REVIEW

Measuring Obesity: Fat or Fit!

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Abstract

Obesity is widely recognized as a major global health challenge because of its strong association with multiple cardiometabolic risk factors including diabetes, hypertension, and coronary artery disease. It compromises the quality of life and shortens life expectancy. This minireview discusses firstly the physiological mechanisms involved in energy homeostasis including peptidergic signalling of hunger and satiety from the GI tract mediated by the gut hormones (ghrelin, CCK, PYY, GIP, GLP-1,), and the status of energy stores from the adipose tissue mediated primarily by leptin, secondly, the field methods used in clinical practice to estimate the degree of obesity and lastly, management of the obese patient.

Key words:

Obesity, fat, lean body mass, body mass index, body fat distribution, leptin, ghrelin, basal metabolic rate

Introduction

Obesity is now spread throughout the world and has become one of the greatest global public health challenges of the 21st century (1-4). It is a complex metabolic disorder resulting in excess body fat relative to the body's skeletal structure (body frame/height). It is brought about by the failure of the physiological mechanisms responsible for energy homeostasis. These hinge chiefly on the integration in the hypothalamus (mainly the arcuate nucleus, paraventricular nucleus, lateral hypothalamic area (LHA), and perifornical area (PFA) of peripheral signals, both neural and hormonal, from the gastrointestinal (GI) tract, the adipose tissue, and both branches of the autonomic nervous system (ANS). Multiple integrated responses from the hypothalamus and other parts of the brain control appetite, feeding behavior, signal hunger or satiety, modulate metabolic pathways, stimulate or inhibit energy expenditure, intake, and storage, preventing wide swings in net energy balance. Consequently, body weight is maintained relatively constant.

Beside the hypothalamus, the ANS, and insulin, key players in this control system are *leptin* ("the satiety hormone") and *ghrelin* ("the hunger hormone) (5-7). Ghrelin is concerned primarily with the organism's immediate needs, meal initiation and short-term regulation of energy supply. Leptin, on the other hand, plays a central role in the long-term regulation of energy balance to ensure the long-term survival of the organism. In addition to its role in energy homeostasis, leptin plays an important role in modulating both innate and adaptive immune responses (8).

Obesity is considered a chronic disease brought about and further aggravated by a long-standing imbalance between energy intake (calories in) and energy output (calories out). Excess energy is stored in the adipose tissue primarily in the form of triacylglycerols. Energy expenditure or output has two components: the basal metabolic rate (BMR), defined as the minimum rate of energy expenditure at rest that is required to maintain vital bodily functions in the post-absorptive or fasting state, plus any additional energy consumed in the course of various physical activities such washing one's hands, doing house chores, gardening, manual labor, competitive sports, or fitness activity (walking, running, biking, swimming, etc.). It is noteworthy that BMR decreases with ages and reduced muscle mass. Women have a lower BMR than men mainly because of a lower muscle mass, occupation, recreation, and media norms.

Obesity is a multifactorial disease influenced by social, socioeconomic, cultural, environmental, and public policy factors in addition to the more proximal elements related to pathophysiology and etiology of the disease. This complexity has been nicely illustrated by Sansbury and Hill (9). They divided the factors causing or influencing obesity into two broad categories; proximal and distal. The proximal causes include the mechanisms and pathways regulating hunger, satiety, nutrient absorption, and energy expenditure. The distal category is further divided into three layers: 1) Social/cultural

environment defined by social norms, family life, 2) Built environment that includes sidewalks, building design, access to parks and trails, and recreation facilities and 3) Policy represented by physical education, dietary guidelines, funding, park budgets, sidewalk standards, and building codes.

Among the fundamental drivers of obesity are sedentary lifestyle promoted by a negative "built environment", and dietary habits, which may be heavily influenced by the widespread availability of relatively inexpensive calorie-dense processed food that is heavily promoted by media campaigns (10). An additional important contributor is genetic predisposition, which is a function of the influence of different genetic variants as well as epigenetic mutations (11,12). These polygenetic factors, rather than those related to diet and lifestyle, are believed to be behind the most severe forms of obesity. For instance, A defective melanocortin-4 receptor (MC4R) is perhaps the most common genetic cause of obesity in humans. Melanocortin and MC4Rs are essential components in leptin's intracellular signaling cascade responsible for its anorexigenic (pro-fasting) effects and long-term energy homeostasis (13).

Genes influence both the input and the output sides of the energy equation. Hormonal deficiency states such as hypothyroidism and growth hormone deficiency are characterized by lower than normal energy expenditure whereas increases in energy intake are observed in genetic diseases such as Prader-Willi syndrome and Cushing syndrome.

Genes determine the expression and circulating levels of multiple endocrine and neuroendocrine secretions and signaling molecules originating from the brain, anterior pituitary, pancreas, both adrenal medulla and cortex, GI tract, and adipose tissue. These and other regulatory molecules together with changes in plasma substrate levels and the activity of the autonomic nervous system (ANS) provide continuous feedback to the hypothalamus concerning the organism's energy status.

The hypothalamus, the *central controller* in the energy control system, receives information from the digestive system via afferent vagal fibers, and hormonal feedback primarily from the endocrine pancreas (insulin), the adipose tissue (leptin), and the GI tract (e.g. ghrelin, CCK, GLP-1, GIP, PYY, etc.). As already pointed out ghrelin and leptin (together with insulin) are key components of the energy control system.

The role of ghrelin

Food intake is subject to neuroendocrine interactions involving a web of hormones, neurotransmitters and complex cascades of signaling molecules required for the activation of specific genes, all aimed at maintaining energy homeostasis.

Many gut peptide hormones have been shown to play a significant role in appetite regulation. These include cholecystokinin (CCK), peptide YY (PYY), gastric inhibitory polypeptide (GIP), and glucagon-like peptide-1 (GLP-1), all of which are appetite suppressors ("satiety hormones"). Ghrelin is the sole known gut peptide that is an appetite stimulant.

The name "Ghrelin" derives from the phrase "growth hormone release inducer" and it signifies growth. It's dubbed the hunger hormone because it stimulates appetite and triggers food-seeking behavior. It's a peptide of 28 amino acids derived from a 94-amino acid prohormone. It is produced primarily by endocrine cells in the fundus of the stomach. The exact adequate stimulus for its secretion is unknown. Small amounts are secreted by the pancreas, intestine, and kidney. Importantly, there are also ghrelin producing neurons in the hypothalamus which might be involved in mediating the central effects of gastric ghrelin.

Gastric ghrelin is secreted only while the stomach is empty and its blood levels are highest just before a meal and lowest immediately after. Activation of ghrelin requires the attachment of n-octanoic acid molecule, a reaction catalyzed by ghrelin O-acyltransferase (GOAT). Ghrelin is the primary orexigenic (pro-feeding) hormone. It plays a key role in the short-term regulation of energy balance; it is responsible for appetite stimulation & meal initiation. It functions as a neuropeptide exerting its effects on target orexigenic neurons in the hypothalamus. Beside inducing hunger it stimulates gastric secretion and GI motility, actions that are mediated by the vagus nerve. Although it does not increase meal or portion size, it does encourage frequent feeding and promotes energy storage and weight gain. Ghrelin also plays a role in the pleasure reward dopamine system via the neurons connecting the ventral tegmental area (VTA) and the nucleus accumbens.

Ghrelin does *not* readily cross the blood-brain barrier. Therefore, gastric ghrelin may not express its full action directly on the brain. Its orexigenic message may be partly relayed via the vagus nerve to the hypothalamus, where it triggers the release of ghrelin from specific ghrelin-producing neurons. It has also been suggested that the stomach-derived ghrelin may be able to gain access to the CNS through portions of the BBB known to be structurally weak and more permeable as in the median eminence and area postrema, in the vicinity of the arcuate nucleus.

Once inside the brain tissue ghrelin binds to receptors on specific target neurons causing them to fire at a higher frequency and to release the inhibitory neurotransmitter GABA, neuropeptide Y (NPY), and Agouti-related protein (AgRP). GABA inhibits the proopiomelanocortin/cocaine-amphetamine related transcript (POMC/CART) neurons thereby inhibiting the release of the anorexigenic (pro-fasting) alpha melanocyte stimulating hormone (α-MSH = melanocortin), while NPY and AgRP stimulate the orexigenic (pro-feeding) neurons in the lateral hypothalamic area (LHA) and the perifornical area (PFA). The net result is a strong orexigenic response (appetite stimulation and food seeking behavior) (Figure 1).

The role of leptin

Leptin (from leptos = thin) (aka the satiety hormone). It's a 167-amino acid peptide hormone produced and released mainly by the adipocytes of the white adipose

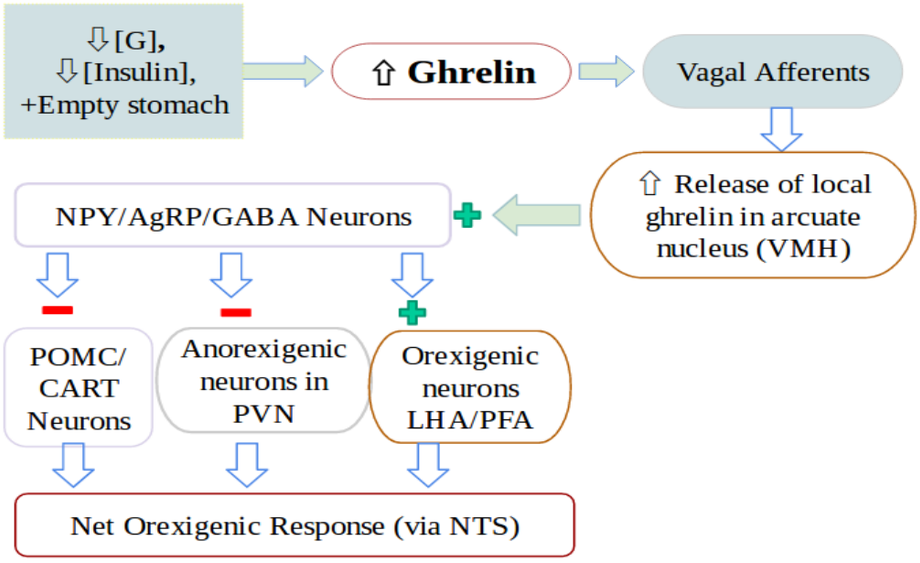


Figure 1. A simplified schematic representation of the sequence of events triggered by the release of gastric ghrelin.

tissue (14). Its blood level is proportional to the size of the body's fat depot. It's also produced in varying amounts in many other tissues including the stomach, liver, placenta, bone marrow, mammary epithelium, ovaries, muscle, and brown adipose tissue. Leptin is the principal component in the control system responsible for long-term energy homeostasis (Figure 2a). It exerts profound effects on feeding behavior, neuroendocrine functions, and various aspects of metabolism. Its deficiency causes morbid obesity. Also, it is clear that the threshold circulating level of leptin capable of triggering its full anorexigenic response varies from one individual to another; individuals with low thresholds tend to maintain smaller fat stores.

Multiple isoforms of the leptin receptor (LepR) exist in the central nervous system (CNS) and peripheral tissues. However, the main isoform has been identified as LepRb, and leptin exerts its effects by engaging several LepRb-bearing subpopulations of neurons each of which regulates specific aspects of energy homeostasis (15-16). Functionally, the energy-related leptin neurons may be divided into two groups: a) Anorexigenic neurons containing POMC/CART and b) Orexigenic neurons containing NPY/AgRP/GABA.

Appetite suppression results from the combined effects of decreasing the activity of the orexigenic neurons and increasing the activity of the anorexigenic neurons (Figure 2b). Increased fat mass and higher circulating levels of leptin trigger a number of anorexigenic responses from the hypothalamus mediated by several neuropeptides and neurotransmitters as already described. The binding of leptin to the external portion of LepRb on the cell membrane of the target neurons of the arcuate nucleus in the ventromedial hypothalamus (VMH) triggers various complex intracellular signaling pathways including Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3), and the insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K) (17). These and other transduction pathways lead ultimately to the cell nucleus and the activation of specific genes and the expression of certain neuropeptides and neurotransmitters that mediate leptin actions (Figure 2c).

Leptin resistance

Hypothalamic *leptin resistance* can develop in the presence of chronic hyperleptinemia and hyperinsulinemia as often occurs in insulin resistant, obese patients. How leptin resistance develops is not fully understood. In such cases the hypothalamic neurons are unable to respond normally to elevated leptin blood levels because of insufficient number of effective hormone-receptor engagements. Leptin resistance may be due to a defect in any of the steps involved in the signalling pathway, including impaired leptin transfer across the BBB, reduced receptor expression (downregulation), receptor phosphorylation, a change in post-receptor signal transduction such as a failure to activate PDE3B which is required for lowering intracellular cAMP level. Yet another possibility is a defect in the POMC/α-melanocortin system, which is a key component of leptin's anorexigenic cascade (21-22).

Both leptin resistance and genetic leptin deficiency result in excessive feeding leading to weight gain and of obesity. R.H. Lustig gives a colorful description of the behavior of the genetically leptin deficient (ob/ob) mice, which he describes as "the rodent equivalents of a 400-pound couch potato". "While normal weight at birth, these mice immediately eat like there is no tomorrow and just sit there - the only time they ever get off their behinds is when you put food on the other side of the cage. Then they'll waddle over to it, devour it, and sit there instead"

Administration of leptin to leptin-deficient patients or laboratory animals results in markedly decreased food intake and increased energy expenditure followed by marked weight loss

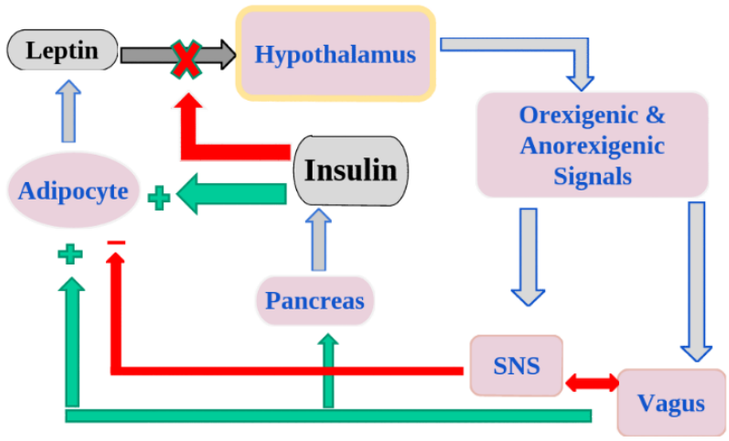


Figure 2a. Simplified schematic of the long-term energy balance control system. The hypothalamus ("the central controller") receives, compares and integrates neural and hormonal feedback signals from the periphery. Chief among these signals are ghrelin, *leptin* and *insulin*. In response, the hypothalamic neurons issue either orexigenic (pro feeding) commands, mainly via the vagus nerve, or anorexigenic (anti feeding) commands, mainly via the sympathetic nervous system (SNS). Green arrows indicate stimulation and the red arrows indicate inhibition. Note the exchange of inhibition between the two divisions of the autonomic nervous system (ANS). Modified after Lustig RH in "Fat Chance": beating the odds against sugar, processed food, obesity, and disease. Penguin Group (USA), 2012

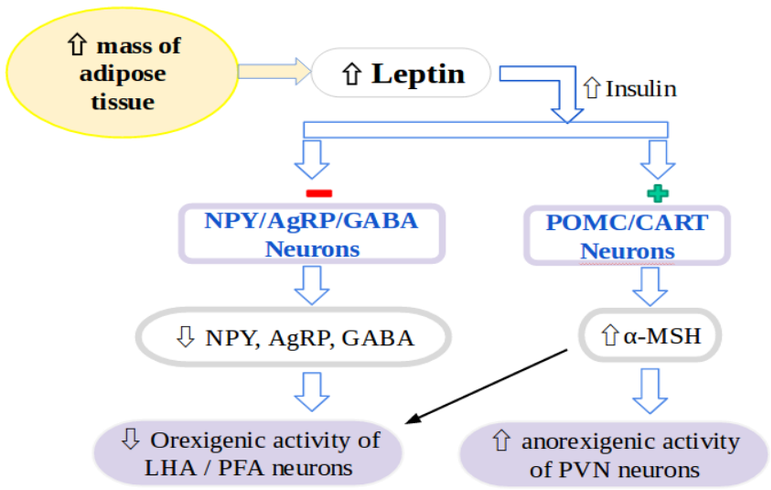


Figure 2b: Schematic representation of the actions of leptin on the two subsets of hypothalamic neurons.

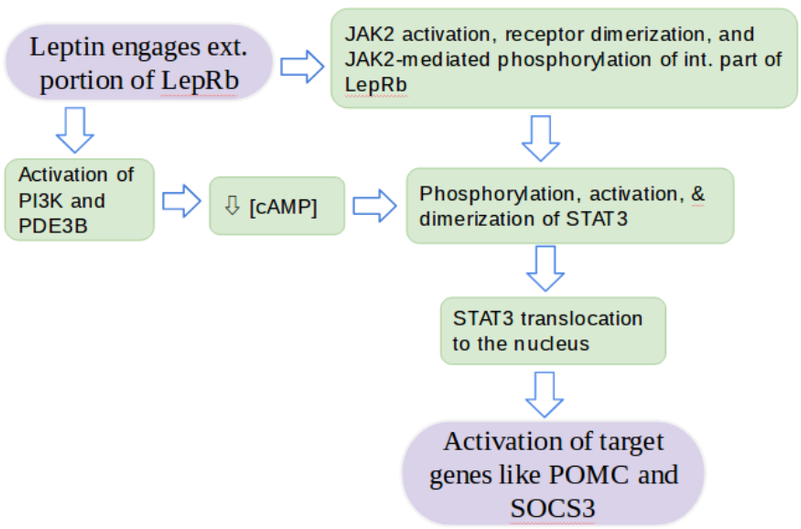


Figure 2c: Leptin signaling through the STAT3 and PI3K-PDE3B-cAMP pathways in the hypothalamus. The cascade leads ultimately to the transactivation of Leptin's target genes including SOCS3, which acts as a negative feedback inhibitor for the JAK2/STAT3 pathway. Abbreviations: cAMP= cyclic adenosine monophosphate; JAK2= Janus kinase-2; PDE3B= Phosphodiesterase-3B; PI3K= Phosphatidylinositol-3 Kinase; STAT3= signal transducer and activator of transcription; SOCS3= suppressor of cytokine signaling-3

Role of the gut hormones

Inducing satiety and limiting food intake is not limited solely to the actions of leptin. As the largest endocrine apparatus, the GI tract produces at least half a dozen endocrine peptides (often called "gut hormones") including cholecystokinin (CCK), peptide tyrosine tyrosine (PYY), oxyntomodulin, and the incretins glucose-dependent insulinotropic polypeptide (GIP) [aka gastric inhibitory polypeptide (GIP)] and glucagon-like peptide (GLP-1).

Collectively, gut hormones represent a major component of the appetite regulatory system and one of several redundant energy control systems. In addition to being essential for the induction of satiety and food avoidance behavior at least during the acute post-prandial stage, they influence metabolism at different phases. They control GI motility and the rate of gastric emptying thereby influencing the fluctuations in the blood levels of glucose and insulin during the meal and postprandially. The lower gut peptides, PYY and GLP-1, are released slowly in response to food intake and their levels remain elevated for hours after a meal. At least the incretins GIP and GLP-1 exert direct action on the pancreas augmenting the effect of glucose on insulin secretion by at least 50% (18). In addition, GLP-1 inhibits glucagon secretion, slows gastric emptying, and has been shown to protect and increase the number of beta cells by promoting growth and inhibiting apoptosis. Peptide tyrosine tyrosine or simply peptide YY (PYY). PYY belongs to a group of peptides known as the tyrosine peptides because they contain several tyrosine residues each. They include PY found only in fish, pancreatic polypeptide (PP), and NPY. PPY is a 36 amino-acid peptide derived from a 94 amino-acid precursor produced in the ileum and the colon, but its level in the blood rises even before food reaches the ileum. PYY readily passes the BBB to reach its receptors (Y2 & Y4) in the arcuate nucleus, where it acts as a satiety messenger like virtually all gut peptides with exception of ghrelin. Mutations in PYY are known to be responsible for cases of severe obesity in male Pima Indians (Arizona, New Mexico). Also, the PYY levels in the blood of anorexic patients are several fold higher than found in normal subjects. PYY agonists are currently in the pipeline of new anti-obesity drugs.
Taken together, these observations explain the profound influence gut hormones have on food intake, body weight, and insulin sensitivity. They also indicate that the gut-brain axis is likely critical not only for the normal physiological mechanisms of energy homeostasis, but also in the pathophysiology of obesity (18-19).

Role of the Autonomic Nervous System (ANS)

The ANS plays a key role in both the short-term and the long term energy control. Integrity of the vagus is essential for ghrelin function. The vagus nerve provides a two-way communication between the brain and the periphery. It connects all parts of the GI tract and the adipose tissue to the hypothalamus (20). Blockade of the gastric vagal afferent abolished ghrelin-induced feeding as well as the production of growth hormone (GH), GH-releasing hormone (GHRH), and neuropeptide Y (NPY). As already noted circulating ghrelin does not normally cross the blood-brain barrier (BBB). Therefore, it is not clear how ghrelin secreted in the stomach acts on the hypothalamus. However, it has been postulated that the message of peripheral ghrelin is conveyed to the hypothalamus by vagal afferent via the nucleus of the solitary tract (NTS), leading ultimately to the release, locally, of ghrelin from specialized ghrelin-producing hypothalamic neurons.

Inhibition of vagal activity reduces GI secretions and motility, results in appetite suppression, and turns off vagal stimulation of insulin-mediated fat deposition (energy storage). In addition, vagal inhibition is accompanied by increased activity of the sympathetic nervous system (SNS) which promotes lipolysis and increases muscle activity and energy expenditure. By contrast low levels of circulating leptin and elevated ghrelin stimulate appetite and have the opposite effects on the ANS; stimulation of the vagus nerve promotes digestion and absorption of food, and stimulates insulin secretion and energy storage. At the same time inhibition of the SNS reduces physical activity to conserve energy. In healthy subjects, the orexigenic response is self-limiting; as the energy stores are restored to their normal level, leptin level rises suppressing energy intake and stimulating energy expenditure.

Comorbidities

Obesity is strongly associated with a number of health problems that the clinician needs to bear in mind when evaluating obese patients. These include type 2 diabetes mellitus (T2DM), dyslipidemia and accelerated atherosclerosis, coronary artery disease (CAD), hypertension (HTN), left ventricular hypertrophy, cor pulmonale, cardiomyopathy, pulmonary hypertension, obstructive sleep apnea, obesity hypoventilation syndrome, intracranial hypertension, stroke, reflux esophagitis, liver disorders (non-alcoholic steatohepatitis or NASH, cirrhosis, cholelithiasis, and gallbladder disease), cancers, and osteoarthritis. Obesity related reproductive complications in females include early puberty, anovulation, infertility, hyperandrogenism, and polycystic ovaries; while in males, there may be hypogonadotropic hypogonadism (23-28).

Obese patients present a significantly higher risk for postoperative complications including deep venous thrombosis (DVT), pulmonary embolism (PE), pneumonia, and wound infection. Depression and other psychologic disorders are not uncommon among obese patients perhaps sometimes stemming from discrimination and social stigma. Mobility may be so impaired in the severely obese that personal hygiene is compromised. Obesity is often present in patients with the disease cluster known collectively as the metabolic syndrome but it is not believed to be the cause of it.

The metabolic or cardiometabolic syndrome is often defined as a cluster of cardiovascular risk factors including hypertension, ⇧WC, dyslipidemia (⇧LDL-C, ⇧TG; ⇩ HDL-C), insulin resistance (glucose intolerance, ⇧HA1c), and elevated pro-inflammatory markers (⇧CRP). In addition to glucose intolerance and hypertension, increased circulating levels of insulin and insulin-like growth factor (ILGF) may lead to dysmenorrhea and virilization in obese adolescents females because of increased production of androgens in the adrenal cortex and the ovaries. By contrast, in obese male adolescents gynecomastia is often observed and is thought to result from adrenal cortical estrone production.

Epidemiological studies indicate that obesity and associated health problems have reached epidemic proportions in the developed countries as well as in the developing countries of the Middle East and North Africa (MENA)(26). Particularly alarming are the data pointing to the rising prevalence of obesity and T2DM among the children in this region. The prevalence of obesity may be as high as 18% among Arab adolescent females and 50% among adult females (27).The medical literature is replete with similarly alarming data for the US, where it's estimated that over 35% of the population are obese and nearly 55% are either overweight or obese (28). In addition to glucose intolerance and hypertension, increased circulating levels of insulin and insulin-like growth factor (ILGF) may lead to dysmenorrhea and virilization in obese adolescent females because of increased production of androgens in the adrenal cortex and the ovaries. By contrast, in obese male adolescents gynecomastia is often observed and is thought to result from adrenal cortical estrone production.

Measuring Obesity

Measuring the mass of body fat directly and accurately requires sophisticated equipment and can be time consuming and expensive. Fortunately, several convenient anthropometric surrogates have been devised and adopted into medical practice to evaluate patients' body composition and determine their healthy body weights. There are several field tools for measuring obesity (Box 1.). Of these, the most popular are BMI, WC, and WHR. Although indirect and imperfect, these "one-size-fits-all" methods are generally fast, easy, inexpensive, and correlate fairly well with the actual mass of body fat in adults as validated by reference measurements using the most accurate, sophisticated methods employed in research such as Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), densitometry, hydrometry, plethysmography, and Dual Energy X-ray Absorptiometry (DEXA) (30-34).

Box 1. Field tools commonly used in measuring obesity:
1. Body mass index (BMI). 2. Waist circumference (WC). 3. Waist-to-hip ratio (WHR). 4. Body Shape Index [ABSI = WC /(BMI2/3 x Ht1/2)] 5.Corpulence or Ponderal Index [PI=mass (kg)/Height3, (meters), used mostly for neonates] 6. Skinfold thicknesses. 7. Bioelectrical impedance.

Body Mass Index (BMI):

The BMI is currently the most popular tool used to assess an individual's adiposity and determine his/her healthy weight. It was first devised in the 1830s by a Belgian statistician named Adolphe Quetelet while working for a life insurance company (31). However, it remained largely forgotten until resurrected and officially adopted by the US NIH in 1985 and by the WHO in 1997.

The BMI is essentially a measure of body weight relative to the person's height or body frame (Box 2). However, most often BMI is obtained by simply plugging the *BWt* and *Ht* values into an app in the smartphone or a calculator program embedded in the web browser-based on BMI values adult patients are classified (per CDC / WHO) as shown in table 1.

An adult is classified as overweight when his/her BMI obese when his/her BMI ≥30. Some clinicians prefer the use of a definition based on percentage of body fat (%BF): For men %BF 21-25% indicates overweight and %BF > 25% indicates obese; females with %BF between 31 and 33% are considered overweight and those with %BF > 33% are classified as obese. Patients with BMI ≥ 35 have a significantly elevated risk of premature death (32-33). Obesity in early adulthood (18-22 years) carries a 40-90% greater risk of premature meath than obesity developed later in life (34). Thus, it is critical for teenagers and young adults to be physically active, eat healthy foods, and maintain healthy weights.

Box 2.: Calculation of Body Mass Index:
BMI is calculated as the ratio of body weight (*Bwt*) in kilograms divided by the height (*Ht*) in meters squared: $BMI = Bwt, kg \div (Ht, m)^2$ Example: *BWt* = 175.6 lbs = 80.0 kg *Ht* = 64.0 inches = 1.63 m $Ht^2 = 2.66\ m^2$ Therefore: BMI = 80.0 / 2.66 = 30.10 *If pounds and inches are used instead of the metric units, the result is multiplied by 703:* *BMI = 175.6 / (64.0)^2 x 703 = 30.10*

For children, body adiposity changes as they mature, and the interpretation of BMI values depends on the child's age and gender (35-37). Also, girls and boys differ significantly with respect to their body fat distribution. BMI-for-age growth charts and tables have been developed and are widely used to classify pediatric patients (2 to 20 years of age)(Figure 5). Children whose BMI-for-Age fall between 86th and 95th percentile are classified as overweight whereas those over the 95th percentile are classified as obese (Table 2).

Table 1. Body weight classification based on body mass index (BMI)

Body mass index	Class
<18.5	Underweight
18.5 - 24.9	Healthy weight
25 - 29.9	Overweight
30 - 34.9	Obese, Class I
35.0 - 39.9	Obese, Class II
≥ 40.0	Obese, Class III

A number of published epidemiological studies suggest that childhood obesity is on the rise. Furthermore, obese children are likely to become obese adults and suffer the health consequences (35-37). Contributing factors include dietary habits, sedentary behavior, and environmental factors. However, genetic predisposition is a major determinant of childhood obesity (38).

Table 2. Pediatric Weight Classification based on BMI-for-Age Growth Charts	
Percentile	Class
<5th	Underweight
5th - 85th	Healthy weight
86th - 95th	Overweight
>95th	Obese

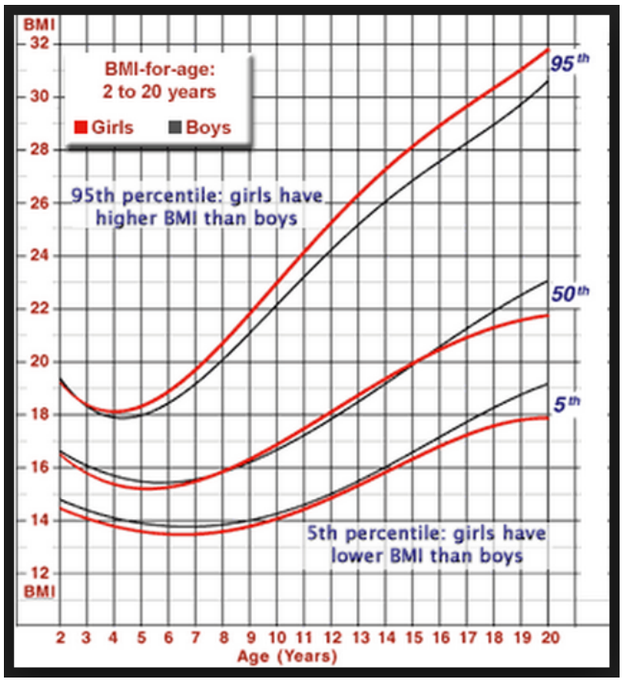


Figure 5: Normal changes in BMI-for age in relation to growth percentiles in children. These charts are used to monitor adolescents for excessive rates of weight gain relative to the increase in height; an increase in BMI-for-age of >1 unit/year puts the adolescent at risk of obesity. US Department of Health & Human Resouces: https://depts.washington.edu/growth/module7/text/page3b.htm

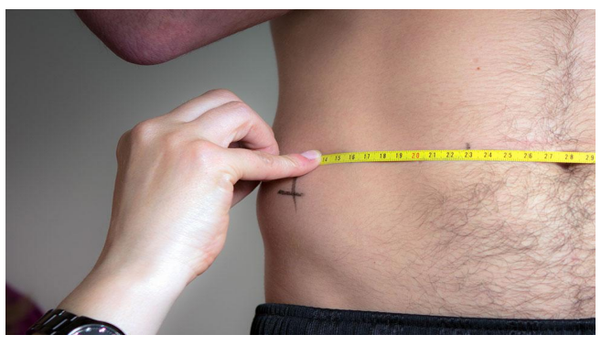
Advantages & Limitations of BMI

Pros: convenient (fast, easy, & free), standardized, correlates well with the body's fat stores in the age range 20-70 years, and is a good predictor of future health problems (32-35).

Cons: It's a one-size-fits-all tool. Because it is based on body weight, it does not distinguish between fat and lean (fat-free) tissues. For some athletes and bodybuilders, a high BMI may be mostly because of exceptionally high muscle mass. Also, in older adults the BMI does not correlate as well with body fat content as it does in younger adults because the rise in body fat content with age is counterbalanced by a decline in lean body mass (due to sarcopenia and osteopenia)(39). It has been demonstrated in postmenopausal women that age-related changes in body composition can be masked by stable BMI. There was no relationship between BMI values and the mortality risk in women 70 -79 years old (33). Furthermore, the BMI provides no information about the distribution of adipose tissue in different body locations, ectopic vs subcutaneous fat (40-42). Central obesity (excessive visceral fat stores), which is indicated by high waist circumference (WC) and waist-to-hip ratio (WHR), is known to be associated with diabetes and cardiovascular diseases to a greater extent than subcutaneous obesity (43-45). There is also evidence linking central obesity (个 WHR) with increased pancreatic cancer mortality independent of BMI (46). Therefore, in order to have a better weight health evaluation it is necessary to obtain not only the BMI, but also the WC and the WHR.

Waist Circumference (WC) and Waist-to-Hip Ratio (WHR)

WC and WHR are important because they afford the clinician a fairly good idea about the pattern of distribution of adipose tissue between visceral and subcutaneous depots. High WC and WHR indicate the presence of excessive visceral fat (often referred to as *central obesity*). The pattern of body fat distribution is an important determinant of the risk of health complications including T2DM, coronary artery disease (CAD), and the constellation of diseases known collectively as the metabolic or cardiometabolic syndrome (47).



A. Before sedentary living

B. While living a sedentary life

Figure 3A and 3B. Measuring waist circumference. Notice in part B the mark indicating the position of the iliac crest; the tape is positioned at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.

WC measurement

The WC is measured using a good quality, flexible non-stretchable measuring tape. While facing the patient, the midway point between the iliac crest and the lower border of the rib cage is located. This corresponds approximately to the level of the belly button. The tape is placed around the circumference at this level making sure it is kept parallel to the floor all around the belly (Figure 3).

Numerical guidelines have been developed to place adult patients in one of three risk categories based the WC values - low, moderate, and high. The cutoff values vary depending on gender and ethnicity. The guidelines shown in Table 1 are used in US, EU, and MENA. However, for Asian patients significantly lower cutoff values are used. Asian men and women have significantly lower limits. For instance, an Asian Indian male with WC>90 cm would fall in the high risk category.

Measuring Hip Circumference (HC)

HC is measured primarily for the purpose of calculating the waist-to-hip ratio (WHR). It is measured at the widest point around the hip and buttocks (Figure 4a). The greater trochanter of the femur is a good landmark to locate and use to guide the placement of the measuring tape (Figure 4b). The patient should be standing straight, relaxed with the feet close together. The tape should be kept horizontal and parallel to the ground. Individuals with extra weight around the middle (central/abdominal obesity; ⇧WC & ⇧WHR) are at a greater risk for T2DM, HTN, dyslipidemia, CAD, and NAFLD than those with extra weight around their hips and thighs (subcutaneous fat). Abdominal obesity is a fairly reliable measure of the potential for health complications and premature death (48). In the US, females with WC>89 cm (WHR >0.85) and males with WC>102 cm (WHR>1.0 inches) are more likely to experience health problems sooner than those with lower values. The WHR is the tool of choice to assess weight health in the elderly, where it is more reliable than either BMI or WC in predicting future health problems (48).

Health risk classification in adult patients based on the WHR is given in table 4. Depending on the pattern of body fat distribution, obese patients are sometimes described as having an “apple” shape (fat around the waist, heavy in the middle) or a “pear” shape (heavy in the hips). Men are more likely to have central obesity (“apple” shaped) and have higher health risk than women who tend to develop mainly subcutaneous adiposity (“pear” shaped).

The preferential deposition of fat in the abdominal and other ectopic locations is probably due to a more limited expandability of the subcutaneous compartment owing to the greater musculature.

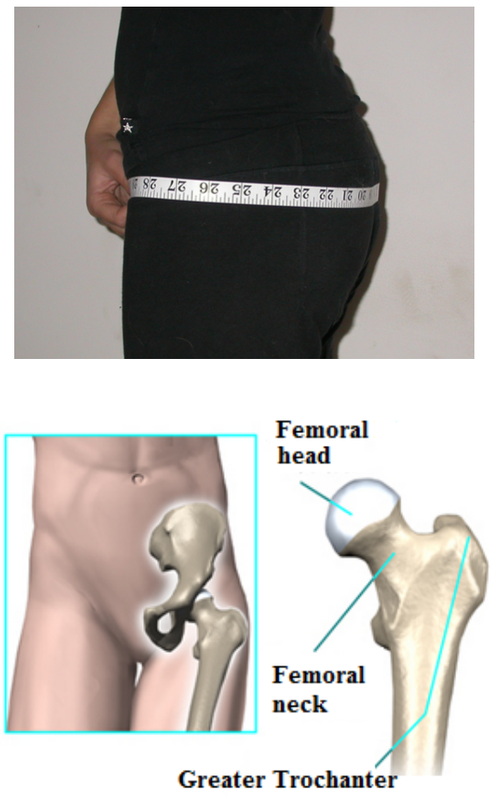


Figure 4. 4a (upper) Measuring the hip circumference (HC). The tape is placed around the widest portion of the buttocks and parallel to the floor. 4b (lower): Locating the greater trochanter to help position the measuring tape correctly for the HC measurement.
Source:
http://www.houstonmethodist.org/orthopedics/where-does-it-hurt/hip/hip-anatomy/

Table 3. Risk of health complications related to waist circumference (WC)*

Risk level	Men		Women	
Low	<94 cm	(<37”)	<80 cm	(<31.5”)
Moderate	94 - 101.5 cm	(37 - 40”)	80 - 88 cm	(31.5 - 35”)
High	≥102 cm	(> 40”)	>88 cm	(>35”)

*These pertain to white caucasians and people in the Middle East and North Africa (MENA).

Table 4: Risk of cardiovascular disease in relation to the waist to hip ratio (WHR)[a]

Risk level	Men	Women
Low	<0.90	<0.80
Moderate	0.90 - 1.00	0.80 - 0.85
High	>1.00	>0.85

[a] WHR= Waist-to-Hip Ratio. Exceptions to this guide include children, adult patients with BMI>34, and those with short stature (<5 feet or <60 cm).

Managing obesity

Obesity is a chronic condition requiring constant management (49-54). Its rising prevalence has spurred efforts to find effective prevention and treatment options. It should be noted that in the case of obesity prevention and treatment are inseparable. Treatment would be ineffective in the absence of concomitant preventative measures.

Obviously, in addition to estimating the degree of obesity and initiating steps to treat and prevent obesity, a comprehensive, initial patient evaluation is necessary. This would include physical examination and standard laboratory studies [fasting blood glucose, HbA1c, fasting lipid panel, liver function test, thyroid function test], and evaluating and managing any comorbidities (49-50). The management of obesity consists of three basic steps (51-54): a diet plus exercise, pharmacotherapy and surgery.

Beside the well-established benefits for the overall health and wellbeing, routine, daily physical activity helps maintain a healthy weight and may promote weight loss and prevent or minimize obesity-associated comorbidities, while behavioral therapy can support dietary changes and physical exercise in everyday life.

Major dietary interventions include:

1. Avoidance of energy dense fast food and sugar-rich drinks including so-called natural fruit juices; generally, the whole fruit is healthier than its juice (55-56).
2. Adaption of a diet consisting of macronutrients of high nutritional quality including vegetables, beans, nuts & seeds (almonds, peanuts, walnuts, flax-seeds, sesame, sunflower seeds, etc), fish, skinless chicken, monounsaturated oils (olive, canola, sunflower, etc) and polyunsaturated oils (e.g., corn oil) , and whole fruits
3. For overweight or obese patients, it may be necessary to take calorie restriction measures resulting in a negative energy balance of around 500 kcal/day. A negative caloric balance may be achieved by reducing portion size and/or practicing periodic caloric desistance such as intermittent fasting (e.g., fasting from sunrise to sunset two days a week or fasting at least 16 hour per day, e.g., between 8 pm and noon the next day). The choice of the calorie restriction strategy depends on patient's overall health and the severity of obesity.

Physical activity has to be tailored to the patient's age, weight, and general state of health and physical fitness. It should include both aerobic and strength exercises and should take place at least three times a week.

Some patients may require additional behavioral modifications such as cessation of smoking and alcohol consumption, regular sleep-wake cycle, etc. All these changes are referred to collectively as lifestyle modifications.

Class II (BMI ≥ 35) and class III (BMI ≥ 40) obese patients (Table 1) may require the use of pharmacologic agents and / or bariatric surgery (stomach reduction). Lower BMI cutoff points are allowed for both drug therapy and surgery if the patient carries additional risk factors such as T2DM, HTN, CAD, or dyslipidemia and accelerated atherosclerosis (59, 61).

Controlled studies indicate that in a period of approximately two years the average obese patient may achieve a 5 kg weight loss by dietary measures and an additional 3 kg by physical exercise. By contrast bariatric surgery can result in the loss of up to 40 kg in the first two years after the operation. Data on the indications, efficacy, and clinical practice guidelines are found elsewhere (57-59).

The impact of pharmacotherapy in the treatment of obesity (60-62) has so far been modest despite decades of focused efforts spurred by the promise of potentially huge profits. The industry has been plagued by false starts and drug failures despite exaggerated claims, multiple contraindications, and serious side effects including fatalities. All this prompted close scrutiny by the regulatory authorities and the withdrawal of a number of anti-obesity drugs from the market (e.g., sibutramine and rimonabant).

At least in the US, there are currently less than a dozen pharmaceutical products used for obesity treatment along with diet, exercise, and other lifestyle changes. With the exception of orlistat (Xenical / Alli), anti-obesity drugs either inhibit hunger or induce satiety. Most of these agents belong to the same category of CNS stimulants (sympathomimetics, anorexiants) such as amphetamine, benzphetamine, dextroamphetamine, diethylpropion, methamphetamine, naltrexone/bupropion combination (Contrave), phendimetrazine, phentermine, and phentermine/topiramate combination (Qsymia). Phentermine, a widely used sympathomimetic amine, is thought to suppress appetite by increasing leptin level in the circulation. Lorcaserin (Belviq) induces satiety by selectively activating the 5-HT2c receptors on the anorexigenic POMC neurons described previously (Figure 2b). Serious CNS, neuropsychiatric, and cardiovascular adverse reactions are not uncommon with these drugs. These include tremors, dizziness, headache, suicidal tendency, arrhythmias, cardiac ischemia, and hypertension. Orlistat which is available over the counter (OTC) in the US (Alli) inhibits fat absorption in the small intestine by deactivating pancreatic lipase. Although its weight loss effect is modest it does reduce the incidence of diabetes significantly. The prescription strength of orlistat is the only anti-obesity drug approved for children (>12 years) in the US. Orlistat suffers from a few unpleasant side effects including fecal urgency, fecal incontinence, oily stools, abdominal pain, and sometimes deficiency of one or more of the fat soluble vitamins (A, D, E, K). Patients who are able to adhere to a well controlled, low fat diet will eventually overcome these side effects and benefit from the drug in the long term. All other OTC products marketed for weight loss have proven neither safe nor effective.

It's important to emphasize that using any of the currently available anti-obesity medications carries significant health risks and the decision to initiate drug therapy must be based on a careful assessment of the risks vs. the benefits. Also, anti-obesity drugs should only be used in conjunction with dietary measures, physical exercise, and lifestyle modifications; relying on pharmacotherapy in futility.

Finally, eating is both a physiological and a social function subject to a myriad of influences including cultural, hedonic, and psychological. This, of course, is in addition to the mechanisms of energy homeostasis which are characterized by a high level of redundancy and extensive overlap with multiple physiological

control systems. Living in an environment that does not encourage physical activity and where energy-dense food is abundant and inexpensive makes it difficult to maintain a healthy body weight, and contributes to the limitation of the various tools currently used to treat or prevent obesity. Therefore, as in the case of smoking cessation, for dietary and lifestyle modifications to succeed over the long term requires not only unwavering commitment and dedication but also significant alterations in the surrounding milieu.

Abbreviations:

AgRP= agouti-related protein; BMI= body mass index; α-MSH= alpha-melanocyte stimulating hormone (melanocortin)
CAD= coronary artery disease; cAMP= cyclic adenosine monophosphate; CCK= Cholecystokinin; GABA= gamma-amino butyric acid; GHRH= growth hormone releasing hormone; GHSR= growth hormone-secretagogue receptor= ghrelin receptor; GIP= Gastric inhibitory hormone; GLP-1= Glucagon-like peptide-1; GOAT= Ghrelin O-acyltransferase HC= hip circumference; HTN= hypertension; JAK2= Janus kinase-2; LepR= leptin receptor; MC4R= melanocortin-4 receptor; NAFLD= non-alcoholic fatty liver disease; NASH= non-alcoholic steatohepatitis; NPY= neuropeptide Y
POMC/CART= proopiomelanocortin/ cocaine-amphetamine-regulated-transcript; PDE3B= Phosphodiesterase-3B PI3K= Phosphatidylinositol-3 Kinase; PPP or PP or PPY= Pancreatic polypeptide PYY= Peptide YY or peptide tyrosine tyrosine; SOCS3= suppressor of cytokine signaling-3; STAT3= Signal transducer and activator of transcription 3 WC= waist circumference; WHR= waist-to-hip ratio

References

1. Lissner L, Visscher TL, Rissanen A, Heitmann BL; Prevention and Public Health Task Force of European Association for the Study of Obesity. Monitoring the obesity epidemic into the 21st century-weighing the evidence. Obes Facts 2013;6(6):561-5.
2. Kohn M, Booth M. The worldwide epidemic of obesity in adolescents. Adolesc Med 2003;14(1):1-9.
3. World Health Organization. The global epidemic of obesity. Geneva, Switzerland: World Health Organization 1997.
4. Corey KE, Kaplan LM. Obesity and liver disease: the epidemic of the twenty-first century. Clin Liver Dis 2014;18(1):1-18.
5. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007;8(1):21-34.
6. Mantzoros CS, Magkos F, Brinkoetter M, Mantzoros CS. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab 2011;301:E567.
7. Gautron L, Elmquist JK. Sixteen years and counting: an update on leptin in energy balance. Clin Invest. 2011;121(6):2087
8. Procaccini C, Jarillo E, Matarese G. Leptin as an immunomodulator. Mol Aspects Med 2012;33:35–45.
9. Sansbury BE, Hill BG. Regulation of obesity and insulin resistance by nitric oxide. Free Radic Biol Med 2014;73:383-99.
10. James WP. The fundamental drivers of the obesity epidemic. Obes Rev 2008;9 (Suppl 1):6-13.
11. Bays H, Scinta W. Adiposopathy and epigenetics: an introduction to obesity as a transgenerational disease. Curr Med Res Opin 2015;2:1-46.
12. Manco M, Dallapiccola B. Genetics of pediatric obesity. Pediatrics 2012;130(1):123-33.
13. Girardet C, Butler AA. Neural melanocortin receptors in obesity and related metabolic disorders. Biochim Biophys Acta. 2014;1842 (3):482-94.
14. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004;89(6):2548-56
15. Leinninger GM, Myers MG Jr. LRb signals act within a distributed network of leptin-responsive neurones to mediate leptin action. Acta Physiol (Oxf) 2008;192(1):49-59.
16. Allison MB, Patterson CM, Krashes MJ. TRAP-seq defines markers for novel populations of hypothalamic and brainstem LepRb neurons. Mol Metab 2015 7;4(4):299-309
17. Hyeong-Kyu Park and Rexford S. Ahima. Leptin signaling. F1000 Prime Rep 2014;6: 73.
18. Wook K, Egan J. The Role of Incretins in Glucose Homeostasis and Diabetes Treatment. Pharmacol Rev 2008;60(4):470-512,
19. Suzuki K, Simpson KA, Minnion JS, Shillito JC. The role of gut hormones and the hypothalamus in appetite regulation. Endocr J 2010;57(5):359-72.
20. Dockray GJ. The versatility of the vagus. Physiol Behav 2009;97:531-6.
21. Sahu A. Intracellular leptin-signaling pathways in hypothalamic neurons: The emerging role of phosphatidylinositol-3 kinase-phosphodiesterase-3B-cAMP pathway. Neuroendocrinol 2011;93(4):201-10
22. Sahu A. Leptin signaling in the hypothalamus: emphasis on energy homeostasis and leptin resistance. Front Neuroendocrinol 2003;24:225-53.
23. Must A1, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282(16):1523-9.
24. Burton BT, Foster WR. Health implications of obesity: an NIH consensus development conference. J Am Diet Assoc 1985;85(9):1117-21.
25. Zhang QQ, Lu LG. Nonalcoholic fatty liver disease: dyslipidemia, risk for cardiovascular complications, and treatment strategy. J Clin Transl Hepatol 2015;3(1):78-84.
26. Abuyassin B, Laher I. Obesity-linked diabetes in the Arab world: a review. East Mediterr Health J 2015 8;21(6):420-39.

27. Badran M, Laher I. Obesity in Arabic-Speaking Countries. J Obesity 2011; 2011:686430.
28. Ogden CL, Carroll MD, Kit BK. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311(8):806-14.
29. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2014;384(9945):766-81.
30. Neamat-Allah J, Wald D, Hüsing A, Teucher B, Wendt A, Delorme S, et al. Validation of anthropometric indices of adiposity against whole-body magnetic resonance imaging--a study within the German European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts. PLoS One 2014;9(3):e91586.
31. Hu F. Measurements of adiposity and body composition. In: Hu F (ed) Obesity Epidemiology New York City: Oxford University Press, 2008; pp:53-83.
32. Carmienke S, Freitag MH, Pischon T, Schlattmann P, Fankhaenel T, Goebel H, et al. General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. Eur J Clin Nutr 2013; 67(6): 573-85.
33. Bea JW, Thomson CA, Wertheim BC, Nicholas JS, Ernst KC, Hu C, et al. Risk of mortality according to body mass index and body composition among postmenopausal women. Am J Epidemiol 2015;182(7):585-96.
34. Hirko KA, Kantor ED, Cohen SS, Blot WJ, Stampfer MJ, Signorello LB et al. Body mass index in young adulthood, obesity trajectory, and premature Mortality. Am J Epidemiol 2015;182(5):441-50
35. Simmonds M, Burch Jane, Llewellyn A, Griffiths C, Yang H, Owen C, et al. The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: A systematic review and meta-analysis. In: National Institute for Health Research Journals Library 2015;19(43):1-336.
36. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet 2010;375(9727):1737-48.
37. Biro FM, Wien M. Childhood obesity and adult morbidities. Am J Clin Nutr 2010;91(5):1499S-505S
38. Chesi A, Grant SF. The genetics of pediatric obesity. Trends Endocrinol Metab 2015 Sep 30. pii: S1043-2760(15)00162-9.
39. Woodrow G. Body composition analysis techniques in the aged adult: indications and limitations. Curr Opin Clin Nutr Metab Care. 2009; 12(1):8-14.
40. Samouda H, Dutour A, Chaumoitre K. VAT=TAAT-SAAT: innovative anthropometric model to predict visceral adipose tissue without resort to CT-Scan or DXA. Obesity (Silver Spring) 2013;21(1):E41-50.
41. Smith U. Abdominal obesity: a marker of ectopic fat accumulation. J Clin Invest. 2015;125(5):1790-2.
42. Rossi AP1, Fantin F, Zamboni GA, Mazzali G, Rinaldi CA, Del Giglio M, et al. Predictors of ectopic fat accumulation in liver and pancreas in obese men and women. Obesity (Silver Spring) 2011;19(9):1747-54.
43. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev 2012; 13(3):275-86.
44. Radzevičienė L, Ostrauskas R. Body mass index, waist circumference, waist-hip ratio, waist-height ratio and risk for type 2 diabetes in women: a case-control study. Public Health 2013;127(3):241-6.
45. Stalls CM, Triplette MA, Viera AJ, Pathman DE, Cohen MG, Rossi JC, et al. The association between body mass index and coronary artery disease severity: a comparison of black and white patients. Am Heart J 2014;167(4):514-20.
46. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol 2015 pii:mdv355.
47. Nazare JA, Smith J, Borel AL, et al. Usefulness of measuring both body mass index and waist circumference for the estimation of visceral adiposity and related cardiometabolic risk profile (from the INSPIRE ME IAA study). Am J Cardiol 2015;115(9):1323.
48. Cameron AJ, Magliano DJ, Shaw JE, Zimmet PZ, Carstensen B, Alberti KG, et al. The influence of hip circumference on the relationship between abdominal obesity and mortality. Int J Epidemiol 2012;41(2):484-94.
49. Bengmark S. Obesity, the deadly quartet and the contribution of the neglected daily organ rest - a new dimension of un-health and its prevention. Hepatobiliary Surg Nutr 2015;4(4):278-88.
50. Wirth A, Wabitsch M, Hauner H. The prevention and treatment of obesity. Dtsch Arztebl Int 2014;111(42):705-13.
51. Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults. American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel, 2013. Obesity (Silver Spring). 2014(Suppl 2):S41-410.
52. Richardson L, Paulis WD, van Middelkoop M, Koes BW. An overview of national clinical guidelines for the management of childhood obesity in primary care. Prev Med 2013;57(5):448-55.
53. Thury C, de Matos CV. Prevention of childhood obesity: a review of the current

guidelines and supporting evidence. S D Med 2015;Spec No:18-23.
54. Kushner RF, Ryan DH. Assessment and lifestyle management of patients with obesity: clinical recommendations from systematic reviews. JAMA 2014; 312(9):943-52.
55. Muraki I, Imamura F, Manson JE, Hu FB, Willett WC, van Dam RM, et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. BMJ 2013;347:f5001
56. Roeder A. Skip the juice, go for whole fruit. Harvard Gazette 2013 http://news.harvard.edu/gazette/story/2013/08/reduce-type-2-diabetes-risk/
57. Thakkar RK, Michalsky MP. Update on bariatric surgery in adolescence. Curr Opin Pediatr 2015;27(3):370-6
58. Mancini MC. Bariatric surgery-an update for the endocrinologist. Arq Bras Endocrinol Metabol 2014;58(9):875-88.
59. Mechanick J, Youdim J Jones D, Garvey W, Hurley, McMahon M, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update. Surg Obes Relat Dis 2013;9(2):159-91

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