

Obesity, Adipose Tissue, Inflammation and Update on Obesity Management

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Abstract

Obesity is a serious, common and growing problem. Obesity can be defined as an excess of body fat. Its clinical management is complex and frequently unsuccessful. It has only recently been regarded as a chronic disease, linked with diabetes, dyslipidaemia and cardiovascular disease. It is increasingly known that obesity is a multifactorial disease; involving genetic determinants that interacting with environmental factors results in obesity. The global epidemic of obesity imposes a major disease burden, particularly cardiovascular disease. There is a clear link between adipose tissue and inflammation, object of the present review. Adipose tissue is considered a dynamic organ with extremely sophisticated functions. Obesity is associated with low chronic inflammation through the secretion of adipokines. Inflammation mediates on the development of metabolic diseases associated with obesity, dyslipidaemia, hypertension and type 2 diabetes. The treatment of obesity has evolved, from short time and simple diet together with increase in physical activity to long-term approaches based on changes in eating behavior and physical habits.

Introduction

It is often unrecognized that although obesity was included in the classic listing of diseases in 1948, the medical profession dismissed it for decades. Two other documents by The London Royal College of Physicians published in 1976 and 1983 [1,2] highlighting obesity as a problem that has been ignored also for the medical profession and governments. This was probably related to the fact that obesity was assumed to be a reversible problem, that could be solved if people only eat less and do more exercise. This misunderstanding persists today.

However, the perception of adipose tissue has changed considerably with the dramatic increase in the incidence of obesity and in obesity-related co morbidities over the past 2 decades. Excess fat is no longer associated with wealth, but is instead recognized as a risk factor for many diseases. Adipose tissue is increasingly being identified as a vital, complex endocrine organ, and not simply as a fat store [3]. In this review,

we update some aspects of the obesity including the relationship between the adipose tissue and inflammation.

Obesity definition and diagnosis

Adipose tissue, almost more than any other tissue, is increasingly being considered contributing to both human well-being and disease processes.

Obesity can be defined as an excess of body fat. Its clinical management is complex and frequently unsuccessful [4]. A surrogate marker for body fat content is the Body Mass Index (BMI), which is widely used both for epidemiological studies and clinical evaluations [5]. Among children and adolescents age and gender cut-off values should be used [6]. A better way to define obesity should be in terms of Body Fat Percentage (BF%) that can be measured by different techniques, from skin-fold measurements to magnetic resonance [7]. Other frequently used methods for determining BF% include Bioelectrical Impedance Analysis (BIA), and Dual-Energy X-Ray Absorptiometry (DEXA), underwater weighing and Air Displacement Plethysmography (ADP). When BF% determination is not available, BMI is the most frequently used surrogate measure of adiposity. However, BMI exhibits notable inaccuracies not precisely reflecting body fat, for instance, the changes in body composition in the different periods of life or the sexual dimorphism characteristics of body adiposity [8]. Since the possibility of measuring BF% is not always available and the relation between BMI and BF% is highly dependent on sex and age, several prediction equations that account for sex and/or age have been published. Recently new predictive equations that may be used as a first screening tool in clinical practice have been published [9].

Obesity pathogenesis

Obesity is a chronic disease like hypertension and diabetes. Mechanistically is the result of an imbalance between the energy ingested in food and the energy expended. As a cause, in addition to a predisposed genetic make-up that promotes fat

deposition, important environmental factors related to nutrient composition, sedentary habits and the involvement of complex systems of reward might play important roles. We are designed with robust adaptive allostatic systems attempting to maintain a specific set point of energy balance. There is evidence that defects in these systems preferentially result in activation of pathways that save energy, making the control of energy balance an almost impossible task, with the current available strategies [10]. Furthermore, we are exposed to an obesogenic environment that includes obesogens [11] together with other factors such as disordered eating behaviors [12-14]. All these aspects make the development of obesity in humans a complex problem (Figure 1).

A variety of endocrine and metabolic changes are associated with overweight and obesity [15,16]. Most of these changes are secondary, because they can be induced by overfeeding and reversed by weight loss. It is not completely clear if some of these hormonal changes may contribute to the pathophysiology of obesity or to perpetuate the obese state. In obesity GH secretion is markedly decreased. The pathophysiological mechanisms responsible for the GH hyposecretion of obesity are probably multifactorial [15,17] and could contribute to maintain the obese state. There are important data that suggest a preponderant role of, the endogenous GH secretagogue, ghrelin in the pathophysiological regulation of body weight [18-21].

The results of the afore mentioned factors are that excess energy is stored in fat cells that enlarge and/or increase in number. This hyperplasia and hypertrophy of fat cells is the pathological lesion of obesity. Enlarged adipose tissue produces the clinical problems associated with obesity, either because of the weight or mass of the extra fat or because of the increased secretion of free fatty acids and peptides from fat cells. The consequences of these two mechanisms are different diseases,

such as type 2 diabetes, hypertension, gallbladder disease, osteoarthritis, ischemic heart disease, some types of cancer, social and psychological disabilities [22,23].

Fat tissue development

In humans, the first fat lobules begin to develop about the fourteenth and sixteenth weeks of gestation, with cranial-to-caudal and proximal-to-distal gradients [24]. By 28 weeks, fat lobules can be detected in all presumptive visceral and subcutaneous white adipose tissue locations [24]. Adipocyte progenitors are derived from multipotent mesenchymal stem cells. These precursor cells are devoid of lipid, but become committed to the adipocyte lineage and are regarded as preadipocytes that have lost the capacity to differentiate into other cell types. The second phase results in the terminal differentiation of these adipocyte progenitors into mature, functional adipocytes.

Peroxisome Proliferator-Activated Receptor (PPAR γ) is regarded as the master regulator of adipogenesis. PPAR γ is a member of the nuclear-receptor super-family, and is both necessary and sufficient for adipogenesis [25]. PPAR γ is not only crucial for adipogenesis, but is also required for the maintenance of the differentiated state.

In addition to adipocytes, adipose tissue contains stromal-vascular cells, including fibroblastic connective tissue cells, leukocytes, macro-phages, and preadipocytes (that are not yet filled with lipids), which contribute to structural integrity and constitute around 50% of its total cellular content [26]. The lipid droplets in adipose tissue can be unilocular, multilocular, or both. Unilocular cells are characteristics of the white adipose tissue while multilocular cells are typically seen in brown adipose tissue.

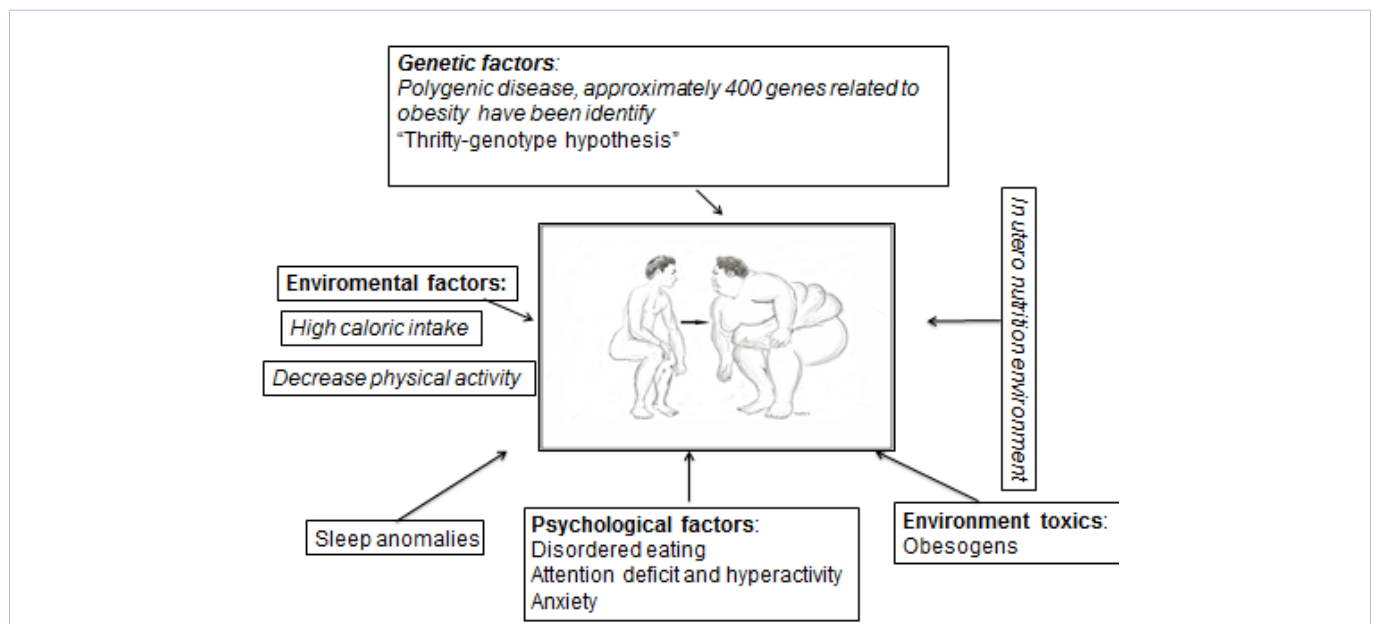


Figure 1: Different factors in Obesity ethiopathology.

Heterogeneity of adipose tissue

The adipose tissue pool in mammals is composed of at least two functionally distinct types of fat: white and brown. White adipose tissue is the primary site of energy storage and the release of hormones and cytokines that modulate whole-body metabolism and insulin resistance [27,28]. Additionally, white adipose tissue can act as a thermal insulator and protect other organs from mechanical damage [29]. Brown adipose tissue uses the chemical energy in lipids and glucose, to produce heat through non-shivering thermogenesis via mitochondrial uncoupling of oxidative phosphorylation of free fatty acids, mediated by the expression of tissue-specific, mitochondrial brown fat uncoupling protein 1 (UCP1) [30]. Like white adipose tissue, brown adipose tissue can affect whole-body metabolism and its activation might lead to new approaches to promote weight loss and increase insulin sensitivity [31,32].

There is a regional distribution of adipose tissue. Adipose tissue is located beneath the skin (subcutaneous adipose tissue), around internal organs (visceral adipose tissue), in bone marrow (yellow bone marrow), and in breast tissue. Conversely, peripheral subcutaneous adipose tissue exhibits an independent anti-atherogenic effect [33] and is not related to many of the classic obesity-related pathologies, such as cancer, heart disease, and stroke, with some evidence that it might even be protective [34].

Cardiac adipose tissue has recently been considered a new specific location of adipose cells [3]. The concept of cardiac adiposity as cardiovascular risk factor is novel. Epicardial adipose tissue is the true visceral fat deposit of the heart [35-37] and is located between the myocardium and visceral pericardium around both ventricles varying in extent and distribution pattern

[36-38]. Pericardial adipose tissue is composed of epicardial and pericardial adipose tissue located on the external surface of the pericardium. Both unfavorable and protective have been attributed to epicardial adipose tissue [39]. Epicardial adipose tissue is an extremely active organ that expresses a higher number of inflammatory mediators and chemokines than subcutaneous adipose tissue, irrespective of BMI [40]. Epicardial adipose tissue thickness is an independent predictor of visceral adiposity [41]. Furthermore, a clear positive correlation was reports between epicardial adipose tissue volume and coronary artery calcium score in several studies [42-44].

Adipose tissue as endocrine organ

White adipocytes are major secretory cells [45], which makes adipose tissue a key endocrine organ. Indeed, adipose tissue is the largest endocrine organ in most humans [28] and is certainly so in individuals who are overweight or obese. For example, approximately 20% of total body weight is adipose tissue in an individual who is lean whereas adipose tissue constitutes almost half of body weight in a person who is obese.

White adipose tissue has been identified as a metabolically active endocrine organ that affects a plethora of body functions including energy and feeding regulation, glucose and lipid metabolism, thermogenesis, neuroendocrine function, reproduction, immunity and most relevantly cardiovascular function. These effects are achieved via the release of important chemical mediators, hormones and adipocytokines or adipokines. The discovery of leptin in 1994 heralded a new era in the study of adipose tissue. Other proteins that are secreted by adipose tissue with important metabolic effects include a number of adipocytokines, such as adiponectin, leptin, resistin, visfatin, apelin, omentin, chemerin, nesfatin and other cytokines,

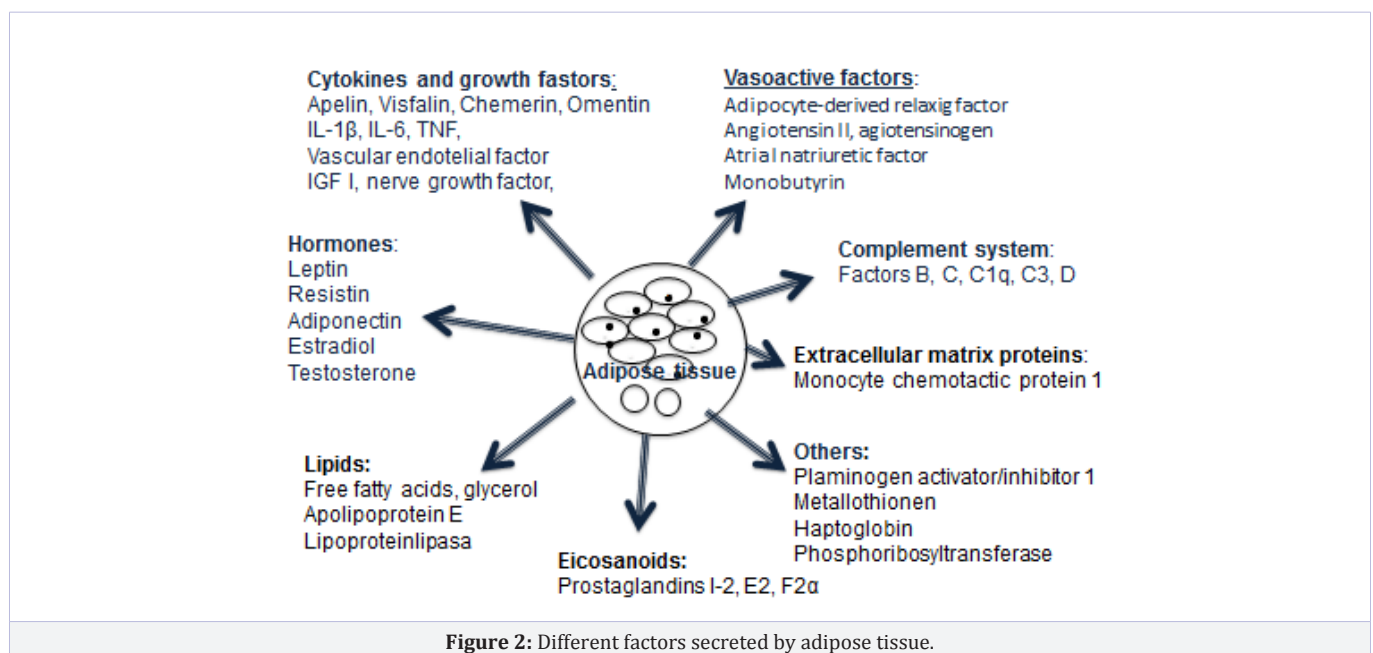


Figure 2: Different factors secreted by adipose tissue.

e.g. Interleukin-6 (IL6), Plasminogen Activator Inhibitor (PAI-1), Monocyte Chemo Attractant Protein 1 (MCP-1) and Tumor Necrosis Factor- α (TNF α). Many others have now been identified and the list is growing [46-47] (Figure 2).

Adipose tissue and inflammation

Adipocytes have intrinsic inflammatory properties. They express multitude of receptors to which pathogens and inflammatory signals bind. In turn, the receptors can induce the secretion of various potent inflammatory cytokines and mediators. Adipocytes express receptors for TNF (TNF receptor superfamily member 1A [also known as p55] and 1B [also known as p75] and the mammalian lipopolysaccharide-activated toll-like receptor 4. Binding to these receptors activates nuclear factor NF- κ B signal transduction pathways [48]. Adipocytes may initiate inflammatory signaling cascades upon activation by IL-1 β , IL-4, IL-6, IL-11, interferon- γ , and fungal cell-wall components [49]. As well as reacting to several mediators of inflammation, adipocytes can induce the expression and secretion of mediators of inflammation, including complement factors B, C3, and D, haptoglobin, hepatocyte growth factor, IL-1 β , IL-6, IL-8, IL-10, IL-15, leukemia inhibitory factor, macrophage migration inhibitory factor, prostaglandin E2, serum amyloid A3 protein, and TNF, as well as Adiponectin, Apelin, Chemerin, Leptin, Resistin, Serpin A12 (also known as vaspin), and visfatin [50]. Adipocytes are not the only cells in adipose tissue to elicit inflammatory responses; resident macrophages can also secrete inflammatory mediators. These macrophages can act independently or synergistically to stimulate inflammation. In addition, the adipose tissue macrophages in diet-induced obesity tend to have a pro-inflammatory (M1) phenotype, involving IL-6, IL-12, and TNF [51]. Furthermore, the adipocytes in individuals who are obese are larger than those in people of average weight, and produce a lower level of adiponectin, but higher levels of pro-inflammatory cytokines such as TNF. Therefore, obesity is associated with systemic inflammation.

Despite using similar pathways and mediators, the inflammatory response in obesity differs substantially in duration and intensity from that observed in the more familiar setting of infection. For instance, infectious inflammation involves short-lived high-amplitude responses, whereas metabolic inflammation like other chronic inflammatory conditions smoulders at low levels for years to decades. Although the underlying mechanisms contributing to these differences are not entirely clear, it seems likely that hormonal or epigenetic programming may permanently reassign certain systemic and tissue-specific parameters, such as body weight and leukocyte activation, in obesity [52].

Inflammatory activation within metabolic tissues potentiates insulin resistance and metabolic disease [52]. Obesity-induced metabolic disease promotes and exacerbates pathology through numerous disease-specific mechanisms; most metabolic disease ultimately arises from obesity's characteristic milieu of chronic low-grade inflammation and insulin resistance. For example, obesity has been recognized for decades as an important risk

factor for cardiovascular disease; however, only recently has that risk been mechanistically understood as a result of obesity's accompanying inflammation and insulin resistance [53]. Similarly, hyperlipidaemia, another well-described contributor to cardiovascular disease, arises as a consequence of inflammatory insulin resistance through increased adipose tissue lipolysis and hepatic lipogenesis. Even the biomechanical dynamics of cardiovascular disease, atherosclerotic plaque formation, remodelling, and rupture are influenced by the inflammatory milieu [53]. Indeed, the efficacy of some antihyperlipidemic therapies, statins and salicylates, correlates with their immunomodulatory potency as much as with their lipid-lowering capacity [54].

Treatment of the Obese Patient

Nowadays, obesity is a major health problem because its prevalence is progressively increasing and there is no indication that current strategies may solve the problem in the near future. In order to treat overweight and obese patients, any intervention that causes a negative energy balance is effective in producing weight loss. This is the basis for the classical use of short-term restrictive diets, resulting mainly in loss of body water and muscle mass, followed by a rapid body weight regain. When treating obese subjects we should bear in mind that obesity is defined by increased body fat, and to reduce such increase of body fat should be our treatment target. It is also important that health professionals consider the obese patient as chronic; consequently the treatment should be programmed for a long period of time.

Emerging evidence support the notion that long-term balanced diet together with increase physical activity can reduce adiposity [55,56]. How can we achieve long-term modification of life-style? Since is well known that change of habits in adults is a very difficult task, Educational therapy and Psychotherapy may help us to obtain positive results [57-59].

In order to treat overweight and grade I obesity it could be enough with the use of a life-style change program, in some cases with the concurrence of behavioral education [58] or psychotherapy [59]. While for grade II and III obese patients, at the beginning of the diagnostic process the existence of concomitant psychological anomalies should be ruled-out [11-13]. Thereafter, the help of a psychotherapist can be useful to facilitate the change of habits [57-61]. In these cases some drugs can be used as adjuvant treatment.

Pharmacotherapy can be used as adjunct (not as substitute) to lifestyle modification. The number of drugs available for the treatment of obesity has decreased in recent years because some of them, in particular dexfenfluramine and sibutramine have been removed from market as a result of serious side effects [62]. The anti-obesity drugs presently on the market in USA are Benzphetamine, Phendimetrazine, Phentermine and Diethylpropion for short-term use. For long-term use were approved Orlistat and recently Phentermine/Topiramate and

Lorcaserin, while in development Bupropion/Naltrexone and Liraglutide [63]. Furthermore, drugs such as fluoxetine use for anxiety control or anticonvulsant as topiramate can help at least temporally [64].

For patients with Grade III obesity the first line of treatment is bariatric surgery. The question is what modality of this kind of surgery should be use in each patient? In general several factors should be taken into account: first the surgeon expertise, the preference of the patient, and it should be bear in mind that obesity is a long-term process and that surgical intervention is not an etiological treatment. For these reasons it could be adequate in young patients to propose first a less complex intervention, such as reduction techniques, if weight regain occurs, another more complex intervention can be used such as by-pass techniques [65-67] (Figure 3).

However, bariatric surgery is not free of complications that are related to the procedure performed. Perioperative death after surgery for obesity occurs in about 2 per 1,000 of operated patients in population based-studies [68]. The more complicated the procedure the higher risk of perioperative death. Dysphagia may occur after laparoscopic adjustable gastric banding. An anastomotic leak after laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy is a life-threatening complication. Gallstone disease is common after surgery for obesity with incidences up to 50% [69]. Furthermore, after all surgical procedures some degree of nutritional deficiency exists, therefore all patients need lifelong vitamin and mineral substitution. The possibility of weight regain after time exist specially after pure restrictive procedures.

An important aspect, as in any chronic disease, is the training of the patient, in order to the future self-care of their disease. This part of treatment promotes the patient autonomy and reduces the cost of long-term treatment. Finally, prevention of obesity must be a public health priority; it has been found that specific

lifestyle and dietary factors are associated with marked weight gain, with a substantial aggregate effect and implications for strategies to prevent weight gain [70,71].

Effects of obesity treatment on patients health

Even modest weight loss of 5% to 10% of the patients starting weight can lead to significant health benefits. People with hypertension who lost a modest 10 pounds over 6 months reduce their systolic pressure by 2.8 mm Hg and their diastolic pressure by 2.5 mm Hg, these reductions were equivalent to reductions of blood pressure induced by some blood pressure medications. Major trials showed the benefits of lifestyle changes, including losing weight and exercising [72,73]. More recent evidence showed that lifestyle intervention was effective in promoting weight loss and improving cardiovascular disease risk factors [74,75].

Regarding to the effect of obesity treatment on inflammatory components, increased epicardial adipose tissue is associated with several features of metabolic syndrome, including significant correlations with the levels of adiponectin, arterial blood pressure, fasting insulin, and LDL cholesterol [40]. Weight loss can be associated with a reduction in epicardial adipose tissue thickness in individuals who are severely obese [76]. This would be a beneficial effect, since growing evidence shows that epicardial adipose tissue might be implicated in the pathogenesis of arrhythmias, coronary artery disease, diastolic dysfunction, myocardial hypertrophy, and valvular disease.

Conclusion

Increase knowledge relating to the diverse structures and functions of adipose tissue are available today. Contrary to the past, adipose tissue is considered a dynamic organ with extremely sophisticated functions. Obesity is associated with low chronic inflammation through the secretion of adipokines. Evidence exists for the role of inflammation on the development

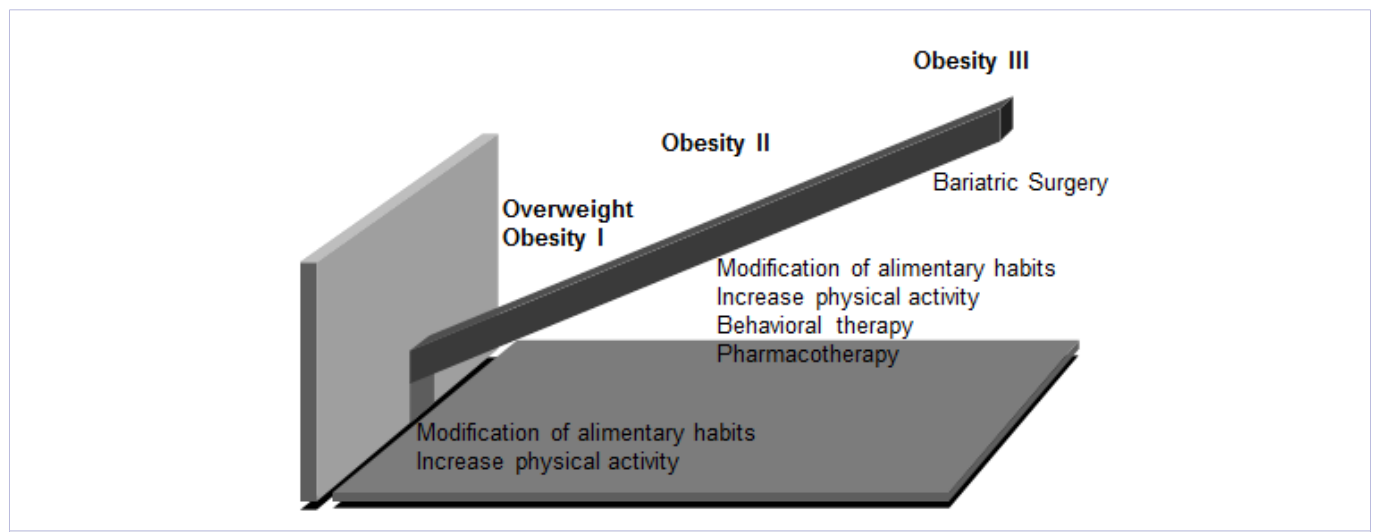


Figure 3: Treatment of obesity according to the degree of adiposity.

of metabolic diseases associated with obesity, such as dyslipidaemia, hypertension and type 2 diabetes. The treatment of obesity has evolved, from short-time and simple diet together with increase in physical activity, to long-term approaches based on changes in eating behavior and physical habits, with the aim of obtaining a slow and sustained decrease in fat mass, avoiding the regain of body weight of the classic treatment.

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