What's Behind the Obesity Epidemic

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1.1 Introduction

Obesity is defined as an abnormal or excessive accumulation of fat that may impair health, and it is a chronic disease that is increasing in prevalence [1].

Global obesity rates have tripled in many countries of the World Health Organization (WHO) European Region since the 1980s, and the numbers of those affected continue to rise at an alarming rate [2].

Based on the latest estimates in European Union countries, overweight affects 30–70%, and obesity affects 10–30% of adults. In the USA 70% of the population are now affected by excess weight or obesity [3, 4].

It is now no exaggeration to state that obesity is an international epidemic. Moreover, it is no longer a disorder of the adult since obesity prevalence in children has accelerated rapidly affecting 21.1% of girls and 18.6% of European boys (Ahrens et al. 2014).

1.2 Definition and Diagnosis

Clinically, obesity is defined on the basis of the body mass index (BMI), calculated as weight in kilograms divided by height in meter squared. The WHO states that for adults, the healthy range for BMI is between 18.5 and 24.9. Overweight is defined as a body mass index of 25 to 29.9, and obesity is defined as a body mass index of 30 or higher (Table 1.1) [2].

These BMI cut points in adults are the same for men and women, regardless of their age.

For clinical and research purpose, obesity is classified into three categories: class I (30–34.9), class II (35–39.9), and class III (>40) [5]. With the growth of extreme obesity, researchers and clinicians have further divided class III into super obesity (BMI 50–59) and super-super obesity (BMI > 60).

The current used BMI cutoff values are based on morbidity and mortality studies in Caucasian population [6]. Several studies observed that some obese patients do not show expected metabolic abnormalities despite their substantial excess of body fat, demonstrating that while obesity increases the possibility of having complications, not every obese patient will develop them [7]. Although BMI is the

Table 1.1 Classification of obesity

Classification	Body mass index category
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese	>30.0
Class I	30.0–34.9
Class II	35.0–39.9
Class III	>40.0

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accepted method to classify obesity and it can be used to predict and evaluate disease risk in epidemiological studies, it does not differentiate the composition of lean versus fat tissue and therefore may lead to erroneous interpretations (Kushner et al. 2009).

Moreover, obese individuals differ not only in respect to the excess fat mass but also in its regional distribution in different body sites. It is important to distinguish between android obesity and gynoid fat distribution, in which fat is allocated peripherally around the body [6].

Indeed, central or visceral abdominal obesity is associated with substantially different metabolic profiles and cardiovascular risk factors than gluteal-femoral obesity. To assess these differences, it is useful to measure waist circumference (WC). Population studies have shown that people with larger WC have impaired health and increased cardiovascular risk compared with those with normal WC within the healthful, overweight, and class I obesity BMI categories. Abdominal fat is clinically defined as a WC of 102 cm or more in men and 88 cm or more in women (Kushner et al. 2009).

In addition to BMI and WC, there are other markers for excess body fat evaluation used for clinical practice, as the skinfold thickness and the waist-to-hip ratio [6].

Next to these descriptive classifications, the presence of obesity-related comorbidities is gaining importance as a discriminating factor, as captured by the Edmonton Obesity Staging System (EOSS) [8] and the Cardiometabolic Disease Staging (CMDS) system [9]. The current trend is to consider two types of obesity, the so-called eumetabolic obesity (not associated with comorbidities) and dysmetabolic obesity (associated with inflammation, insulin resistance, dyslipidemia, hypertension).

Finally, direct measure of body mass fat, through magnetic resonance imaging (MRI), computed tomography (CT), dual-energy X-ray absorptiometry (DXA), bioimpedance analysis, and total body water, is gaining interest to assess the obese phenotype, but more studies are needed before either can be routinely recommended for office use.

1.3 Pathogenesis and Etiology

The etiology of obesity is multifactorial, involving a complex interaction among genetics, hormones, and the environment [10]. Body weight is regulated by a multifaceted system, including both peripheral and central factors. *Ghrelin* is a circulating peptide hormone, originally isolated from the stomach, but it has also been identified in other peripheral tissues, such as the gastrointestinal tract, pancreas, ovary, and adrenal cortex. It is the only known peripherally acting orexigenic hormone and is responsible for stimulating appetite [11]. *Leptin*, another product of adipocytes, is also a central mediator of inflammation in obesity [12]. Leptin acts as a dominant long-term signal responsible for informing the brain of adipose energy reserves. In addition to adipose tissue, leptin is also produced in small amounts in the stomach, mammary epithelium, placenta, and heart. Leptin binds to specific receptors on appetite-modulating neurons and the arcuate nucleus in the hypothalamus, giving information about the status of the body energy stores, and it inhibits appetite. Leptin-deficient mice that lack leptin receptors have been shown to be hyperphagic and obese. True leptin deficiency in humans is rare; however, obese humans are, in part, leptin resistant.

Other factors involved in the regulation of body weight are *peptide YY* (PYY), secreted by the L cells of the distal small bowel and colon and released after a meal, by its signals to the hypothalamus cause delayed gastric emptying, thus reducing gastric secretion [13]; *cholecystokinin* (CCK), produced in the gallbladder, pancreas, and stomach and concentrated in the small intestine, released in response to dietary fat, regulates gallbladder contraction, pancreatic exocrine secretion, gastric emptying, and gut motility, which acts centrally by increasing satiety and decreasing appetite; and *glucagon-like peptide-1* (GLP-1), whose biological activities comprehend stimulation of glucose-dependent insulin secretion and insulin biosynthesis, inhibition of glucagon secretion and gastric emptying, and inhibition of food intake. Several other hormones, collectively indicated as adipokines, are produced by the adipocytes. The key secretory products are tumor necrosis factor-alpha (TNF-α), whose role in obesity has been linked to insulin resistance; interleukin 6 (IL-6), a pleiotropic circulating cytokine linked to

inflammation, impairment of host defenses, and tissue injury; and adiponectin, an adipokine derived from plasma protein, which is insulin sensitizing, anti-inflammatory, and antiatherogenic.

Secondary pathologic causes of obesity include drugs and neuroendocrine diseases (hypothalamic, pituitary, thyroid and adrenal) (Table 1.2) that should be excluded by the endocrinologist before other treatments are commenced.

Table 1.2 Etiology of obesity

Environmental causes
Dietary factors
Lack of physical activity
Lifestyle factors
Neuroendocrine obesity
Hypothalamic obesity Trauma Tumors Inflammation Surgery Increased intracranial pressure
Cushing's syndrome
Hypothyroidism
PCOS
Growth hormone deficiency – Hypogonadism – insulinoma and hyperinsulinaemia – pseudohypoparathyroidism
Drugs
Antipsychotics
Antidepressants
Anticonvulsants
Steroids
Adrenergic antagonists
Serotonin antagonists
Oral hypoglycemic agents
Genetic and congenital disorders
Prader-Willi syndrome
Bardet-Biedl syndrome
Leptin deficiency
Albright hereditary dystrophy
Alstrom-Hallgren syndrome
Cohen syndrome
Carpenter syndrome
Beckwith-Wiedemann syndrome
Pseudohypoparathyroidism type 1a
Pregnancy and menopause
Eating disorders and psychological causes
Bulimia nervosa
Stress
Anomalous eating habits
Depression, lack of confidence, and self-esteem
Social factors

1.4 Associated Comorbidities

Obesity is associated with chronic comorbidities [14, 15], physical or psychological symptoms, and/or functional limitations, which can have a substantial, negative impact on quality of life (stages 2–4 EOSS) [16] and mortality (stages 2–4 CMDS system) [3].

The most well-established weight-related comorbidities are insulin resistance, type 2 diabetes (T2D), and cardiovascular disease, the risks of which are proportional to BMI. Other recognized complications associated with overweight and obesity include obstructive sleep apnea, non-alcoholic fatty liver disease, osteoarthritis, polycystic ovary syndrome, and increased mortality [16, 17]. Hereafter are discussed the most frequent complications of overweight/obesity.

1.4.1 Insulin Resistance, Type 2 Diabetes, and Metabolic Syndrome

Obesity is often associated with the development of adipose tissue (AT) inflammation. Obesity-induced inflammation is a chronic, low-grade inflammation that produces much lower levels of circulating cytokines compared to classical immunity inflammation. It particularly resembles the inflammation observed in atherosclerosis, which is one of the complications of metabolic syndrome along with insulin resistance and lipid dysregulation [18]. Thus, obesity-induced inflammation may be a different kind of inflammation, namely, one that is the result of overnutrition and stress pathways that drive abnormal metabolic homeostasis (e.g., high levels of lipid, free fatty acids (FFA), glucose, or ROS). There is increasing evidence showing that inflammation is an important pathogenic mediator of the development of obesity-induced insulin resistance [19]. Adipose tissue (AT) contains immune cells, and obesity increases their numbers and activation levels,

particularly in AT macrophages (ATMs). Other pro-inflammatory cells found in AT include neutrophils, Th1 CD4 T cells, CD8 T cells, B cells, dendritic cells (DCs), and mast cells.

AT in obesity acts as an endocrine organ that regulates the production of various hormones and cytokines, which include TNF-α and IL-6. More recently identified adipokines that promote inflammation include resistin, retinol-binding protein 4 (RbP4), lipocalin 2, IL-18, angiopoietin-like protein 2 (ANGPTL2), CC chemokine ligand 2 (CCL2), CXC chemokine ligand 5 (CXCL5), and nicotinamide phosphoribosyltransferase (NAmPT) [20]. Systemic metabolic inflammation can affect pancreatic islets through distinct mechanisms, contributing to beta cell failure in type 2 diabetes (T2D).

Obesity associated to hypothalamic inflammation is accompanied by the loss of the first phase of insulin secretion.

The risk of developing T2DM proportionately doubles with every 5–7.9 kg gain in weight. Conversely, T2DM impairs other weight-related problems, particularly heart failure, obstructive sleep apnea (OSA), and hypogonadism. The marked increase in the prevalence of obesity has played a major role in the 25% increase in diabetes. According to data from NHANESIII, two-thirds of the men and women in the USA with diagnosed type 2 diabetes have a BMI of 27 kg/m^2 or greater. The risk of developing diabetes increases linearly with BMI [21].

1.4.2 Hypertension

Hypertension is about six times more frequent in obese than in lean individuals [22]. Among men, the prevalence of high blood pressure increased progressively with increasing BMI, from 15% at a BMI of <25 kg/m^2 to 42% at a BMI of ≥30 kg/m^2. Women showed a pattern similar to that of men; the prevalence of hypertension being 15% at a BMI of <25 kg/m^2 to 38% at a BMI of ≥30 kg/m^2 [23]. Obesity is associated with increased blood flow and vasodilatation. Although cardiac index (cardiac output divided by body weight) does not increase, cardiac output and glomerular filtration rate do [24].

Increased renal sodium retention also contributes. Other factors considered responsible for obesity-related alterations include enhanced sympathetic tone, activation of the renin-angiotensin system (RAS), with elevations of circulating renin, angiotensinogen, and angiotensin II, despite the increased renal sodium retention, hyperinsulinemia, structural changes in the kidney, and elaboration of adipokines [24].

1.4.3 Dyslipidemia

The typical dyslipidemia of obesity consists of increased triglycerides (TG) and FFA, decreased HDL-C with HDL dysfunction and normal, or slightly increased LDL-C with increased small dense LDL [25].

The development of small dense LDL in obesity is mainly due to increased TG concentrations and does not depend on total body fat mass [26]. The concentrations of plasma apolipoprotein (apo) B are also often increased, partially because of hepatic overproduction of apo B-containing lipoproteins [27, 28].

1.4.4 Cardiovascular Disease

The incremental increases in left ventricular filling pressure and volume throughout time may produce chamber dilation. This leads to increased wall stress, which predisposes to an increase in myocardial mass and eventually to left ventricular hypertrophy, typically of the eccentric type. Left atrial enlargement may also occur, due to left ventricular hypertrophy (LVH) in long-standing obesity and/or the effects of concomitant hypertension, and as a consequence may mediate the risk of atrial fibrillation associated with obesity. Age and cardiac hypertrophy predispose to left ventricular systolic dysfunction. Moreover, lipid deposition can impair tissue and organ function because the size of fat around key organs may increase organs

modifying their function. Also, lipid accumulation can occur in ectopic sites, within nonadipose cells, and contribute to cell dysfunction or death (lipotoxicity).

Thus, through different mechanisms (increased total blood volume, increased cardiac output, LVH, left ventricular diastolic dysfunction, lipotoxicity), obesity may predispose to heart failure. [29].

1.4.5 Female Dysfunctions

Age of menarche generally occurs at a younger age in obese than in normal-weight girls, and there is evidence that in adolescent and young women, the age of onset of obesity and menstrual irregularities are significantly correlated.

Fertility seems to decline in women with increasing obesity, whether they have or do not have polycystic ovarian syndrome (PCOS). Mechanisms by which obesity influences the pathophysiology and clinical expression of PCOS are complex and not completely understood [30]. However, obesity is believed to play a distinct pathophysiological role in the development of hyperandrogenism in women with PCOS. Insulin acts as a true gonadotropic hormone [31]. At ovarian level, by acting through its own receptors and the insulin growth factor (IGF) receptor type I, insulin synergizes LH action and stimulates ovarian steroidogenesis both in granulosa and thecal cells. Moreover, insulin seems to increase pituitary sensitivity to gonadotropin-releasing hormone (GnRH) action, overstimulating ovarian androgen production. The GH/IGF-1 system has a role in favoring altered ovarian androgen secretion and granulosa cell function in PCOS [31]. IGF-1 bioavailability appears to be reduced in obese than in normal-weight PCOS women, as a consequence of the combined low GH and high insulin levels, which depends on obesity per se [32].

The association between obesity and infertility in women has long been recognized. Epidemiological studies have demonstrated that in the fertile period of their life, obese women frequently present with menstrual cycle alterations and chronic or intermittent anovulation [32, 33].

Obesity may affect fertility and reproduction in women by disturbing spontaneous ovulation, by interfering with the efficiency and outcomes of assisted reproductive technology, and by worsening the physiological process and delivery in pregnancy [34].

1.4.6 Male Dysfunctions

There is a well-known link between obesity and testosterone deficiency (hypogonadism), and although there appears to be a complex interplay between body composition, obesity, androgen levels, vascular disease, and T2DM, the exact mechanisms, which lead to hypogonadism in obese men, have yet to be determined. Male obesity is commonly associated with testosterone levels within the hypogonadal range. An increased aromatase activity within adipocytes results in the peripheral conversion of testosterone into estradiol and a subsequent rise in serum estradiol levels. Estradiol exerts a negative feedback effect on LH secretion and suppresses the hypothalamic-pituitary-testicular (HPT) axis, thus leading to a reduction in plasma testosterone levels and secondary hypogonadism. Inflammatory mediators associated with obesity may also contribute to the suppression of the HPT axis. Inflammatory mediators may exert a direct inhibitory effect on the HPT axis or may contribute to secondary hypogonadism through indirect mechanisms such as worsening of insulin resistance [35]. Hypogonadism can itself worsen obesity and promote increased fat mass that in turn may worsen the hypogonadal state.

Erectile dysfunction and reduced male fertility are associated with obesity and are thought to be mediated by low testosterone levels and by the elevated levels of several pro-inflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-8), and C-reactive protein (CRP) [36]. Obesity has been linked to reduced sperm count,

increased DNA fragmentation in sperm, and reduced sperm motility in proportion to the degree of obesity [32].

1.4.7 Osteoarthritis

Osteoarthritis (OA) is the most common rheumatic disease in the world and represents the first cause of disability in the world after 40 years old [37]. The primary etiology of OA in obesity tends to be persistent loading during joint movement and locomotion, but inflammatory and metabolic characteristics of obesity affect joint health as well [38]. The risk of knee osteoarthritis is strongly and proportionally associated with BMI. Obese individuals are at increased risk of distal extremity injuries and tendinopathies.

1.4.8 Obstructive Sleep Apnea

Several respiratory complications are associated with obesity. Obese patients have an increased demand for ventilation and breathing workload, respiratory muscle inefficiency, decreased functional reserve capacity, and expiratory reserve volume. These often result in a ventilation-perfusion discrepancy, especially in the supine position. Sleep apnea is defined as repeated episodes of obstructive apnea and hypopnea during sleep, together with daytime sleepiness or altered cardiopulmonary function. The prevalence of sleep-disordered breathing and sleep disturbances rises dramatically in obese subjects, and obesity is by far the most important modifiable risk factor for sleep-disordered breathing.

Obesity increases the prevalence of sleep-disordered breathing tenfold. This rise in incidence is proportional to weight gain [12, 29].

1.4.9 Cancer

There is a strong association between elevated BMI and cancer risk and between BMI and cancer mortality related to esophageal, colon, rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin lymphoma, multiple myeloma, and prostate cancer. Obesity leads to 20–35% of all the cancers. The major candidates relating obesity to cancer are those cytokines that cause insulin resistance: leptin, IL-6, TNF-a, adiponectin, and FFAs [39, 40]. Insulin resistance and hyperinsulinemia promote the production of insulin-like growth factor-1 (IGF-1). Many cancer cell lines, including prostate and colon, have IGF-1 receptors. Visceral adipocytes, by way of lipolysis, increase the circulating level of FFAs that may have cancer potential both directly, by causing cellular proliferation, by directly stimulating IGF-1, and indirectly, through insulin resistance [12].

1.4.10 Psychological Disorders

Obesity may also have psychological effects: obese individuals have a greater likelihood of experiencing depressive symptoms than non-obese individuals [odds ratio 1.26, 95% confidence interval (CI) 1.17–1.36] ($p \leq 0.001$), so it is important to consider both diseases and their possible association due to major health cost and involvement in life quality [3, 41].

Conclusions

Obesity is a heterogeneous disease, and individualizing therapy is mandatory. Treatment approaches should take into account the underlying causes of obesity. If a complication from obesity exists, targeting both the excess weight and the comorbid disease would be desirable to improve benefit.

The American Association of Clinical Endocrinologists (AACE), the American Medical Association, the Obesity Society (TOS), and the Endocrine Society all classify obesity as a disease and recognize that it requires treatment [3, 42].

Modest weight loss with lifestyle modification programs can have long-term health benefits, including improved lipid and glycemic control and reduced risk of T2DM. However, low adherence can severely prejudice their long-term weight loss efficacy. Bariatric

procedures seem to be more effective than nonsurgical interventions in terms of weight loss and may decrease the long-term risk of comorbidities, as well as overall mortality. However, bariatric surgery is not suitable or feasible for all people with obesity. Pharmacological options have the potential to connect the treatment gap between lifestyle modifications and bariatric surgical procedures [3], but target individual complications may result in problematic polypharmacy [3]. An appropriate therapeutic approach aimed primarily at treating the causes of obesity and to achieve a reduction in body weight is needed in order to reduce obesity comorbidities.

The case for a preventive approach to the obesity epidemic is compelling. Obesity poses one of the most significant threats to population health that is currently faced.

Key Points

1. Obesity is defined on the basis of the body mass index (BMI) based on morbidity and mortality studies in the Caucasian population.
2. The etiology of obesity is multifactorial, involving a complex interaction among genetics, hormones, and the environment.
3. The most well-established weight-related comorbidities are insulin resistance, type 2 diabetes (T2D), and cardiovascular disease, the risks of which are proportional to BMI.

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