are likely to influence the response to dietary interventions.[22] Obesity runs in the family, as, compared to general population, its occurrence is five times more likely in first degree relative of obese subjects and two times more likely in the first-degree relatives of overweight individuals.[35]

However, obesity is rarely a single-gene disease, apart from few cases of Mendelian and monogenic obesity that manifest with early, severe fat excess. In the remaining of cases, multiple genes are most probably involved, as more than 250 genes or chromosome regions with the potential to influence body weight have been identified.

The role of genetic factors is modulated by the environment, i.e., an obesogenic environment helps those obesity-prone to develop obesity, while those lacking this predisposition stay slim or gain only a few kilograms.[22]

In fact, the ability to store energy for times when food was scarce was a survival advantage in the community of hunters and gatherers of prehistoric humans. Fat cells are able to store energy very effectively and to release it in times of need, allowing human to survive starvation for as long as several month.[12] Those who lacked this ability were removed by natural selection. What was then beneficial is nowadays detrimental, as the same metabolic efficiency is driving the excessive accumulation of fat.[12] One can say the humans are metabolically equipped to resist starvation, but lack adaptive mechanisms to abundance.

Stress and psychological factors

There is a bidirectional relationship between psychological stress and obesity, however it is not clear which is the cause and which is the effect. For sure, anxiety, depression, distress, emotional eating, and altered cortisol secretion are commonly encountered in overweight and obese subjects.[2,11,22]

Psychological stress can be a consequence of obesity because of social and economical discrimination experienced by many obese individuals. On the other hand, stress may induce obesity by stimulating cortisol secretion and by inducing a compensatory food behavior (binge eating, excessive carbohydrates intake in stressful situations). Positive and negative moods are associated with significantly larger meals, compared with neutral moods. Furthermore, stress management and learning of coping behaviors are associated with long-term maintenance of weight loss.[22]

Factors associated with life stage or events and other factors

Obesity is more frequently encountered in individuals who were overweight or obese in childhood and adolescence. Other physiological states that are associated with weight gain are pregnancy and menopause.[2,11]

Aging is a natural process characterized by a slow-down of metabolic processes and reduced physical activity. Gradual weight increase has been observed with age.[7]

Quitting smoking, marriage, giving up sport, holidays and festivities that disrupt the daily routine are life events associated with a higher risk for weight gain.[11] Lower socioeconomic status is linked to overweight and obesity, especially in black women.[7,22]

A variety of other factors such as virus infection of fat cells, energy supply from bacterial fermentation of indigestible food components, psychosocial factors, sleeplessness or poor quality of sleep and early life programming were also suggested to play a role in obesity, but supporting evidence is poor.[36]

Pathogenesis

Basically, obesity is the consequence of a long-term imbalance between energy intake and expenditure that favors deposition of the resulting excess as fat. This imbalance can be the result of either the increase of the food intake, the decrease of energy expenditure or, more frequently, of the combination of the two.[2,7,9,12] The intimate mechanisms of this process is largely unknown, despite intensive research in the field.

Body weight is subject to a finely tuned regulation that constantly adjusts the energy expenditure to the energy intake. A weight increase of only 10 kilograms during a lifetime represents a minor 0.1% of calories ingested in the same period, which shows remarkable precision.[7]

Human and animal studies have demonstrated that weight is maintained within certain limits, much similar to other body homeostatic systems.[37] Body weight set point is a concept suggesting that for each individual there is a certain level at which the body weight is

maintained, and displacement from this level induces adaptatory changes that try to return the weight to the predefined level. An individual body weight set-point can change during a lifespan and apparently this is what happens in obese subjects, who switch to a higher level and will resist subsequent attempts to reduce excess weight.[38-40]

Regulation of body weight is done by upper neurological centers that control the peripheral systems involved in energy balance, with the aim to adjust intake to expenditure. The balance between energy intake and expenditure depends on how the brain is informed about the current energetic status, reflected by energy stores (represented mainly by fat). The whole process involves bidirectional signaling between the control and effector systems. (Fig. 2)

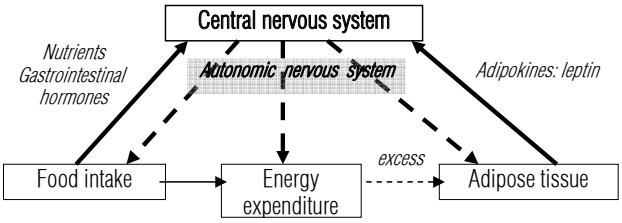

Figure 2. The players of the body weight regulation.

Energy balance in humans

Human metabolism is governed by the second principle ot thermodynamics, i.e. energy stores = energy intake - energy expenditure.[2]

Energy intake is represented by the calories contained in food and drink ingested. Caloric value of macronutrients is 4 cal/g for proteins and carbohydrates, 9 cal/g for fats and 7 cal/g for alcohol. Fibers provide 1.5 cal/g.[2]

Total energy expenditure (TEE) is composed of basal or resting metabolic rate (BMR), metabolic response to food (dietary-induced thermogenesis, specific dynamic action of food or thermic effect of feeding- TEF), adaptive thermogenesis, and energy needed for physical activity (PA). Additional energy is needed in special groups: to support growth in children and in women during pregnancy, and for milk production during lactation.[6]

BMR makes 45 to 70 % of daily TEE and is the energy needed to support functions essential for life (cell function and replacement, protein synthesis, maintenance of body temperature, continuous function of internal organs, all metabolic processes). BMR is influenced mainly by age (decreased in older people), gender (higher in males), body size and composition (increases parallel with the muscular mass).[6] BMR is approximately 60 kcal/h for men and 50 kcal/h for women. BMR is either measured by indirect calorimetry, or computed from equations such as Harris Benedict ad Mifflin, that take into account age, height, and weight.[42] (Table 7) A more simple formula for BMR uses only weight: males: 716 + 15 x W (kg), females= 716 + 12 x W(kg), but needs adjustment for age (- 5 % for 30-35 years, - 10% for 36-49 years, -15% for 50-69 years and -20% for 70 years or older).[22]

Table 7. BMR equations.

Harris-Benedict equations:
For men:BMR= (13.75 x IW) + (5.0 x H) - (6.76 x A) + 66
For women:BMR= (9.56 x IW) + (1.85 x H) - (4.68 x A) + 655
Mifflin equations:
For men: BMR= (10 x W) + (6.25 x H) - (5 x A) + 5
For women:BMR= (10 x W) + (6.25 x H) - (5 x A) - 161

W=actual weight in kg, IW= ideal weight, in kg, H=height in cm, A=age in years

TEF is the energy needed for the ingestion and digestion of food, and for the absorption, transport, processing and deposition of nutrients. It accounts for approximately 10% of TEE.[2]

PA represents the second most important component of TEE, and the most variable of all, ranging from 20% in sedentary individuals to 50% of TEE in active subjects. It is composed of activities of daily life ("obligatory" PA) and by discretionary physical activities, such as regular practice of exercise or sports, participation in individual or social leisure activities.[2]

Estimation of TEE is done by multiplying BMR with an activity factor that depends on the level of physical activity: 1.2-1.4 for inactive, 1.5-1.8 for moderately active, and 1.9-2.3 for very active.[22]

Adipose tissue

Classically, the adipose tissue was considered to have two primary functions: to store excess energy as triglycerides and to release fatty acids and glycerol for metabolism at distant sites, in response to various signals.[43] If the energy balance is positive, the excess is stored as fat in the adipocytes, that contain more than 90% of body energy reserve. Normally, the adipose tissue constitutes 12 to 20% of body weight in man, and 20 to 30% in woman, but increases significantly in obesity to such extent its calorie content can triple.[6]

A third function, recently recognized and increasingly important, is to release into the blood numerous substances, the adipokines, that exert their action either locally (autocrine or paracrine action) or at distant locations (hormones), much like an endocrine gland. These substances play an important role in

metabolic regulation: leptin, adiponectin, resistin, agouti-related peptide, TNF-α, angiotensinogen are but a few of adipokines.[42,44]

Leptin is one factor released by the fat cells and acts on its specific receptors found in the hypothalamus stimulating the satiety center, thus reducing the food intake; concomitantly leptin blocks the central action of neuropeptide Y, a potent stimulator of food intake. Low levels of leptin were found in some forms of obesity, but in the majority of cases leptin is increased, suggesting a state of leptin resistance.[45]

Central nervous system

The brain exerts its control through the hunger and satiety centers located in hypothalamus: solitary tract nucleus (integrative center), ventromedial hypothalamus (satiety centers), paraventricular and lateral hypothalamus (hunger centers). Experimental lesions of these centers lead to extreme alteration of food intake.[12]

Hypothalamic centers are informed on the availability of peripheral nutrients through nutrient-induced peripheral signals such as leptin, insulin, gastrointestinal hormones (colecystokinin, ghrelin), neurotransmitters, and via direct metabolic signaling through levels of plasma nutrients (glucose, free fatty acids, amino acids). These substances either stimulate (ghrelin, neuropeptide Y, melanin concentrating hormones, growth hormone releasing hormone, galanin) or decrease (colecystokinin, α-MSH, corticotropin releasing hormone, glucagon-like peptide 1, leptin) food intake. Some, though, exert a dual action, depending on the type of receptor bound (norepinephrine, serotonin).[43]

As a response to nutrient availability, these hypothalamic regions exert a negative feedback (via autonomic nervous system) on food intake, on endogenous glucose production and on adipocytes metabolism.[12]

Endocannabinoid system has been identified as a new player in controlling appetite, food intake and energy balance. Endocannabinoids are amides (anandamine and arachidonoylglycerol) synthesized from membranar phospholipids and act in various brain locations (including mesolimbic reward circuits and hypothalamus.[46] They are the main endogenous agonists of cannabinoid receptors.

Cannabinoid receptors were discovered as the sites of action for Cannabis sativa derivates such as hashis and marijuana, are located in the brain (CB1) but also in peripheral organs (CB2) and have multiple roles in modulation of central and peripheral functions. The endocannabinoid system modulates rewarding properties of food by acting at specific mesolimbic areas in the brain.[47]

In the hypothalamus, CB1 receptor and endocannabinoids are part of the systems controlling appetite and food intake. Furthermore, the endocannabinoid system was shown to also exert a peripheral action on adipocytes, hepatocytes, the gastrointestinal tract, and, possibly, skeletal muscle, being also involved in controlling energy expenditure.[47,48]

Stimulation of cannabinoid receptors is followed by increased food intake and lipogenesis, while cannabinoid blockage has been associated with a reduced appetite and increased lipid oxidation.[49]

TREATMENT OF OBESITY

Ideally, successful treatment of obesity would be defined as normalization of body weight and its indefinite maintenance, which, in the light of current results, seems a utopia.[43]

So far treating obesity has produced disappointing results, as, even if many programs have achieved weight reduction, the risk of regaining it once the treatment has ended is extremely high. More than 80% of those who lose weight regain it , unless a weight maintenance program is instituted for long-term, most probably lifelong.[50]

Causes for weight relapse include returning to previous dietary habits and the decrease in BMR that occurs with the restrictive diets prescribed for weight reduction.[22,41]

Thus, therapy goals were redefined as follows: to reduce body weight and to maintain a lower body weight over the long term; or at least to prevent further weight gain.[41]

A reasonable goal for the first 6 months of therapy would be a reduction of 10% from initial weight. Even if modest, this decrease has significant and immediate impact on the associated health risks: decrease in systolic and diastolic blood pressure, glucose and improvement of lipid profile.[31] Table 8 presents realistic goals for weight reduction.[22]

Table 8. Treatment goals for weight loss.[22]

Duration	Weight	Waist circumference
Short term	1-4 kg/month	1-4 cm/month
Medium term	10% of initial weight	5% after 6 weeks
Long term	10-20% of initial weight	88 cm (women) 102 cm (men)

Weight maintenance is defined as a gain of less than 3 kilograms at 2 years after ending the treatment phase, or the sustained 4 cm reduction in waist circumference, or a reduction in initial weight of 5 percent or more and the maintenance of this loss for at least one year.[22,41]

In fact, since obesity is a chronic condition, it seems logical that treatment should continue a lifetime. In other words, a weight loss program should be mandatory followed by a maintenance program, which is a less restrictive variant of the initial treatment.

National Weight Control Registry (NWCR) is a United States database that contains self-reported data from subjects who were successful in losing weight and keeping it off for at least one year. According to NWCR, most frequently reported measures were: combination of diet and exercise, participation in a formal program (e.g., Weight Watchers), professional help (dietitian, psychologist), frequent weighing, calorie count, and limitation of food quantity. Interestingly, 91% of them had previous unsuccessful attempts to lose weight, while 77% mentioned an emotional or medical motivation for the successful attempt.[52]

Some studies found that weight maintenance or less weight regain at follow-up were predicted by an initial weight loss of more than 20 kg, eating breakfast, and a low-fat intake coupled with increased activity level.[53-56]

Weight loss is recommended in the following groups:[22,41]

- BMI $\geq$ 30 kg/m^2, regardless of other risk factors;

- BMI between 25 and 30 kg/m^2 or with a waist circumference > 102 cm (men), > 88 cm in women, associated with two or more of the following: cigarette smoking, hypertension, low HDLc, high LDLc, impaired fasting glucose or diabetes, family history of premature cardiovascular disease, age above 45 years in men, above 55 years in women.

Weight loss therapy is not indicated in pregnant or lactating women, severe psychiatric or somatic conditions, which could be worsened by the caloric restriction.[13]

Treatment approaches include dietary changes, increase in physical exercise, behavior modification, pharmacotherapy, and surgical procedures, and are more effective when used in combination. A brief description of main features of these approaches is subsequently presented, and treatment results for each method summarized for comparison in Table 9.

Table 9. Comparative efficiency of various obesity treatment modalities - at 1-2 years follow-up (compiled from Ref. 22).

Approach	Mean weight loss at 1-2 years follow up
VLCD	-4.2 kg (without behavior and lifestyle measures during maintenance phase)
	-11.8 kg (if lifestyle and behavior measures are added during maintenance)
LCD	-6.7 kg
Reduced energy diets	-3.9 kg
Meal replacement	-6 kg
Exercise	
-alone	-1.8 kg
-with diet	-3 kg
Behavior therapy	-4.8 kg
Sibutramine	
-alone	-5.6 kg
-with diet	-10.8 kg
Orlistat + low fat diet	-8.4 kg
Biliopancreatic diversion	-53 kg
Gastric bypass	-46 kg
Gastroplasty	-41 kg
Laparoscopic gastroplasty	-31 kg

Dietary interventions consist of calorie-control diets and popular diets.

Calorie control diets aim at limiting the number of calories ingested daily and depending on calorie restriction are classified in: starvation, very low calorie diets, low calorie and restricted energy diets, and meal replacement programs.[57]

Starvation diets (0-400 kcal/day) include fasting and results in a loss of lean body mass and mineral loss due to diuresis. Currently their use is restricted, due to severe side effects.[58]

Very low calorie diets (VLCDs) provide 400-800 kcal/day and are high in protein (min. 1 g/kg of body weight). Also known as protein-sparing modified fasts, VLCD use a premixed liquid comercially available from pharmacy (e.g. Optifast), or may be made up of normal foods (meat, fish, poultry, vegetables), but need vitamin and mineral supplementation. They are reserved for patients with a BMI > 30 kg/m^2, who failed other methods and should be conducted under specialized supervision.[58] Although weight loss occurs at a fast pace (1.5-2.5 kg/week, up to 26 kg at the end of treatment phase), long term results prove these diets are not superior to low-calorie diets, as weight regain follows the resumption of normal eating pattern.[59] Using behavior modification and drug therapy in the post-treatment phase counteract weight regain. Therefore, return to normal feeding needs to be gradual (8 weeks or longer), using partial VLCD.[22]

Low calorie diets (LCD) and reduced energy

or balanced-deficit diets are the more commonly used interventions that modify the macronutrient composition of the diet. Total energy intake is mildly restricted in reduced energy diets, to produce a deficit of 500-1000 kcal/day, while the restriction is more important in low-calorie diets, where energy intake is controlled to be 1000-1200 kcal/day.[22,57] The expected initial weight loss is 0.5-1 kg/week in reduced energy diets, versus 1-1.5 kg in LCD.[11] These diets are moderate in fat (20% to 30%), high in carbohydrate (55-60% of calories) and moderate in protein (15-20%). Salt intake is limited to 6 g/day, while calcium is recommended at 1000-1200 g/day and fibers 20-30 g/day.[60]

Other studies demonstrated a beneficial effect on weight loss of high calcium intake (1200-1300 mg/day), in form of dairy products or calcium supplements, if added to hypocaloric diets.[61,62]

Meal replacements are prepared meal plans or supplements (such as vitamin- and mineral-fortified shakes, soups and bars) that substitute a normal meal. They contain approximately 200 calories per serving and approximately 50% to 60% carbohydrate, 30% protein, and 10% fat. The replacements help control calorie intake but also reduce sensory stimulation and the need to make decisions about portion size.[58]

Popular diets are a 30 billion $ per year industry in the United States and attract individuals by promising rapid and effortless weight reduction.[58] The basic principle of these diets is a change in favor of one or another nutrient, claming that this change stimulates weight loss. Popular diets may be successful on short-term as they are hypocaloric. Sometimes vitamin and mineral supplementation is needed in unbalanced popular diets. Based on their content, they can be classified as:[60]

- High-fat (55% to 65%), low-carbohydrate (<100 g per day) - Atkins diet;
- High-protein, low carbohydrate diets - Zone diet;
- Low-fat (11% to 19%), and very-low-fat (<10%), very-high-carbohydrate (>65%), moderate-protein diets (10-20%): Ornish diet, Pritkin diet.

It has been much debated whether diet composition in macronutrients makes any difference in weight loss. Diets either low-fat (20-25%) or high-fat (40% fat), high carbohydrate (55-60%) and low-carbohydrate (<100 g/day) produce similar weigh loss, as long as they are hypocaloric.[63,64] Furthermore, no long-evidence is available to confirm the potential benefits of low-carbohydrate, high-fat and high protein, compared with numerous evidences supporting the low-fat approach.[22] Low carbohydrate diets may be better tolerated as ketogenesis is stimulated.[60]

Other diet plans that are worth mentioning are modified-fat diets and low glycemic index diets.

Modified-fat diets consist in replacing saturated fat with monounsaturated fatty acid from olive oil, nuts, avocado and is designed based on Mediterranean diet. If also energy restricted, these diets will produce a weight loss similar to other energy-restricted diets.[22]

Low-glycaemic index diets recommend intake of foods with a low glycemic index (GI). The GI is used to measure the relative rise in blood glucose after a standard amount of dietary carbohydrate. Low GI foods include: non-starchy vegetables, legumes, fruits, and dairy products, while most refined grain products, potatoes and sugar-containing food have a high GI. Proposed recently as effective in inducing weight loss, these diets be beneficial, but long-term data is missing.[22]

A popular diet using GI is the one proposed by Montignac, which, in addition to advising consumption of low GI, recommends certain food combinations and bans others and dismisses calorie count as unnecessary.[65] Except for the low GI theory, the rest of the recommendations in the Montignac diet lack scientific foundation.

It is difficult to review all popular diets currently in use, as there are very numerous. However, the reader should learn to assess them in terms of energy and nutrient content and compare them with the dietary approaches outlined above, already available and scientifically proved.

Behavioral interventions

Behavioral modification relies on analysis of behavior aimed at detecting what are the circumstances associated with eating, exercise, or thinking habits.[2] Following identification, attempts are made to correct behaviors associated with an unhealthy lifestyle and weight gain, for example emotional, night-time or binge eating, negative thoughts, reduced self-esteem.[22] Strategies that have been useful in programs for weight loss and maintenance include self-monitoring, stimulus control, cognitive restructuring, stress management, social support, physical activity, and relapse prevention.[57]

Physical activity

Physical activity alone promotes only modest weight loss compared to diet, as for example half-an-hour of brisk walking burns only 150 kcal, the amount contained in a 30 g chocolate bar. However, even if no weight loss is achieved, regular exercise has cardiovascular beneficial effects, and long-term studies

show that a regular exercise pattern is a key factor for long-term weight maintenance.[31,53,56]

Regular exercise such as walking, cycling, and swimming is a helpful adjunct to diet. Walking is particularly attractive because it is accessible and safe. An exercise duration of 30-45 minutes/day 3-5 days/ week is the recommended starting point for physical activity modification, although lower levels may be needed in severely obese, deconditioned individuals. Once the fitness improves, duration and intensity may increase. Daily physical activity can also be enhanced by reducing time spent in front of TV, taking stairs instead of elevators, and by performing various house and garden light work.[22,41]

Pharmacological interventions

Several drugs have been confirmed to promote weight loss in controlled trials. Used in combination with lifestyle interventions (diet and exercise), anti-obesity drugs are more effective than used alone and may be beneficial in the maintenance phase.[63]

Based on their mechanisms of action, antiobesity drugs can be classified as central nervous system (CNS) agents that act mainly by inhibiting food intake (appetite suppressants), and peripheral agents that inhibit nutrient absorption in the digestive tract (anti-absorptive).

Pharmacological treatment is indicated for patients with a BMI $\geq$ 30 kg/m^2 or for patients defined as overweight (BMI 25-29.9 kg/m^2) if significant obesity-related comorbidities are present , as well as for those who failed to lose weight on a program of diet, exercise and behavior therapy.[2,22,41]

Central nervous system agents act by interfering with neurotransmitters, either stimulating the release or by blocking their uptake. Consequently, neurotransmitter concentration increases in the CNS and acts by inhibiting appetite or hunger (noradrenergic drugs) or by stimulating satiety (serotonin and dopamine reuptake inhibitors).

Phentermine and diethylpropion are the only noradrenergic drugs currently approved for short term use, less than 6 months. Other drugs in this class have been banned due to severe side effects: addiction-for amphetamine, hemorrhagic stroke, in case of phenylpropanolamine.[66]

Neurotransmitter reuptake inhibitors block the reuptake of serononin, norepinephrine and dopamine, thus increasing their concentration in CNS and leading to satiety. Although several drugs in this class have been proved to reduce weight (fenfluramin, bupropion and sibutramine), sibutramine is the only one approved for long-term use. Fenfluramin has been associated with valvular fibrosis and pulmonary hypertension and has been removed, while bupropion is an antidepressant with no current indication in obesity.[63] Selective serotonin reuptake inhibitors, such as fluoxetine (Prozac) may also be associated with weight loss but are not approved for the treatment of obesity.[66]

Sibutramine (Reductil, Meridia) is a norepinephrine and serotonin (5-HT) reuptake inhibitor that produces significant weight loss in the first year of treatment, especially if associated with diet. Weight is maintained for at least 2 years, with continuous treatment an improvement of lipid and glucose profile has also been noted. Sibutramine is administered in a single daily dose of 5, 10 or 15 mg. Cardiovascular side effects (increases in blood pressure and heart rate) preclude its use in patients with uncontrolled hypertension, coronary heart disease, cardiac dysrhythmias, congestive heart failure, or stroke.[22,63,41,66]

Bupropion is an antidepressant that was found to have weight loss properties. It is used in nicotine addiction but is not approved for the treatment of obesity.[66]

A newcomer in the group of centrally-acting anti-obesity drugs is rimonabant (Acomplia), a selective blocker of cannabinoid receptor 1 (CB1). Rimonabant acts both centrally, inhibiting food intake, and peripherally, promoting lipolysis. Effectiveness of rimonabant was demonstrated in four large trials (RIO-North America, RIO Europe, RIO Lipids and RIO-Diabetes). In RIO North America, a mean decrease in body weight of 6.3 kg was recorded after one year therapy with 20 mg of rimonabant daily.[67]

Therapy with rimonabant is also associated with favorable changes in serum lipid levels and an improvement in glycemic control in prediabetes patients and in type 2 diabetic patients. At the same dose, rimonabant significantly increased cigarette smoking quit rates, compared with placebo. Rimonabant seems to be well tolerated, with mild nausea as the most significant side effect.[67-69]

Orlistat (Xenical) is the only peripheral anti-obesity agent in use. It is a potent and selective pancreatic lipase inhibitor, is not absorbed in the gastrointestinal tract and acts entirely in the lumen of the small intestine, reducing fat absorption by about 30%. It is administered with meals, 120 mg three times daily. Side effects are the consequence of increasing fat content of the stool, most commonly oily spotting, flatus with discharge, fecal urgency, oily stools, incontinence. Orlistat in association with hypocaloric low fat diet results in an average weight

loss of 10 kg and improves weight maintenance one year after a six-month period of conventional dieting.[22,63,70]

A large number of investigational drugs for treatment of obesity is undergoing extensive testing, such as antiseizure agent topiramate, leptin analogues, ciliary neurotrophic factor, neuropeptide Y antagonists, proopiomelanocortin, adiponectin; GLP-1 agonists (extendin-4, liraglutide, dipeptidyl peptidase IV inhibitors), and agents that increase resting metabolic rate (selective β-3 stimulators/ agonist, uncoupling protein homologues, and thyroid receptor agonists).[44]

Non-prescription herbal supplements such as chromium and chitosan have proved ineffective in producing weight loss. Products containing effedrine and caffeine (e.g., guarana-mahuang herbal supplement) were showed to induce weight loss greater than placebo, but can have toxicity and significant cardiovascular side effects (arrhythmias), and thus their use is not recommended.[66]

Bariatric Surgery

Surgery that results in restricted food intake or absorption is the most effective weight-loss treatment in severely obese patients. Surgery is usually indicated for patients with a BMI greater than 40 kg/m^2, or greater than 35 kg/m^2 and serious medical co-morbidities, although it is increasingly used in patients with BMI < 35 kg/m^2.[22,41]

Surgically-induced weight loss results in a marked reduction in some of the co-morbidities associated with obesity (particularly diabetes) and an improvement in quality of life. Although it may appear expensive relative to other treatments (e.g., the direct cost of vertical banded gastroplasty is almost 6000 US dollars) obesity surgery is one of the most cost-effective treatments available.[22]

Surgical procedures available today can be classified in two categories, depending on the mechanism of how the weight loss is achieved: restrictive procedures (gastroplasty and Roux-en-Y gastric bypass) and malabsorptive procedures (biliopancreatic diversions). These procedures have produced the best results to date.[71,72]

Gastric bypass creates a small upper pouch of the stomach (usually 30 ml in volume), with a narrow opening, connected by a Roux-en-Y procedure to the intestine. It causes some malabsorption as well. It is widely performed because it results in significant and permanent weight loss in most patients and is relatively safe.[22] Recently, it has been performed laparoscopically and is as effective as the open procedure.[72]

Gastroplasty limits the size of the stomach by stapling or the attachment of an external ring or adjustable band, retaining the natural passage of food. Modern procedures are represented by vertical banded gastroplasty, silastic ring gastroplasty and gastric banding, as well as laparoscopic adjustable gastric banding. These techniques are safe and effective and currently make up the majority of all surgical procedures.

Gastric banding is less invasive, adjustable and more easily reversed than vertical banded gastroplasty and gastric bypass, but it is associated with a higher reoperation rate.[22,72,73]

Biliopancreatic diversion with or without duodenal switch is considered the most effective procedurefor the extremely obese patients. The biliopancreatic diversion procedure diverts bile and pancreatic secretions from the duodenum to the ileum and thus decrease nutrient, particularly fat, absorption.

Biliopancreatic diversion with duodenal switch is a variant of biliopancreatic diversion, with a partial gastrectomy- to restrict the amount of food eaten- and pylorus preservation. Gastrointestinal side effects may appear secondary to malapsorption (diarrhea), as well as some vitamin defficiencies.

Biliopancreatic diversion reduces mean BMI from 51.6 to 30 kg/m^2 after two years, with successful long-term maintenance and normalization of cholesterol and glycemia.[22,71-73] Figures 3-5 present three of the surgical procedures used in obesity.

Laparoscopic gastric banding is now by far the most widely used technique, representing around 95% of all bariatric procedures, except in the US, where the most common obesity procedure is gastric bypass.[71]

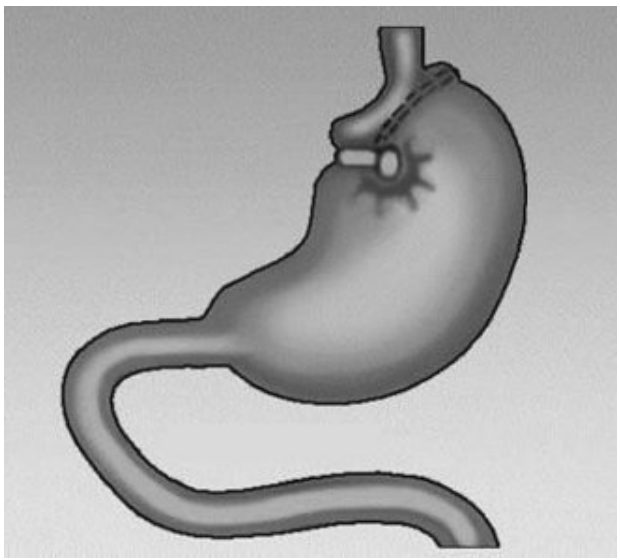

Figure 3. Vertical banded gastroplasty.[74]

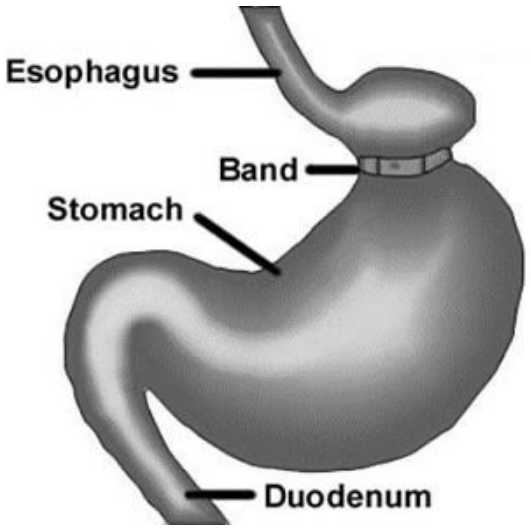

Figure 4. Adjustable gastric banding.[74]

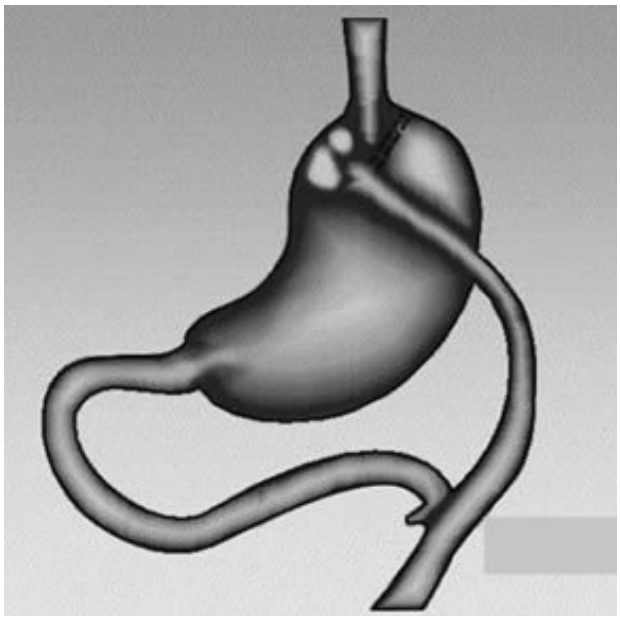

Figure 5. Roux-en-Y gastric bypass.[74]

Lipectomy is the surgical treatment of regional adiposity and is not a treatment for obesity per se. Recent animal studies suggest that lipectomy may have undesirable side effects: the animals developed a metabolic syndrome with significant hypertriglyceridemia, a relative increase in intra-abdominal fat, and insulin resistance.[22]

CONCLUSIONS

Obesity is a common and serious disease for numerous reasons, one of the most important being the great burden it imposes on the health care systems, due to its comorbid conditions. While scientists agree there is a genetic predisposition for weight gain, the environmental changes are considered major contributors to the current obesity pandemics. Despite extensive research aimed at identifying the underlying pathogenetic mechanisms for development of obesity, the gaps in knowledge are still important and may explain the failure of current antiobesity therapy. Although various treatment approaches have been used (diet, exercise, medications, surgery), most of them produce only modest results, and many patients return to their baseline weight once the treatment period is over. Successful weight loss should be mandatory followed by long term maintenance programs. Bariatric procedures have been so far the most effective in reducing weight excess, but their use is currently recommended only in very obese subjects.

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