An Approach to Obesity as a Cardiometabolic Disease: Potential Implications for Clinical Practice

José Sabán-Ruíz*, Martin Fabregate-Fuente, Rosa Fabregate-Fuente, Ana Alonso-Pacho, Cristina de la Puerta González-Quevedo, Susana Tello Blasco, Asunción Guerri, Alcira Andrés and Delia Barrio

Endothelium and Cardiometabolic Medicine Unit, Internal Medicine Service, Ramón y Cajal Hospital, Madrid, Spain

Abstract: Obesity is a multifactorial disease that is currently developing a threatening tendency towards becoming the main cause of chronic disease in the world. Obesity can induce type 2 diabetes mellitus, dyslipidemia, cardiovascular disease and other chronic disorders with high social and health costs. Obesity was firstly described in 2000 as a cardiometabolic disease, even before Metabolic Syndrome, type 2 diabetes mellitus and coronary disease were considered as such. In this chapter we recover this approach to obesity, which has remained almost forgotten for the last decade. In obese subjects, adipokines and miokines interact to promote reticulum stress, insulin resistance, metabolic inflexibility and endothelial dysfunction. These pathological processes are amplified when hyperglycemia is present, leading to an increased risk for atherosclerosis. A number of potential implications for clinical practice are derived from the cardiometabolic state underlying obesity and its comorbidities. The first step in the therapeutic strategy against obesity should be the correct diagnosis of its causes and the promotion of lifestyle changes including physical exercise and a healthy diet. In the usual case of failing to achieve results, we can still resort to the pharmacological therapy. While awaiting the release of new drugs, topiramate, alone or combined with phentermine, has been proposed as a novel anti-obesity drug, showing relevant effects not only on weight loss but also on cardiometabolic alterations and biomarkers, even though new studies should clarify the mechanisms of these findings. Finally, our own experience with topiramate is described, focusing on its effects upon weight loss and inflammatory markers.

Keywords: Adipokine, adiposity, adiposopathy endoplasmic reticulum stress, anti-obesity drugs, atherosclerosis, cardiometabolic disease, coronary heart disease, diet, endothelial dysfunction, inflammation, insulin resistance, lifestyle changes, metabolic inflexibility, miokine, obesity, physical activity, topiramate, weight loss.

*Address correspondence to José Sabán-Ruíz: Endothelium and Cardiometabolic Medicine Unit, Internal Medicine Service, Ramón y Cajal Hospital, Madrid, Spain; E-mail: psaban@gmail.com
INTRODUCTION

Obesity constitutes a multifactorial pathology whose acquired influences exceed genetic factors, and nowadays threatens to become the major cause of chronic disease in the world [1], with high social and health costs [2]. The medical expenditure related to the treatment of obesity in the USA was $147 billion in 2008, which has doubled in the course of the last ten years [3]. WHO definition [4] for obesity is a body mass index (BMI, weight/(height)$^2$) greater than or equal to 30, while overweight is defined as a BMI between 25 and 30 kg/m$^2$. Within obesity, different grades have been defined according to BMI: Grade 1 (BMI from 30 to less than 35), Grade 2 (35 to less than 40) and Grade 3 (40 or greater) [4].

According to WHO data [4], every year at least 2.8 million of deaths are caused by overweight and obesity, being the fifth leading risk for global deaths. Moreover, overweight and obesity account for 44% of the diabetes burden, 23% of the coronary heart disease and between 7% and 41% of certain types of cancer. The most recent data on obesity prevalence in the US show that more than one out of three adults and almost 17% of children and adolescents were obese in 2009-2010. With regard to sex, differences have diminished in the last years, with men reaching almost identical prevalence than women. A higher prevalence of obesity has been observed among older women compared with younger women, but there were no age-related differences by age among men [5]. In 2007-2010, 20% of US adults had Grade 1 obesity, 9% Grade 2 obesity, and 6% Grade 3 obesity, whereas 33.3% of adults over 20 years were overweight (and not obese) [6]. In European countries, the prevalence of overweight in 2008 was 58% among males and 51% among females, whereas the obesity prevalence was 20% in males and 23% in females. Worldwide data show that 34% of males and 35% of females had overweight, whereas the prevalence of obesity was 10% in males, 14% in females and 12% in both genders [7]. The Figs. 1 and 2 show the prevalence of overweight and obesity worldwide.
Figure 1: Prevalence of overweight. Source: World Health Organization.

Figure 2: Prevalence of obesity. Source: World Health Organization.
In this scenario, a current strategy leading to improve six cardiovascular health metrics (weight, blood pressure, physical activity; diabetes, total cholesterol and smoking) could prevent 24-30\% of the CHD deaths expected in 2020 [8]. Four of these items keep a direct relationship with obesity as a cardiometabolic disease (weight, sedentary lifestyle, blood pressure and diabetes). Future prevention of cardiovascular disease necessarily involves acting now energetically without further delay. A better understanding of the pathophysiology involved in obese will help us in this hard and arduous task.

At present, different prevention strategies against the worrying prevalence of obesity have been implemented, especially in the childhood period. But hitherto, these approaches have not shown results, so we have to act improving the compliance with conventional therapy. There is a triple obesity treatment objective: a) at short term, lowering weight; b) at medium term, reducing cardiovascular risk factors associated; c) at long term, stopping the cardiovascular events and the obesity comorbidities, such as arthrosis or obstructive sleep apnoea syndrome. Regarding weight reduction, several studies focused on obesity therapies have confirmed that a moderate reduction of initial body weight could have positive results such as significant improvements in blood pressure and/or serum lipid concentrations, increased insulin sensitivity or improved glycaemia [9-12]. The “Look AHEAD Study” has shown that a body weight reduction of 7\% improves glycemic control and cardiovascular risk factors in subjects with type 2 diabetes [13].

Traditionally, therapies for weight loss have been based on lifestyle changes: mainly diet and exercise or a combination of both. This is still a useful tool for this purpose, but it faces a great disadvantage: compliance by obese or overweight subject is usually low [14]. Thus, when these measures fail, a fact that is very frequently verified in daily clinical practice, the pharmacological treatment of obesity constitutes an effective alternative which should not be postponed. In order to stop this epidemic, the American College of Physicians published in 2005 the first obesity guideline [15], which was based upon the results of two previous meta-analysis on recent therapies for weight loss [16, 17]. In this guideline, pharmacological treatment is presented as a useful alternative for patients who have failed with treatments based upon life-style changes such as diet and/or
exercise, becoming “resistant” to these therapies. Drug therapy is considered to be suitable for subjects with BMI higher or equal to 27 Kg/m², especially for those (a very frequent circumstance in this range of BMI) who present obesity-related morbidities such as Type 2 diabetes mellitus or impaired glucose tolerance, dyslipidemia and/or high blood pressure.

The National Institutes of Health (NIH) also recommends that adults with a BMI > 35 Kg/m² with serious associated comorbidities such as sleep apnoea, obesity-related cardiomyopathy or severe joint disease may also be candidates for bariatric surgery [9]. However, the experts’ opinion is to run out all treatment options before carrying out this surgery. The place of so the called “Metabolic Surgery” [18] for the treatment of type 2 diabetes exceeds the purpose of this chapter.

In the last years, several drugs have been used for the treatment of obesity: orlistat [19, 20], an inhibitor of gastric and pancreatic lipases; selective serotonin reuptake inhibitors (SSRIs) [21]; sibutramine, a serotonin-norepinephrine reuptake inhibitor which is structurally related to amphetamines [22, 23]; and rimonabant, a selective cannabinoid receptor antagonist (CB1) [24, 25]. However, all of these drugs produce severe side effects, especially sibutramine [26] and rimonabant [27, 28].

Human appetite is controlled by neurological networks in the Central Nervous System (CNS), more precisely by serotonergic, opioid, dopaminergic and cannabinoid systems, which are regulated in a very precise and complex way by intricate signalling pathways [29]. With regard to these neural pathways, despite the evident failure of current drugs (amphetamine derivatives, fenfluramine, sibutramine, rimonabant) [30], several additional gut hormone-based treatments for obesity are under investigation, with particular focus on leptin, ghrelin, peptide YY or pancreatic polypeptide [31], due to its participation together with the neural pathways involved in appetite.

While awaiting the release of new drugs, topiramate (TPM), an antiepileptic drug (AED), also approved as a treatment for migraine headaches, has been proposed as a novel anti-obesity drug. Furthermore, the combination of TPM plus
phentermine, an appetite suppressant, has been recently approved for chronic weight management in overweight or obese adults [32].

The main purpose of this chapter is to position obesity as a cardiometabolic disease with an underlying vascular damage. In this sense, it is necessary to differentiate syndromes related to obesity such as Metabolic Syndrome (MetS), Cardiometabolic Syndrome (CMS) and Cardiometabolic Risk (CMR), and the role of overweight in each other. It is also important to analyze the role of low-grade inflammation or metaflammation in fat tissue, as well as two new metabolic phenomena, Metabolic Inflexibility and Endoplasmic Reticulum Stress, and their interaction with the vascular triad (Endothelial Dysfunction, Oxidative Stress and Vascular Inflammation). In this context, new drugs should consider the mechanisms related to the physiopathology of obesity as a cardiometabolic disease, and not only in the weight loss in a narrow sense.

**PATHOGENESIS OF OBESITY**

The pathogenesis of obesity is influenced by interactions among several factors including inherited genetic features, a dysfunctional appetite regulation and the energy consumption. It is also influenced by behavioural, physical or psychological factors, cultural identity, education level, and socioeconomic status.

**Genetic Factors**

There is a genetic basis upon which environmental factors interact in the development of obesity [33]. Moreover, there are some forms of obesity transmitted by both recessive and dominant modes of inheritance. Amongst them, the Prader-Willi syndrome is the most common. Obesity, as many of the most prevalent diseases in human being, is thought to be polygenic, although there are some very rare types of monogenic obesity [34, 35].

Up to now, genetic variation in the FTO (Fat Mass and Obesity Associate) gene has the largest effect on BMI since Frayling and colleagues found a strong association between this gene and human obesity in 2007 [36]. Many others mutations associated with the nutrient intake and energy expenditure have been described, although they are beyond the purpose of this chapter.
In summary, as genetic disorders represent only a small fraction of the obese population, they cannot explain the magnitude of the obesity.

**Energy Expenditure and Nutrient Imbalance**

Obesity results from a chronic energy imbalance, as food intake over-matches the body's energy output. Increase in body weight and body fat with age cannot be associated with an increased caloric intake, but rather to a reduction in energy consumption, as energy requirements decline with age. Resting metabolism, defined as the total energy required by the body in a resting state, typically represents about 70% of total energy expenditure. It depends mainly on age, sex, body weight, drugs and genetics, and it is closely related to fat-free body mass as well as to body surface area because of its relationship to heat loss from the skin [37].

The other key player in obesity is appetite. It is regulated by specific molecular processes and neural pathways which are ultimately integrated at hypothalamus [38, 39], producing the expression of behavior and the associated subjective sensations [40]. Food intake is controlled by the complex integration of hormonal signals from the gut, pancreas, liver and fat.

Hunger and satiety are the psychological experiences regulating food intake behavior. Handling energy balance demands extensive coordination from the central nervous system (CNS), as the regions controlling energy homeostasis are accessible to numerous circulating hormones as well as the information from the sensory experience of eating and from peripheral receptors related to the ingestion and the utilization of food nutrients. These include signals from receptors in the gut and metabolic changes in the liver. Cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and amylin are the chemical signals related to satiety [38], whereas ghrelin, a peptide hormone, is involved in the short-term regulation of appetite. Blood levels of ghrelin secreted by the stomach and duodenum are raised during fasting and decreased after food intake. In addition, these appetite pathways also involve other signals from receptors within the CNS detecting circulating levels of nutrients, their metabolites and other substances, such as glucose [39].
Daily food intake and eating behavior are not only related to appetite and satiety, but also respond to processes of energy storage and the status of the body’s energy stores [41]. Lipostatic signals including leptin and insulin, or levels of cytokine signals, such as the IL-6 and TNF-α, may also be influenced by adipose tissue.

**PATHOPHYSIOLOGY OF OBESITY AND ITS RELATIONSHIP WITH CARDIOMETABOLIC SYNDROME**

**The Importance of Type of Fat and Body Distribution**

With regard to obesity in humans, a wide array of research has focused on white adipose tissue (WAT). Although brown adipose tissue (BAT) depots were thought to disappear shortly after the perinatal period, recently positron emission tomography (PET) imaging using the glucose analog F-deoxy-d-glucose (FDG) has shown the existence of functional BAT in adult humans. BAT is activated in response to cold stimulation, [42], as a energy-dissipating mechanism responsible for “adaptive thermogenesis” in adults during cold stress. In this context, adipocytes within WAT can be converted into multilocular adipocytes (known as “browning-WAT” or “beige” adipocytes) expressing UCP1, a mitochondrial protein capable of uncoupling the activity of the respiratory chain from ATP synthesis, which plays a key role in heat production. Whereas BAT has been extensively studied in rodent models [43], both in vivo and in vitro, there is still a lack of human models to assess critical factors involved in the induction of thermogenic response within adipocytes. Although even in subjects with relatively large depots, BAT accounts just for 20 kcal/day during moderate cold stress, recent discoveries on thermogenic BAT in human adults has opened a new field for innovative strategies in the fight against obesity and its associated diseases. Even so, further research is required in order to clarify the conversion and metabolism of white-to-brown converted adipocytes, which would enable the development of new therapeutic strategies targeting overweight/obesity [44].

The physiopathological effects of adipose tissue are related to the specific site where fat is stored [45-47], besides other factors such as genetic factors, gender, age, and physical exercise [48]. There is a clear functional distinction between visceral or intraperitoneal fat, extraperitoneal (peripancreatic and perirenal) and intrapelvic (gonadal/epididymal and urogenital) adipose tissues,
all of them presenting a higher metabolic activity than subcutaneous peripheral adipose tissue [49].

Classically, obesity is classified into two types according to fat mass distribution. The “android type” obesity, also called central or abdominal obesity, and the “ginoid” or peripheral obesity. Central obesity, characterized by the storage of the excess of fat in the upper part of the body, is typically related to male individuals, although this fat distribution is also present in women, especially during the menopausal and post-menopausal period, as well as in elderly subjects, both men and women [50]. Although it is always present in Caucasian subjects with BMI higher than 30 kg/m², also subjects of medium or even low BMI may develop central obesity. Moreover, abdominal obesity is strongly associated with associated with Metabolic Syndrome (MetS), Cardiometabolic Risk and Cardiovascular Disease [51].

As explained in the introduction, obesity has been defined according to the Body Mass Index (BMI), although it leads to a not very accurate assessment of obesity, since it does not take into account differences in body composition and body fat distribution [52, 53]. However, despite its limitations, diagnosis of obesity and overweight in epidemiological studies is assessed according to BMI [54]. With regard to Cardiometabolic disease, a concept that includes essentially obesity, MetS, diabetes mellitus and atherosclerosis, several alternatives to BMI have been proposed to assess fat mass, such as waist circumference, skinfold thickness measurements (with calipers), underwater weighing, bioelectrical impedance, dual-energy X-ray absorptiometry (DXA) and computerized tomography. In clinical practice, waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), are useful tools for assessing adiposity/obesity, providing a better approach to cardiometabolic risk than BMI [55, 56]

In addition to the abdominal fat, two locations of fat in obesity could take part in the active form of the disease that later we will name “adiposopathy”: pericardial fat and fatty liver (Figs. 3 and 4). Pericardial fat, also known as epicardial fat when assessed by echography [57], is strategically located next to coronary vessels. This ectopic fat depot has been recently correlated to BMI, visceral adipose tissue (VAT), metabolic risk factors, insulin resistance and coronary
artery disease [58-61]. In a study by Rosito et al., [62], VAT showed a stronger correlation to Cardiovascular Risk than pericardial fat, but these fat depots were associated with vascular calcification, which suggests that they may exert local toxic effects on the vasculature. According to this attractive cardiometabolic hypothesis, epicardial fat could contribute to the pathogenesis of coronary heart disease in a straightforward manner.

Figure 3: Pericardial fat.

Figure 4: Hepatic steatosis.

On the other hand, nonalcoholic fatty liver disease (NAFLD) is the most important cause of chronic liver disease and it is considered the hepatic manifestation of the obesity, especially in subjects with Metabolic Syndrome and/or type 2 diabetes mellitus. The prevalence of NAFLD in the general population reaches 15-20%, whereas nonalcoholic steatohepatitis (NASH), an advanced stage of the disease, affects 3% of the population. NAFLD includes a wide range of liver damage, from simple steatosis or accumulation of triglycerides in the liver to inflammation (NASH), fibrosis and cirrhosis [63-65]. Subjects with
steatosis and NASH present liver oxidative stress, which is a plausible mediator of cellular injury, inflammatory recruitment, and fibrogenesis. CYPs 2E1 and 4A, the microsomal oxidases involved in fatty acid oxidation, can reduce molecular oxygen to produce prooxidant species, increasing oxidative stress [66]. Both in obese and non-obese cohorts of non-alcoholic patients without hereditary hemochromatosis, high serum ferritin levels increase risk for steatosis [67]. The benefits of iron reduction are still unclear, and the final decision to treat such patients should be individualized [68].

**INSULIN RESISTANCE (IR) AND ITS RELATIONSHIP WITH METABOLIC SYNDROME (METS) AND TYPE-2 DIABETES MELLITUS (T2DM)**

Insulin resistance (IR) is a pathophysiological phenomenon that usually occurs along with weight gain. Moreover, weight increment and IR may be accompanied by a MetS. Around one third of obese subjects will develop T2DM, but if we take into account pre-diabetes, this figure raises over 50%, which is the percentage of patients with hyperglycemia. T2DM development requires not only IR but also a genetic susceptibility of β-cell in addition to others factor which take part in β cell dysfunction [69].

MetS history starts in 1921 when Eskyl Kylin, a Swiss physician, related for the first time the occurrence of high blood pressure to diabetes. This association was confirmed one year later by Gregorio Maranon, a Spanish physician, on the same medical publication (Zentralblatt für Innere Medizin). In 1923, Kylin [70] widened the concept, adding the diagnosis of hyperuricemia. Later in 1929 Samuel A. Levine [71] not only added new components to this concept, such as the presence of dyslipemia, but also underlined the importance of the cardiovascular risk associated to smoking, foreseeing 30 years in advance to what was much later demonstrated in the Framingham Study [72], thus laying the first stone of what today is denominated “Cardiometabolic Risk (CMR)”.

In 1936, Harold Percival Himsworth, used the term Insulin Insensibility in those diabetic patients who were non-responders to that hormone [73]. In 1947 J. Vague [74], a French doctor, underlined the difference in body fat
distribution between genders and later in 1956 related abdominal obesity to an increased risk of diabetes, atherosclerosis, gout and uric lithiasis [75]. The association between obesity, dyslipidemia and diabetes was named Plurimetabolic Syndrome by Avogadro and Crepaldi in 1967 [76], highlighting its relationship with coronary risk.

In 1979, De Fronzo et al., [77], described IR, quantified by the clamp technique, as an essential element in the T2DM physiopathology. As IR was observed not only in diabetics but also in non-diabetic patients, a deficit in insulin secretion, later showed of multifactorial origin, was suggested as necessary for T2DM development.

MetS was dubbed as X Syndrome by Reaven [78] in the 1980s including hyperglycemia, high blood pressure, low HDL-cholesterol, high triglycerides and IR; and later by Kaplan as Deathly Quarter [79], adding central obesity with impaired glucose tolerance, hypertriglyceridemia and high blood pressure. However, the term Metabolic Syndrome, previously used by Hanefeld and Leonhardt [80], was later imposed on. In 1997 DeFronzo and Ferranini deepend in the IR concept, coining the Insulin Resistance Syndrome term [81] (Fig. 5).

**Figure 5:** History evolution of the Metabolic Syndrome (MetS) concept.
Nowadays, MetS is considered to be between T2DM and cardiovascular disease, taking part in the development of both processes, but not simultaneously. Table 1 shows the ATP III-2005 criteria for MetS.

After reviewing the evolution of the Metabolic Syndrome concept and its relationship with IR, the following provides an in-depth revision of the physiological mechanisms involved in IR. The most important physiological action exerted by insulin is to allow the entrance of the plasma glucose into the cell. This is carried out through a biological phenomenon called activation of the trans-membrane transport for which two previous phases are necessary: the translocation of the glucose transporters (named GLUT) from the microsomes to the plasmatic membrane and their phosphorylation to convert them into “GLUT-P”, which is the active form. The entrance of glucose into the cell also depends on the so called “mass action effect”, which is independent of insulin, so that glycemic levels promote the uptake of glucose by a direct action upon GLUT. But this mechanism is impaired in both type 1 and type 2 diabetes. This peculiar phenomenon was named “resistance to glucose” by Del Prato and De Fronzo [82]. However, it is necessary to clarify that the insulin receptor does not only allows glucose enter to the cells through the GLUT transporter, but also facilitates its metabolism, by activating particular enzymes which are key factors in its metabolic pathway, including storage and oxidative routes.

The first question we should ask ourselves is: in a normal cell, what mechanisms regulate the activation cascade of the insulin receptor? This cascade is activated by an enzyme called Rad, which is a GTP (Guanosine-5’-triphosphate) hydrolase related to PC-1, a plasmatic membrane protein. Both molecules are involved in the inhibition of the physiological actions of insulin. Some authors attribute to PC-1 a role in insulin resistance, when this membrane protein is over-expressed, as it is the case in the obesity [83].

IR is evidenced by the failure of endogenous insulin to hinder hepatic gluconeogenesis and to induce glucose peripheral uptake. Such dysfunction is compensated by increasing insulin levels (hyperinsulinemia) [84]. Peripheral insulin resistance emanates from interaction the interaction between liver, adipose tissue and skeletal muscles, when altered insulin signaling stems from altered
insulin receptors and post-receptor defects. These alterations include an imbalance between the two insulin receptor isoforms, decreased insulin receptor affinity, improper insulin receptor kinase activity, decreased autophosphorylation and impaired glucose transporter translocation and activation [81].

Table 1: NCEP ATP III 2005: Metabolic Syndrome (MetS) criteria

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>≥ 102 cm</td>
</tr>
<tr>
<td>Men</td>
<td>≥ 102 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>&lt; 40 mg/dl</td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dl</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dl</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥ 130 mm Hg / ≥ 85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 100 mg/dl</td>
</tr>
</tbody>
</table>

MetS diagnosis if ≥ 3 risk factors are present

Hyperinsulinemia is classically defined as a basal level of insulin higher or equal to 16 mU/l, or more recently by a quite lower basal value (higher than or equal to 10.9 mU/l) [85], which constitutes a useful cut-off point for IR. Hyperinsulinemia is a constant in the MetS, but is not a required criterion for its diagnosis. It is possible to present a level of insulin 10-fold higher than the normal range with normal glucose plasma levels. However when both are elevated many other parameters such as triglycerides, HDL-cholesterol and blood pressure result in raised values. In particular, among obese normotensive patients hyperinsulinemia is more prevalent than insulin resistance (38% vs. 26%) [86], although the mechanisms causing hyperinsulinemia in absence of insulin resistance still remain unclear. Nevertheless, when hyperinsulinemia appears, insulin resistance becomes aggravated.

With regard to blood pressure, hyperinsulinemia is involved in four potential hypertensive mechanisms: the activation of the Sympathetic Nervous System (SNS), the hypertrophy of the smooth muscle cells, the renal sodium retention and the increase of intracellular levels of calcium [87]. Moreover, clinical trials as the
“San Antonio Heart Study” have confirmed that hyperinsulinemia is a key factor in the development of hypertension [88]. Both hypertensive and normotensive subjects showed a positive correlation between serum insulin concentrations and blood pressure.

Hyperinsulinemia also comes along with raised levels of PAI-1 (Plasminogen-Activator Inhibitor-1), a serine protease inhibitor. PAI-1 is the main inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), the activators of plasminogen and hence fibrinolysis, and it appears to be also associated with endothelial dysfunction, left ventricular hypertrophy and coronary disease [89].

According to data obtained from nondiabetic subjects in the Framingham Offspring Study, IR might not be the only precedent condition in MetS, but also other independent physiological processes may be involved [90]. Recently, IKKβ/NF-κB in the mediobasal hypothalamus, in particular in the hypothalamic POMC (proopiomelanocortin) neurons, has been proposed as a primary pathogenic link between obesity and hypertension [91]. In addition, subjects presenting insulin resistance are also at risk for developing other pathologies such as non-alcoholic fatty liver disease, polycystic ovary, and certain types of cancer, among others [92].

The genetic underpinning of the MetS and its individual risk factors is reflected in the substantial heritability observed in different ethnic groups for the individual syndrome components including the IR [93]. So, adiposity evaluated by BMI or WC has been found to be highly heritable, with estimates ranging from 0.52 to 0.80, IR and fasting insulin ranging from 0.24 to 0.61, fasting triglyceride and high-density lipoprotein cholesterol (HDL-C) ranging from 0.20 to 0.47 and 0.60 to 0.78, respectively (Table 2) [93]. The range of heritability estimates for systolic, diastolic, and pulse blood pressures are 0.30 to 0.37, 0.24 to 0.37, and 0.21 to 0.63, respectively and were similar in White and Eastern African cohort studies. Although studies assessing the heritability of MetS itself, rather than its individual risk factors, are less common, a range from 0.13 to 0.42 has been reported in several studies [94-96].
Genetics is especially important in the development of diabetes mellitus, but it is not the only cause. The multiple causes involved in $\beta$-cell dysfunction are represented in Fig. 6 according to Unger [97] and LeRoith [98].

Table 2: Heritability of MetS components and MetS itself [93]

<table>
<thead>
<tr>
<th>MetS Components</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiposity (BMI/WC)</td>
<td>0.52 - 0.80</td>
</tr>
<tr>
<td>IR &amp; Fasting glucose</td>
<td>0.24 - 0.61</td>
</tr>
<tr>
<td>Fasting TG</td>
<td>0.20 - 0.47</td>
</tr>
<tr>
<td>High HDL-C</td>
<td>0.60 - 0.78</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.30 - 0.37</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.24 - 0.37</td>
</tr>
<tr>
<td>Pulse</td>
<td>0.21 - 0.63</td>
</tr>
<tr>
<td>MetS</td>
<td>0.13 - 0.42</td>
</tr>
</tbody>
</table>

Figure 6: Multiple causes involved in $\beta$-cell dysfunction. IR together with beta-cell alteration from multifactorial origin and genetic susceptibility lead to the development of diabetes. Abbreviations: IAAP: islet amyloid polypeptide; IR: Insulin Resistance.
FREE FATTY ACIDS, VICTIMS OR EXECUTIONERS IN THE OBESE SUBJECT? SYSTEMIC LIPOTOXICITY, INCLUDING B-CELL DAMAGE

In the context of obesity, circulating free fatty acids or non-esterified fatty acids (NEFA or FFA) are among the first victims of insulin resistance (IR), as the normal antilipolytic action of insulin is lost in the early stages of the IR. On the other hand, increased FFAs levels are of paramount concern in the pathogenesis of obesity-related diseases, becoming a very dangerous executioner in the obese patient. These actions are influenced by many factors, such as: i) patient situation regarding ingestion of food; if the subject is fasting or at postprandial state; ii) how active are other body organs (muscle, liver) in metabolizing free fatty acids; iii) the degree to which adipose tissue stores free fatty acids in the form of triglycerides.

With regard to FFAs, one of the key points is that the impaired ability of adipose tissue to suitably store free fatty acids results in increased levels of circulating FFAs, which may significantly contribute to the metabolic disease. As subcutaneous adipose tissue is the largest fat depot (making up 80% of body fat), it produces most of the FFAs [99]. Nevertheless, an increase in visceral adipocyte hypertrophy and/or visceral adipose tissue often increases FFAs delivery to the liver through its portal drainage, which may promote hepatic “lipotoxicity”. This increased delivery of FFAs to the liver has been associated with the development of hepatic-mediated insulin resistance and dyslipidemia [100, 101]. This fact explains that although visceral adipose tissue is considered the main responsible for metabolic disease generation and/or aggravation, subcutaneous fat has pathogenic potential [102]. In addition, some patients present impaired ability to metabolize intramuscular fat [103], which may result in ectopic FFA storage in muscle and the accumulation of “toxic” intramyocellular lipids such as diacylglycerol, fatty acyl coenzyme A and ceramides [104]. This lipotoxicity promotes IR in the muscular tissue [105]. Moreover, FFAs may also damage pancreatic β-cell, and this pancreatic lipotoxicity may contribute to type-2 diabetes mellitus development in subjects genetically predisposed [106, 107]. The role of certain fatty acids in the beta-cell dysfunction through its interaction with GPR-40 receptors will be discussed later in this chapter.
Hypothalamic sensing of circulating lipids and modulation of hypothalamic endogenous fatty acid and lipid metabolism are proven mechanisms involved in body energy homeostasis [108, 109]. Enzymes such as AMP-activated protein kinase (AMPK) and fatty acid synthase (FAS) as well as intermediate metabolites as malonyl-CoA and long-chain fatty acids-CoA (LCFAs-CoA) play a key role in this neuronal network, pooling peripheral signals with neuropeptide-based mechanisms. Recent evidence have shown that impaired lipid metabolism and accumulation of specific lipid species in the hypothalamus leads to “hypothalamic lipotoxicity”, resulting in adverse effects on hypothalamic neurons and causing endoplasmic reticulum (ER) stress in the hypothalamus [110], which contributes to the development of MetS [111].

Finally, of particular interest is “cardiac lipotoxicity”. Excess lipid accumulation in the heart is associated with decreased cardiac function both in human and animal models [112]. The mechanisms are still unclear, but it may result from either toxic effects of intracellular lipids (acylcarnitines) or excessive fatty acid oxidation (FAO) [113, 114]. In subjects with MetS, both cardiac PPARγ overexpression and use of PPARγ agonists are associated with heart failure. A significant association between accumulation of long chain fatty acyl carnitines and poor cardiac function has been observed in subjects with coronary disease. These compounds may be associated with effects on sarcolemmal ion channels, resulting in cardiac arrhythmias [115], which are the main cause of death in heart failure patients. Future development of specific inhibitors of carnitine acyltransferase may be a promising therapeutic strategy to attenuate the incidence of severe arrhythmias associated with coronary heart disease.

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN. FROM ADIPOSITY TO ADIPOSPATHY

Adipose tissue is more than just the storage place for lipids, an energy reservoir. It is a highly active metabolic and endocrine organ secreting a range of peptides known as adipocytokines with both local and remote actions [116, 117]. These have been lately renamed as adipokines, since they are not only produced by the adipocytes. Some of these peptides can be more accurately termed adipose-derived hormones, among which leptin and adiponectin have a critical role in obesity-related processes.
Adipokines [118, 119], including IL-1-β, IL-6, IL-8, IL-10, TNF-α, TGF-β, acylation stimulating protein (ASP), visfatin, apelin and the acute-phase proteins (serum amyloid A, PAI-1), are involved in appetite, lipid metabolism, insulin sensitivity, vascular homeostasis (endothelium), blood pressure regulation, lipid and glucose metabolism and energy homeostasis [120, 121].

Figure 7: Adiposity vs. adiposopathy. Both are accompanied by overweight but the patient with adiposity is a “metabolically-healthy overweight subject” +Kg: Weight gain.

The term adiposity refers just to an excess of adipose tissue. However, when adiposity results in functional abnormalities, including endocrine and immune disorders, the term adiposopathy or “sick fat” [48] has been recently proposed to better describe this metabolic disease. Adiposopathy characterizes the pathogenic enlargement of fat cells and fat tissue leading to adverse clinical consequences including the most common metabolic diseases encountered in obese subjects in clinical practice such as type-2 diabetes mellitus (the most severe form of adiposopathy), prediabetes, high blood pressure, dyslipidemia and MetS [104, 122]. Moreover, some factors such as age or sedentary lifestyle may also convert adiposity into adiposopathy (Fig. 7). In summary, adiposity and adiposopathy are both accompanied by overweight, but the patient with just adiposity is a “metabolically-healthy overweight subject” [123, 124].

Adiponectin

Adiponectin, or “adipocyte complement-related protein” is a 30 Kd protein secreted by the adipocyte, being the most abundant inflammatory mediator expressed in white adipose tissue (WAT). In healthy subjects, adiponectin levels are around 5-10 µg/ml [125]. This hormone exerts both metabolic and vascular
actions. Metabolically, it is directly involved in hepatic and peripheral glucose metabolism. In the liver, adiponectin diminishes the hepatic production of glucose, while at a peripheral level, it improves insulin resistance. Decreased adiponectin plasma levels have been described in obese subjects and patients with T2DM. In addition, adiponectin regulates energy balance [126], reducing the triglyceride content of muscular and hepatic tissues as well circulating levels.

With regard to vasculature, adiponectin modulates cell adhesion to the endothelium. Both metabolic and vascular actions are always opposite to those exerted by two other adipokines: TNF-α and resistin (Fig. 8).

**Figure 8:** Adiponectin is released by adipose tissue, and promotes Metabolic and vascular actions on muscle tissue, liver and vasculature, such as increased FFAs oxidation and insulin sensitivity, as well as decreased triglycerides, glucose and vascular inflammation. FFAS: free-fatty acids. TG: triglycerides.

Adiponectin is responsible for the entire inhibition of VCAM-1 (Vascular Adhesion Molecule-1) and inhibits partially ICAM-1 (Intercellular Adhesion Molecule-1), both induced by resistin. In addition, it has also been observed that adiponectin inhibits signaling from NF-kappaB [127] through cAMP (Cyclic Adenosin Monophosphate). On the other hand, adiponectin also exerts a
beneficial action on nitric oxide (NO) released by the endothelial cells, which seems to be directly dependent on NOSe (Endothelial Nitric Oxide Synthetase) activation. Moreover, Iwashima et al. [128] reported a direct relationship between lower levels of adiponectin and hypertension, independently of other components of MetS. This is a remarkable fact in the context of obesity and the MetS, as similar effects had been described with regard to other adipokine, leptin.

Resistin

Resistin is a cysteine-rich adipokine produced by the monocyte in humans and primates, and by the adipocyte in rodents [129]. Resistin levels are increased in obese [130] and smoking patients[131], but in spite of its name, resistin has a controversial role in IR [132]. Recently this adipokine has been related to advanced atherosclerosis [133] and heart failure [134]. Previously, in vitro studies had associated resistin with an increase in the mRNA expression of adhesion molecules VCAM-1 and ICAM-1 as well as in MCP-1 (Monocyte Chemotactic Protein-1) and Endothelin-1 (ET-1), a peptide produced by the endothelial cells [135]. However, the relationship between resistin and CRP has shown mixed results [130, 131]. In any case, while resistin being related to CV risk could be expected, its involvement in atopic dermatitis and asthma atopic in childhood [119], as well as to primary asthma in obese adults, even predicting the response to glucocorticoids, may be considered as surprising [136, 137]. It should be noted that leptin has been also associated with asthma [138].

Moreover, in the last years, the adiponectin/resistin ratio has been defined as a useful indicator for the assessment of obesity-related health problems [139].

6.3. Leptin

Another important factor to take into account in the context of obesity and inflammation is leptin. This molecule, involved in energy homeostasis, is the product of the so called “ob-gene” [121]. Leptin also regulates appetite, and its absence or deficiency has been demonstrated to cause obesity in animal models [140]. Accordingly, hypothalamus and the adipocyte itself are the targets for leptin. Leptin receptor belongs to the superfamily of receptors for cytokines class I, while STAT (Signal Transducer and Activator of Transcription) proteins serve as
intracellular messengers, which become activated when their tyrosine residues are phosphorilated.

With regard to central nervous system, leptin regulates appetite in animals, acting in two different ways: both stimulating and inhibiting appetite [140]. Nevertheless, the role played in appetite regulation in humans is still unclear. Both in animals and humans leptin increases the sympathetic tone [141], which may be responsible for high blood pressure in MetS subjects. It has been suggested that these patients present resistance to the metabolic actions of leptin, regardless of its hypertensive effect [142]. Moreover, leptin has been proposed as a cardiovascular risk biomarker [143].

THE ROLE OF OBESITY IN CARDIOMETABOLIC SYNDROME AND CARDIOMETABOLIC RISK

Historical Perspective

In the last decade two new terms, “Cardiometabolic Syndrome” (CMS) and “Cardiometabolic Risk” (CMR), have emerged as an amplified evolution of Metabolic Syndrome (MetS) with different nuances. But even more interesting in our contexts, the term “cardiometabolic” appeared for the first time in a medical article related to obesity: Pescatello and Van-Heest in 2000 [144].

In 2001, Sowers, Epstein and Frölich, experts from the American Diabetes Association (ADA), coined the term CMS putting together the classic components of MetS, such as central obesity, hyperglycemia, hypertriglyceridemia, low-HDL-cholesterol, high blood pressure and IR, and IR-related new factors such as loss of the circadian rhythm of the blood pressure, hyperuricemia and microalbuminuria. Alongside these, they also included the “Pearson risk biomarkers”, which are indicators of systemic inflammation, namely C-Reactive protein (CRP) levels, endothelial dysfunction, oxidative stress and hypercoagulability (Fig. 9).

In 2005 Khan, Buse, Ferrannini and Stern, also ADA experts, used the term Cardiometabolic Risk (CMR) instead of MetS, but with a difference with respect to CMS: CMR complements the risk associated with MetS adding classic risk factors not related to IR, such as family history of cardiovascular disease, sedentary life-style, hypercholesterolemia and smoking (Fig. 10).
Figure 9: Relationship between Metabolic Syndrome (MetS), Cardiometabolic Syndrome (CMS) and Cardiometabolic Risk (CMR). Abbreviations: ED: endothelial dysfunction; LDL-c: LDL-cholesterol.

In fact, CMR and CMS are not different concepts, but complementary. While CMR defines a non-quantifiable clinical risk, unlike the classical cardiovascular risk scores, CMS is a pathophysiological concept, and thus it is a pivotal notion in this chapter. The differential key: if we include biomarkers of inflammation, oxidative stress, endothelial dysfunction and prothrombotic state, we should rather refer to CMS, otherwise CMR.

Figure 10: Cardiometabolic Syndrome. Abbreviations: LDL-C: LDL-cholesterol, ApoB: apolipoprotein B; HDL-c: HDL cholesterol; TG: triglycerides; IR: insulin resistance.
Obesity as a Low-Grade Inflammatory Disease: Metaflammation

The anatomical-functional base of obesity as a cardiometabolic disease is a chronic low-grade inflammation or “metaflammation” [145] that compromises the fat and the vascular stroma. So, it involves not only the adipocyte of WAT, but also the SVF (Stroma-Vascular Fraction), consisting of macrophages, endothelial cells, progenitor cells and leukocytes. As a result of inflammation, the obese patient presents increased levels of IL-6, TNF-α, resistin and leptin, along with reduced adiponectin [146]. In obese subjects WAT is infiltrated by macrophages, which at the same time constitute a great source of pro-inflammatory cytokines. The latter is consistent with the fact that weight loss is associated with a reduction in the rate of macrophage infiltration into WAT, and subsequently with a reduction in the levels of circulating inflammatory cytokines and interleukins [147, 148]. The molecules produced by immune cells and adipocytes, such as cytokines or reactive oxygen species (ROS), can activate important stress pathways and disrupt critical metabolic processes involved in obesity as the insulin signalling cascade and regulation of energy homeostasis [149]. Examples include their participation in lipid metabolism inhibiting lipoprotein lipase (LPL), and subsequently increasing the production of triglycerides in the liver, leading to hypertriglyceridemia, typical in the MetS.

Besides the inflammation-involved molecules already described, which are secreted by adipose tissue, there are many other key cells, such as pre-adipocytes, endothelial cells, fibroblasts, and immune cells [150], which are related to the health of the tissue involved in the pathogenesis of obesity.

WAT monocyte-macrophage system, besides releasing resistin, also produces two other factors involved in both inflammation and IR: CXC ligand 5 [151] and macrophage inflammatory protein (MIP)-1α [152]. In addition, granulocyte-macrophage colony-stimulating factor (GM-CSF), a proinflammatory cytokine that induces myeloid-lineage differentiation of hematopoietic stem cells, may also take part in obesity-related inflammation, involving central (hypothalamic neurons related to food intake) and peripheral (WAT increase) mechanisms [152, 153].

With regard to anti-obesity drugs, these may act on reducing inflammatory markers in a direct, indirect or mixed way. Those drugs achieving a double goal, weight loss and modulation or improvement of their underlying metabolic and
immunological states, would be the best choice as anti-obesity drugs. Thus, reducing or at least modulating the inflammatory state associated with the excess of body fat through drugs whose molecular targets are implicated in the synthesis and release of pro-inflammatory mediators generated at the adipocyte, would result in effective therapies not only to treat obesity, but also, what is more important, its complications.

Many authors are drawing attention to the fact that weight loss is not only a matter of diminishing BMI below values of 30 or 25 kg/m². Obesity, when is linked to inflammation places obese subjects at moderate to severe cardiovascular risk [154].

**Adipose Tissue Inflammation in the Origin of Insulin Resistance**

According to recent data, plasma levels of inflammatory mediators, such as TNF-α and IL-6, are increased in obesity and type 2 diabetes, raising questions about the role played by these cytokines in the mechanisms underlying inflammation in insulin resistant states [155].

TNF-α, also called “caquectine”, is secreted by adipocytes, macrophages and lymphocytes. This cytokine induces resistance to insulin when it is overproduced at skeletal muscle and/or adipocytes. The most likely explanation is that TNF-α interferes with the insulin signalling cascade. Thus, TNF-α would be over-expressed in the adipose tissue of subjects suffering from MetS, leading to a state of IR. According to Hube et al., [156], this would constitute a “defensive mechanism” to avoid further fat accumulation in the obese subject. Such hypothesis was outlined for the first time by Eckel in 1992, suggesting that insulin resistance protects from gaining more weight [157].

In accordance with these theories linking TNF-α and IR, TNF-α would act by inhibiting glucose transport and facilitating lipolysis, and thus producing free fatty acids, which is just the opposite to insulin action. The inhibitory role played by TNF-α on the signalling cascade of insulin is not based on its lipolitic activity, but rather on the inhibition of the phosphorilation cascade of insulin by activating protein kinase C (PKC) enzymes [158].
Meanwhile IL-6, produced in WAT by adipocytes, macrophages and stroma vascular fraction (SVF) cells [155, 159, 160], could be directly involved in the onset and/or development of metabolic states of IR and its associated health complications [161, 162]. This theory arises from the fact that IL-6 receptor belongs to the “cytokine class I receptor family” involving JAK/STATs (Janus kinases/signal transducers and activators of transcription) signal transduction pathway. Interplay between IL-6 and insulin signalling pathways results in decreased insulin action, and thus leading to a insulin resistant state [163, 164]. With regard to vascular damage, IL-6 induces CRP production in the liver by activating JAK/STATs mediators which enable the CRP gene expression [165].

Cross-Talk Between Inflamed Adipose Tissue and other Tissues

According to some authors [166], as visceral fat grows larger, the influence of monocytes in the interstitial area between adipocytes also becomes greater, since they establish a sort of “dialogue”. This theory has changed the way we used to conceive these biological phenomena. Accordingly, adipose tissue is not only composed of adipocytes, but also of Stromal-Vascular Fraction (SVF), including endothelial cells, stem-cells and leucocytes. Regarding the adipokines produced by adipose tissue, only adiponectin and leptin are produced by adipocytes, while it is not clear if resistin is synthesized and secreted by other types of cells also present in adipose tissue. The remaining hormones secreted by visceral WAT are released by the macrophage. These findings contribute to confirm the idea that we are speaking of an inflammatory state when dealing with obesity. Most of visceral WAT macrophages derive from bone marrow, while just a small proportion come from mitotic division.

MCP-1 (Monocyte Chemoattractant Protein) is one of the molecules involved in the recruitment of macrophages from the bone marrow into the adipose tissue. It is synthesized by the adipocyte in collaboration with the endothelial cells from the SVF. The endothelial MCP-1 is stimulated by leptin, so that adipocyte has a double role in this process. On the other hand, MCP-1 activates the circulating monocyte, increasing the expression of CD11-b. Once the monocyte is “called”, it leaves the vessel and enters into the adipose tissue. In order to remain within the WAT, the monocyte requires the presence of the macrophage inhibitory factor (MIF) and the macrophage colony-stimulating factor (M-CSF).
A dysfunctional or impaired adipose tissue does not cause metabolic disease on its own. Actually, what takes place is a sort of “dialogue” or “cross-talk” with other tissues and organs, what determines whether endocrine and immune responses from adipose tissue end up causing the metabolic disease [104]. The pathogenic responses during positive caloric balance are modulated by several organs [104]. One of the best described pathogenic responses of dysfunctional adipose tissue, which is an example of this dialogue, is the concept previously described as adiposopathy. In postprandial state, increased insulin secretion stimulates FFAs storage in adipose tissue and other body tissues, resulting in reduced circulating FFAs. In the hours following initial insulin release, FFAs levels gradually tend to increase again [167]. During positive caloric balance, fat gain can result in adipocyte hypertrophy and adipose tissue dysfunction, leading to impaired storage of FFAs within adipocytes and IR. Lack of balance between lipolysis and lipogenesis in adipose tissue increases both fasting and postprandial circulating FFAs in IR [168]. In such a situation, adverse metabolic consequences of increased FFAs, such as hepatic IR and dyslipidemia [103], depend on whether or not the liver is able to manage the pathogenic responses of adipose tissue. In this scenario, a negative caloric balance would be expected to improve adipose tissue function and FFA storage in adipose tissue, as well as reducing circulating FFAs and lipid delivery to skeletal muscle, and thus reducing lipid storage in skeletal muscle, which may improve insulin sensitivity [169]. Likewise, type 2 diabetes mellitus is often developed when obesity comes along with pathogenic endocrine and immune responses from the adipose tissue, including an increased release of FFAs. In this situation, a genetic limitation in the ability of β-pancreatic cells to release insulin would result in an even further impairment in insulin secretion [170]. Moreover, adipose tissue is also known to have important interactions with the immune system, heart, brain, endothelium, kidneys, endocrine glands or gastrointestinal tract, what potentially may lead to a number of metabolic alterations [104].

Recently, the importance of targeting adiposity dysfunctionalities when approaching to obesity treatments has been pointed out, since this therapeutic goal does not only lead to loss of excessive weight, but also improves patient general health. If the patient has an adiposopathy-induced metabolic disease (e.g., Type 2
diabetes mellitus, dyslipidemia, and/or high blood pressure), then weight loss interventions may reduce adipocyte hypertrophy and visceral adiposity, and thus improve adipose tissue pathogenic endocrine and immune responses, and subsequently metabolic disease [171]. This paradigm is a key issue in the treatment of obesity.

**Metabolic Inflexibility and Endoplasmic Reticulum Stress Underlying Obesity**

In addition to IR, two concepts have been recently coined to “complete the picture” of a more accurate and comprehensive explanation of the physiological phenomena converging in obesity and its associated morbidities: the so called “Metabolic Inflexibility” (MI) and the Endoplasmic Reticulum (ER) Stress.

MI characterizes lean healthy subjects. It was first introduced by Kelly, from the University of Pittsburg, in 2000, who redefined the term four years later [172]. The main features of MI lie upon the idea that a healthy organism counts with a great adaptability to the fat from diet, so it is able to suitably metabolize this fat, while maintaining body weight. This process is mediated and/or conditioned by genetic and hormonal factors. On the contrary, metabolically inflexible subjects present decreased adaptability to fat ingestion, and when this occurs, a fat accumulation is promoted, and thus weight gain as food intake increases. Besides, neither the plasma levels of FFAs nor insulin oscillate depending on the postprandial state (absorptive/postabsorptive), both rather remain unchanged. In addition, consumption of local glucose at muscular tissue is increased and consumption of postprandial glucose is decreased. In this MI state, FFAs are stored in muscle and liver as triglycerides. Thus, although they do not directly interfere with carbohydrate metabolism, they can lead to IR by interfering with the insulin signaling cascade [173]. The Metabolic Flexibility is considered the ability to switch from fat to carbohydrate oxidation, what appears to be usually impaired in insulin-resistant subjects; however, this Metabolic Inflexibility is mostly the consequence of impaired cellular glucose uptake [174]. MI has been recently observed by Berk et al., in postmenopausal Afro-American women [173], justifying the proneness of this population to suffer from MetS.
MI is closely related to IR, and both processes are intimately linked to a third one, which might be regarded as the metabolic cornerstone of Cardiometabolic Syndrome: Endoplasmic Reticulum Stress is the difficulty to discharge “old and useless” proteins that arises in the ER, probably as a consequence of MI and adiposopathy. This is likely to be due to the accumulation of dysfunctional fat, even though it really is a “protein catabolic dysfunction” [175]. ER is a critical cellular organelle, where protein, lipid, and glucose metabolism is integrated, and where lipoprotein secretion and calcium homeostasis takes place. Activation of chronic inflammation and impairment of ER and mitochondria function that may follow to adiposopathy can feed-forward and contribute to further deterioration of the already dysfunctional or unhealthy lipid profile, by reducing fatty acid oxidation, promoting lipolysis, and stimulating the lipogenesis process de novo.

Inflammatory mediators, as explained above, are increasingly secreted as fat accumulation grows, and can promote lipogenesis and impair mitochondrial respiratory chain function. On the other hand, altered lipid profile can also promote inflammation. Thus, they cross-interact and, in a synergic manner, enhance each other.

Finally, ER stress (Fig. 11) activates inflammatory cascades such as JNK (c-Jun N-terminal kinase) pathways, and increases the generation of ROS, leading to mitochondrial calcium overload, and activating lipogenesis. Mitochondrial dysfunction, oxidative stress, a low-grade systemic inflammation (metaflammation) and lipogenesis further exacerbate ER stress by impairing protein folding, protein overloading (acute phase proteins of inflammation) and lipid overloading (lipogenesis) [175].

Cytokines as TNF-α and IL-6, as well as fatty acids activate two main inflammatory pathways that lead to the disruption of insulin action: JNK/AP-1 (c-JUN NH2-terminal kinase-activator protein-1) and IKK-NF-κB (inhibitor κB kinase-nuclear factor κB). Both pathways are related to molecules involved in unfolded protein response (UPR) signaling. Moreover, ER is a major source of ROS, and oxidative stress emanating from the ER can also activate both JNK/AP-1 and IKK-NF-κB pathways, and thus potentially lead to IR [176]. ER stress is
previous to IR, initiating the development of IR and inflammation of adipose tissue in obesity and T2DM [177].

Figure 11: Metabolic Inflexibility: interactions among insulin resistance, metabolic promoters, inflammatory mediators and Endoplasmic Reticulum (ER) stress. Abbreviations: PKR-like endoplasmic reticulum localized kinase; JNK: c-jun N-terminal kinase; IKK: Inhibitor of IκB kinase. IRS-1/2: Insulin receptor substrates.

Hence, impaired lipid metabolism, systemic low grade inflammation, IR, MI and ER Stress that are present in obesity can trigger and develop a Cardiometabolic Disease, which encloses not only the dysfunctions that compose the MetS, but also cardiovascular disturbances with their own pathogenic mechanisms.

**Endoplasmic Reticulum Stress in β-cell Dysfunction of T2DM and its relationship with GPR40 and Transcription Factors FOX01 and PDX-1**

As previously discussed, proper folding, maturation, storage and transport of proteins take place in the endoplasmic reticulum (ER). Accumulation of unfolded proteins as well as extreme energy and nutrient fluctuations (glucolipotoxicity,
hypoxia) may cause disturbances in the ER lumen and result in beta-cell stress. This activates the unfolded protein response (UPR), a complex signaling network, which tries to restore natural ER function through reduced translation and degradation of misfolded proteins, and increased transcription of ER chaperones in order to augment protein folding capacity. If UPR fails to recover normal ER function, it launches cellular apoptosis [178].

On the other hand, β-cell may become defective during IR only if there is a special susceptibility to develop diabetes mellitus, which occurs in about one third of obese patients. The earliest reaction to peripheral IR is to increase insulin production and release resulting in hyperinsulinemia, which promotes an increase in beta-cell mass as a result of increased beta-cell replication. However, animal and human models have shown that, after the onset of diabetes, there is a gradual deterioration in beta-cell function and mass.

In addition to ER stress, the Forkhead Transcription Factor (FOX01), oxidative stress and GPR40 receptor are also involved in β-cell dysfunction.

FOX Family (named Forkhead by a couple of ectopic structures in drosophila) is a set of proteins also called "winged helix" for his appearance in the crystallographic study. While they are genes in invertebrates, in mammals they are a family of transcription factors. Unlike other transcription factors, it does not contain homeodomains or zinc-fingers, but a distinct type of DNA-binding region including around 100 amino acids. The FOXO transcription factors in mammals are four: 1, 3, 4 and 6. FOX01 is involved in fundamental cellular processes such as apoptosis, responses to oxidative stress, cellular proliferation, cellular differentiation, and regulation of energy metabolism. On the other hand, oxidative stress and activation of the c-Jun N-terminal kinase (JNK) pathway induce the nucleocytoplasmic translocation of the pancreatic transcription factor PDX-1, which leads to pancreatic beta-cell dysfunction. The forkhead transcription factor FOXO1/FKHR plays a role as a mediator between the JNK pathway and PDX-1. Under oxidative stress conditions, FOXO1 changes its intracellular localization from the cytoplasm to the nucleus in the pancreatic beta-cell line HIT-T15. The overexpression of JNK also induces the nuclear localization of FOXO1, but in contrast, the suppression of JNK reduces the oxidative stress-induced nuclear
localization of FOXO1, suggesting the involvement of the JNK pathway in FOXO1 translocation [179].

With regard to oxidative stress, high glucose concentrations promote oxidative stress through an increase in the production of ROS in a variety of cell types, including beta cells. When intracellular glucose concentrations exceed the glycolytic capacity of the β-cell, excess glucose is shunted to enolization pathways, resulting in superoxide (O$_2^-$) production. In addition, beta cells express low levels of antioxidant enzymes, and therefore they are highly sensitive to oxidative stress [180].

Fatty acids may take part in β-cell dysfunction in two ways: a) a long term exposure to elevated levels of short and medium-chain FFAs impairs β-cell survival and insulin secretion, an alteration called “lipotoxicity”. Intracellular FFA metabolism underlies the inhibitory effects of FFAs on beta-cell function. b) a short-term variety of physiological responses induced by the long-chain FFAs by means of the activation of GPR40 receptor. GPR40 (or free fatty acid 1 receptor [FFA1R]) is highly expressed in pancreatic β-cells. Deletion of GPR40 in transgenic mice results in impaired, but not suppressed, insulin release responses to intravenous glucose and lipids. This is further supported by the observation that loss-of-function mutations of the GPR40 gene in humans are associated with altered insulin secretion. Interestingly, GPR40 mediates FA-stimulated insulin secretion from the β-cell not only directly but also indirectly via regulation of incretin secretion (GLP1 and GIP). Nowadays, GPR40 agonists are under development as a therapy to treat T2DM [181].

The importance of cell-membrane receptors coupled to the G protein (GPCRs) is not limited to GPR40. Other GPCRs, expressed in beta cells and/or intestinal L cells, include the G protein-coupled receptors 119 (GPR119) and 120 (GPR120). Both receptors increase circulating insulin levels through a direct insulinotropic action on β-cells, and also mediating fatty acid stimulation of incretin secretion. Moreover, GPR19 could also act as a fat sensor [182].

**Involvement of Muscle in Metabolic Dysregulation of Obese Patients**

In a cardiometabolic context, muscular tissue may be considered as a large organ. Like most organs, except for endothelium and nerve tissue, striate muscle needs
insulin to allow glucose getting into the cell. Until recently, skeletal muscle was strongly related to IR in T2DM [183], but not in obesity. Recent evidence has shown that a group of substances, named myokines or skeletal muscle-derived factors directly released by the muscle cells, play a major role in the IR related to overweight. Myokines can be divided into three groups according to their role in IR. Irisin helps to defend the muscle cell against the IR [184]. Musclin and IL-6 increase IR [185]. IL-6, with a dual origin (adipose and muscular tissue), plays a pivotal role in the pathophysiology of IR in the obese patient. Finally IL-15 and myostatin appear to be neutral. IL-15 is involved in immune response, but it has no proven action on metabolism. Meanwhile, myostatin, also known as "growth differentiating factor-8" or GDF-8, inhibits muscle growth in order to keep it within a certain limit [186], which might indirectly influence irisin levels.

**Irisin**

Physical exercise has been extensively related to a number of cardiovascular benefits independently of weight loss, including preservation of skeletal muscle, which plays an important role in fat metabolism. Irisin, a hormone secreted by the muscle has been considered an “exercise mimetic” [184], acting as a mediator of those benefits. In presence of obesity, irisin release is increased [187], attempting to counteract the associated IR. Irisin secretion is firstly expressed in muscle as the type I membrane protein precursor FNDC5, which is proteolytically cleaved and secreted into the circulation [188]. Irisin and FNDC5 secretion are increased in response to overexpression of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), as takes place after aerobic exercise-training [189]. After irisin exposition there is a brown-fat-like development in specific depots of white adipose tissue (WAT), which results in increased energy expenditure, leading to a modest but significant weight loss, and improved glucose tolerance [190]. So, lower circulating irisin levels have been associated with T2DM. In particular, obese subjects with T2DM present lower irisin levels than non-diabetics, which may contribute to increase IR in this subgroup [191]. One plausible explanation to this fact could be the lower abundance of PGC-1α in skeletal muscle, as patients with early-onset type 2 diabetes display abnormalities in the exercise-dependent pathway that regulates the expression of PGC-1α [192]. In the future, therapies targeting irisin could have a place as adjunct to training
and weight loss therapies in obese patients. In addition, this myokine could exert positive actions in T2DM prevention.

**Musclin**

Musclin, released by type IIb muscle fibers, is markedly regulated by nutritional status and insulin levels [185, 193]. When circulating levels of insulin are increased, an obesity feature, the muscle secretes musclin as a regulatory mechanism, inducing a very special “protective” IR by activating Akt/protein kinase B [194]. This defensive mechanism against overaction of insulin is mediated by the FOXO1 (forkhead box O1) [195], a transcription factor usually associated with beneficial actions (i.e. antioxidant, anti-atherosclerosis and antiaging) [196]. The role of insulin in musclin secretion suggests a self-regulated phenomenon, so that musclin secretion would be also slowed by the IR itself. In the presence of malnutrition, musclin levels are reduced to facilitate the entrance of insulin into the cell.

The role of FOXO1 as a mediator of insulin in musclin secretion is not its only action with regard to the muscle tissue, as it is also involved in sterol regulatory element binding protein 1c (SREBP1c) and cathepsin-L expression. SREBP1c is a master regulator of lipogenic (triglycerides accumulation) liver gene expression in adipose tissue and skeletal muscle [197]. FOXO1 is inversely correlated to SREBP1c in muscle tissue. On the other hand, expression of cathepsin-L, a lysosomal cysteine protease associated to intracellular protein breakdown, is up-regulated in the skeletal muscle during starvation [198, 199], suggesting a role for the FOXO1/cathepsin L pathway in fasting-induced muscle atrophy [200].

Accordingly, an interesting question arises, why does FOXO1, usually working as a protector, increase the production of cathepsins and decrease the irisin levels? An attractive hypothesis could be a reduction in reticulum stress, being the atrophy action a side effect.

**The Emerging Role of Endothelium in Adiposopathy**

Once IR and Endothelial Dysfunction (ED) stata are settled, their pathological courses follow parallel ways, running towards type 2 diabetes mellitus and
atherosclerosis respectively. Nevertheless, a remarkable author in the field of inflammation and obesity, John Yudkin (Washington Hospital, London) proposed an attractive theory in 1997, considering ED as a previous step to IR and atherosclerosis in a joint way. According to this theory, while ED plays a key role in the atherogenesis, in the case of capillaries and small veins, ED is actively engaged in the occurrence and onset of IR.

Nowadays there is strong evidence to support this theory. The blockage of the synthesis of Nitric Oxide (NO) by L-NMMA (an analogue of L-Arginine), has demonstrated not only to weaken the endothelium-dependent vasodilation (EDV), but also the glucose capture mediated by insulin [201]. These investigations are consistent with those obtained several years before in knock-out mice NOSe and NOSn (neuronal nitric oxide synthetase). Rodents lacking these enzymes developed IR in early states [202].

On the other hand, the production of Radical Oxygen Species (ROS) by the endothelium would attract macrophages. These release cytokines, which promotes IR, just as we have already seen regarding IL-6. The production of this pro-inflammatory mediators in diabetic subjects would result amplified as a consequence of an auto-oxidation process of the glucose. It would be induced by its free entrance through the GLUT-1 transporters, what does not require insulin. Thus, the production of ROS by the endothelium would add to that produced by the adipocyte itself [203]. On the other hand, as a consequence of the release of cytokines by the macrophages, a stimulation of the synthesis of NOSi can be induced and that overproduction could interfere with the action of insulin in the muscle cell.

**THE “VASCULO-METABOLIC” THEORY (VMT)**

This fascinating theory consists of two main pathogenic arms. On one hand, the Vascular Triad includes endothelial dysfunction, oxidative stress and vascular inflammation. On the other, the Metabolic Triad is composed by IR, MI and ER stress. The anatomical substrate remains the same as in the conventional paradigm, namely low-grade fat inflammation and activation of adipose tissue stroma, but according to this new theory, it is interpreted in a bidirectional way, what constitutes its added value (Fig. 12)
The VMT understands vascular damage as occurring in a parallel way to metabolic damage, and not as a mere consequence of the first one. Moreover, this theory incorporates metabolic elements of paramount importance when compared with the conventional theory, which relies basically upon IR alone. The presence of MetS, which is much more prevalent in obese subjects, amplifies the pathogenic phenomena in both directions. In the case of T2DM, only present if there is a genetic susceptibility of β cells, it will enhance this even more due to the fact that this dysfunction incorporates a new key element, to configure an integrated “puzzle” of “health damage”. This crucial element are the so called “Advanced Glycation End Products” (AGEs), whose interaction with AGEs from the endothelium increase oxidative stress, what explains the higher vulnerability of endothelium to hemodynamic phenomena and to the vascular damage exerted by oxidized LDL in diabetic patients.

**Figure 12:** The VMT theory consists of two pathogenic arms: the Vascular Triad (endothelial dysfunction, oxidative stress, vascular inflammation) and the Metabolic Triad (metabolic inflexibility, reticule stress and insulin resistance). The “added value” of this newly coined theory is that although the anatomical substrate is the same as in the conventional one, hereby it is understood in a bidirectional way. Abbreviations: ROS: reactive oxygen species; AGEs: advanced glycation end products; CRP: C-Reactive Protein; RE: reticulum endoplasmic.

In both triads C-reactive protein (CRP) could take part in an active way. CRP, an acute-phase reactant predominantly synthesized in the liver, is an inflammatory marker that is also a classical and well-known biomarker of vascular disease. However, due to its anatomical proximity with fatty tissue, it could be reasonable to think that CRP is also involved in fat inflammation, amplifying alterations resulting from this inflammation such as the release of more adipokines. Baseline CRP levels are strongly associated with subsequent cardiovascular events independently of LDL-cholesterol and other known cardiovascular risk markers [204, 205]. Adipose tissue is a rich source of immune-related mediators, such as...
IL-6 and TNF-α, that are involved in the inflammatory response. CRP is, in turn, under the control of these proinflammatory cytokines [120].

As a result, obesity is a major determinant of CRP in adults [206]. In 2000 Festa et al. [207] studied the relationship between of CRP and the components of IR syndrome in the non-diabetic population of the Insulin Resistance Atherosclerosis Study (IRAS). CRP levels and a number of metabolic disorders were positively correlated. BMI, systolic blood pressure, and insulin sensitivity (IS) were also independently associated with CRP levels. On the other hand, population-based cohort studies of American children and adolescents have shown higher CRP concentrations in overweight subjects than in normal-weight subjects [208]. Several studies in obese children have also shown higher serum CRP levels in subjects with higher BMI and waist circumference [209, 210].

The response of cytokines to weight loss has shown mixed results, with most of studies showing at least trends towards improvement in adiponectin, leptin, TNF-α, IL-6, and CRP [211-215]. This reduction would certainly contribute to disable the two triads of vascular-metabolic theory. However, individual control of each risk factor seems also key to stop the process, especially the LDL-cholesterol, which plays a pivotal role in the vascular component of the endothelial dysfunction, on account of the high vulnerability of endothelium to even moderate levels of LDL-cholesterol, especially in obese diabetic patients [216].

Finally, within the VMT, the relevant role of circulating cathepsins in obesity-related cardiometabolic processes should be noted. As previously described, cathepsin is involved in skeletal muscle, but it also acts on the vascular wall. So, as extracellular proteases, contribute to extracellular matrix remodeling and interstitial matrix protein degradation, as well as to cell signaling and cell apoptosis in heart disease. Accordingly, both serum cathepsins S and L and cystatin C, an endogenous cathepsin inhibitor, have been proposed as promising biomarkers of coronary artery disease and aneurysm [217]. Even though the therapeutic use of cystatin C has not been assessed yet, other cathepsin inhibitors as proline-derived compounds have been already synthesized and successfully evaluated [218].
The Endothelial Dysfunction (ED) as a Cause of Insulin Resistance (IR)

Rodent models of endothelial dysfunction provide important insights into the relationship between ED and IR [219]. The pivotal role of endothelium in regulating metabolic actions of insulin is evident by the presence of IR and hypertension in eNOS knockout mice. These animals also present microvascular changes including rarefaction of capillary density and reduced insulin-mediated glucose disposal, increased triglyceride and FFA levels, decreased energy expenditure, defective beta-oxidation, and impaired mitochondrial function [220]. These findings suggest that endothelium-derived NO has additional and direct metabolic effects on mitochondrial function. Mice with partial eNOS deficiency (eNOS +/-) are insulin sensitive and normotensive, but when they are under a high-fat diet, also develop IR and hypertension [221]. Thus, partial defects in endothelial function characterized by reduced NO bioavailability are enough to cause cardio-metabolic abnormalities (insulin resistance and dyslipidemia) under pathogenic conditions (e.g., caloric excess, physical inactivity, inflammation), as observed in humans. Several studies suggest that ED is an independent predictor for the incidence of diabetes [222-225]. In the Women's Health Initiative Observational Study higher levels of circulating E-selectin and intercellular adhesion molecule-1 (ICAM-1) were strongly related to increased risk of diabetes [224]. Similarly, in the Framingham Offspring Study, plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor (vWF), both circulating plasma markers of endothelial dysfunction, were independently associated with increased risk of diabetes [223].

The Insulin Resistance as a Cause of Endothelial Dysfunction (ED)

At the cellular level, the impairment in pathway-selective PI3K-dependent signaling pathways is a key feature of IR. Meanwhile other insulin signaling branches including Ras/MAPK-dependent pathways remain relatively unaffected. This fact has relevant pathophysiological implications because metabolic IR is typically accompanied by compensatory hyperinsulinemia to maintain normal values of plasma glucose. Hyperinsulinemia overdrives unaffected MAPK-dependent pathways, promoting an imbalance between PI3K- and MAPK-dependent functions of insulin. Lipotoxicity, glucotoxicity, and inflammation that contribute to IR states differentially affect PI3K and MAPK pathways through multiple independent and
interdependent mechanisms in the endothelium. The imbalance between PI3K/Akt/eNOS/NO and MAPK/ET-1 vascular actions of insulin caused by hyperglycemia, dyslipidemia, and inflammatory cytokines may contribute to both altered metabolic and vascular actions of insulin [219]. So, compensatory hyperinsulinemia that typically accompanies pathway-selective insulin resistance (in PI3K pathways) activates unopposed MAPK pathways leading to ED and to increased pro-hypertensive pro-atherogenic actions of insulin [226].

Subjects with metabolic IR show simultaneous impairment in insulin ability to induce vasodilation. Diminished insulin-stimulated blood flow and glucose uptake is present in patients with various cardiovascular diseases such as essential hypertension, heart failure and microvascular angina. A diminished effect of insulin to induce vasodilation has been observed in subjects with obesity, T2DM and polycystic ovarian syndrome [227-230]. Thus, there may be similar genetic and acquired contributions to both IR and ED.

**THERAPEUTIC IMPLICATIONS OF THE CARDIOMETABOLIC APPROACH TO OBESITY**

Therapeutic strategy against obesity requires firstly a diagnosis of exclusion of secondary causes of obesity, such as Cushing's disease, hypothyroidism, binge eating disorder, Prader-Willi syndrome or hypothalamic tumour. Then it is time to design personalized targets as well as a stepped course of treatment from lifestyle changes to bariatric surgery when indicated, going through pharmacological therapy.

Bariatric surgery, such as Roux-en-Y bypass or gastric banding, is effective for weight loss as well as in the improvement of some of the obesity-related pathologies, since this techniques reduce adiposity and adiposopathy, recovering adipose tissue function [231]. However, due to all the concerns about perioperative mortality, surgical complications and frequent needing of reoperation, these methods are usually reserved for morbidly obese subjects.

**Lifestyle Change Therapy**

Lifestyle changes such as personalized diets and/or practicing physical exercise, frequently do not achieve good results as therapies for weight loss, mainly due to
very low motivation and compliance, and most of the patients give them up [14]. When these methods are accompanied by psychological therapies, such as cognitive behavioural therapy, rate of success tends to be higher, but these treatments have intrinsic difficulties to be delivered on a mass scale and long-term results are frequently disappointing [232].

However, a challenge for the clinician and the patient is that public health initiatives promoting nutritional weight loss and physical activity, as well as commercial nutritional weight loss plans, have met with limited success in both individuals and populations [233]. Here, the following fact should be highlighted: searching and selecting personalized suitable treatments for obese subjects is medically justified, because even just a 5% weight loss in overweight patients may improve pathogenic adipose tissue responses, and subsequently a handful of metabolic dysfunctions and cardiovascular risk conditions [234, 235].

A number of studies in obese adults and children have shown that even moderate weight loss through dietary changes and physical exercise is effective in preventing and managing obesity-associated disorders [236]. However, only few studies have focused on the effect of hypocaloric diets on systemic inflammation [237-239]. Despite exceptions, most of them agree in the results: there is a decrease in leptin, TNF-α, IL-6, IL-8 and PAI-1 levels, as well in the complement C3, but adiponectin and MCP-1 do not show any changes. Also in overweight/obese children and adolescents, significant reductions in IL-6, CRP or fibrinogen levels were found when hypocaloric diet and moderate physical activity were followed [239].

Beyond weight loss, a lifestyle change intervention should include improvements in diet and physical activity leading to achieve a reduction in cardiometabolic risk (hypertension, diabetes, metabolic syndrome and coronary risk) [56]. In this scenario, the biological impact of Mediterranean diet (MD) and regular physical exercise on cardiometabolic risk is outlined below.

**The Mediterranean Diet as a Model of Healthy Eating**

The Mediterranean diet (MD) has been widely considered as a model of healthy eating associated with a reduction in both total mortality and coronary heart disease (CHD) mortality [240, 241]. This is a current issue due to the PREDIMED Study
[242-244], even though it is focused just on certain components of the MD (olive oil and nuts) rather than in the MD as a global concept of diet. In this study the main target is not weight loss, but the behaviour of biomarkers and cardiovascular events, aiming to analyze for the first time in a large cohort study the biological impact of a type of diet in vascular health. Cardiometabolic benefits associated to the regular consumption of olive oil, rich in oleic acid (ω-9 monoinsaturated acid) and vitamin E, as well as nuts, high in vitamin E, omega-3 fatty acids (ω-3 fatty acids) and magnesium, were already known [245, 246].

However, the MD includes essentials aspects beyond those considered in the PREMIDED study:

a) The MD is low in saturated fat, which has metabolic and vascular implications. These fat acids induce insulin-resistance [247] and endothelial dysfunction [248]. On other hand, whereas most of western diets provide excessive amounts of omega-6 fatty acids respect to omega-3 fatty acids intake [249], the MD is rich in fatty fish with high content of ω-3. Eicosapentanoic acid, the most important ω-3 acid fat derived from fatty fish has demonstrated anti-inflammatory and antiplatelet actions [250], as well as an adiponectin-dependent anti-atherosclerotic effect that may be beneficial for the prevention of vascular complications in diabetic patients [251].

b) The MD is rich in fruits and vegetables, and thus high in antioxidants and flavonoids, which showed a clear cardiovascular preventive role in the INTERHEART study [252]. The MD is especially rich in lycopene, a carotene found in tomatoes, which has showed protective effects on coronary risk [253-255].

c) The MD is low in proteins, which was related in the DIOGENES Study to a lesser inflammatory status, as measured by high-sensitivity C-reactive protein [256].

d) Red wine is a usual component of MD, and its moderate consumption could play a role in preserving the endothelium [257].
Physical Activity Beyond Weight Loss

Traditionally a chapter dedicated to obesity addresses physical activity as a therapeutic tool to achieve weight reduction. This approach is as simple as wrong, since a number of studies, including the INTERHEART Study [252] have demonstrated that physical activity has cardiometabolic benefits beyond weight loss. So, maintaining or improving cardiorespiratory fitness has been related to a lower risk of all-cause and CVD mortality, as well as longevity regardless of changes in BMI [258]. Improved physical conditioning has been also associated with reduced arterial stiffness [259].

Regular aerobic exercise, and even modest physical activity, has shown to prevent the age-related decline in vascular endothelial function [260-262], suggesting an important mechanism by which regular aerobic exercise reduces the risk for cardiovascular disease. Physical activity has a beneficial impact on endothelial progenitor cells (EPC), which play an important role in repairing endothelial injury. Xia et al., have demonstrated for the first time that physical exercise attenuates age-associated reduction in endothelium-reparative capacity of EPC by increasing CXCR4/JAK-2 signaling [263].

Anti-Obesity Drugs

General Considerations

In the last fifty years anti-obesity drugs (AOD) have emerged as a complementary approach to life-style changes, before resorting to surgery. Surgery should be always the last step in the therapeutic strategy, but an in-depth discussion on this subject exceeds the purpose of this chapter. ADO approach lies in the use of drugs which reduce the consumption of food or its absorption and/or increase energy expenditure [264]. Nevertheless, this way has also been quite disappointing, owing to the fact that many of these new drugs had at one point to be withdrawn from the market due to the occurrence of a great deal of unacceptable side-effects. In this scenario, advances in research on the neurological basis of appetite and energy homeostasis have resulted in the development of a handful of targets for potential AOD development [265].
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Travelling back to the time when the anti-obesity drugs arrived to the market, we find that the first ones were the centrally-acting sympathomimetics, such as amphetamine derivatives like desoxyephedrine, phentermine and diethylpropion [266], which were very popular in the 1950s and 1960s, but increasing concern about abuse potential and cardiovascular risk led to their decline in the 1970s [30]. In the 1980s their use was substituted by serotonin (5-HT)-releasing agents such as fenfluramine and desfenfluramine [30]. From their start-point, this sort of drugs presented the potential to produce hyperpulmonary hypertension, but this side effect was “counteracted” by the benefit of the also important weight loss provided.

**Phentermine: The Oldest Anti-Obesity Drug**

Phentermine, approved only in US in 1959, is among the oldest AOD. Phentermine is an appetite suppressant agent, chemically related to amphetamine, but without its addictive potential. Phentermine has a medical use for short-term obesity treatment (≤ 12 weeks) because it presents multiple adverse effects, although there is no large-scale studies on this issue. This sympathomimetic amine anorectic is indicated as a short-term adjunct in a regimen of weight loss based on lifestyle changes and caloric restriction in the management of obese patients with an initial BMI ≥ 30 kg/m² or ≥ 27 kg/m² in the presence of concomitant cardiovascular risk factors (e.g., diabetes, hypertension, dyslipidemia) [267].

Phentermine is contraindicated in patients with unstable cardiovascular disease or cardiac dysrhythmias, uncontrolled high blood pressure and hyperthyroidism. In addition, phentermine is not recommended for patients with a history of drug and/or alcohol abuse or taking monoamine oxidase inhibitors, and it should be used with caution in patients under treatment with other agents acting on the CNS (e.g., increasing adrenergic responses). Phentermine side effects include, palpitations, tachycardia and increased blood pressure, irritability, anxiety, diaphoresis, dizziness, insomnia, headache, euphoria, dysphoria, mouth dryness, diarrhoea and constipation [267].

In the early 1990s, the use of a combined treatment including phentermine plus fenfluramine started to be a general practice in the US [268]. But unfortunately,
only a few years later, phentermine was reported to cause cardiac valvulopathy in combination with fenfluramine or dexfenfluramine. The role of phentermine in the etiology of valvulopathy has not been well established, as there were also cases of valvular heart disease in patients taking phentermine alone [269].

Studies on the possible effects of phentermine upon adiposopathy are very scarce, showing limited to effects upon adipogenesis, FFAs and adipose tissue endocrine and immune responses [270]. Short-term studies suggest that weight loss associated with phentermine may have some beneficial actions on lipid profile [88], with mixed effect on blood pressure [271].

Recently, in July of 2012, a combination of phentermine and topiramate has received the FDA approval to treat obesity under the trade name of Qsymia® [32]. This issue will be further discussed later in this chapter.

**Amphetamines for Weight Loss: high efficacy but low tolerability**

Amphetamines started to be used for weight loss purposes in 1938 [272]. Monoamine neurotransmitters reduce appetite by decreasing neuropeptide Y, and increasing pro-opiomelanocortin [273] and anorexigenic peptide, termed ‘cocaine and amphetamine-regulated transcript’ (CART), which is located in the hypothalamus, [274]. Amphetamine action mechanisms on central nervous system (CNS) include an increase in dopamine, norepinephrine and serotonin activity. Amphetamines are sympathomimetic agents which act upon obesity by increasing energy expenditure through diverse mechanisms, such as increasing thermogenesis [275], although this has been mainly studied in animals, while only a handful of clinical trials have shown that effects in humans [276-278]. Therefore, at least at doses prescribed for weight loss, the long-term effects of amphetamines on total energy balance still remain unclear. On the other hand, amphetamines have potential toxic effects for CNS and other adverse systemic effects, including increased blood pressure, tachycardia and euphoria, as well as a high potential for abuse and addiction [279].

**The Main Anti-Obesity Drugs in the Last 12 Years**

In Europe, three more agents were later approved for the long-term clinical management of obesity and related morbidities:
1. Sibutramine (Meridia® and Reductil®).

2. Rimonabant (Acomplia®).

3. Orlistat (Xenical® and Alli®).

**Sibutramine**

Sibutramine is a serotonin and norepinephrine reuptake inhibitor used for promoting weight loss in patients who have failed with lifestyle changes. In January 2010 it was suspended from the European market by the European Medicine Agency (EMEA), due to growing concerns about its potential negative effects on cardiovascular risk, according to the SCOUT study (Sibutramine Cardiovascular Outcome Trial) [280], a review of clinical trials including almost 10,000 overweight or obese patients at high risk of cardiovascular disease. The study randomly assigned patients to either treatment with sibutramine or placebo, and compared weight loss results assessing at the same time occurrence of cardiovascular events after a follow-up period of six years. As patients taking sibutramine presented significantly higher risk of cardiovascular events, the Committee for Medicinal Products for Human Use (CHMP) considered that it should not be prescribed in obese and overweight patients. In addition, subjects with previous cardiovascular conditions who were taking sibutramine had an increased risk of non-fatal myocardial infarction and non-fatal stroke, but not of cardiovascular death or death from any cause. In 2010, the FDA also withdrew sibutramine from the US market.

Sibutramine is a β-phenethylamine [281] that, when administered in doses ranging from 5 to 15 mg/day and combined with adequate lifestyle changes induces a significant body weight loss (around 5-10%). Sibutramine achieves weight loss by increasing satiety and reducing appetite. The selective inhibition of the reuptake of serotonin and noradrenaline within the hypothalamus [22] is the mechanism that underlies this effects. In addition, it has also demonstrated to lower plasma triglyceride levels, but unfortunately it has also been linked to increased blood pressure and heart rate [282]. Moreover, sibutramine has shown to reduce serum levels of proinflammatory mediators such as CRP, IL-6, and TNF-α when taken during 3 to 6 months [283].
Human brain produces two different kinds of endocannabinoids: anandamide and 2-arachidonoylglycerol (2-AG) [284]. They are synthesized on demand and work in a reverse direction, from postsynaptic neurons where they are synthesized to presynaptic neurons where they bind to receptors. Two specific endocannabinoid receptors have been identified: CB₁ and CB₂ receptors. CB₁ receptor is thought to mediate the psychotropic actions of cannabis and be involved in the modulation of food intake and adipogenesis. It is expressed at high levels by brain cells and several peripheral tissues including heart and adipose tissue, gastrointestinal tract and adrenal gland. CB₁ knockout mice show a lean phenotype that appears to be resistant to diet-induced obesity and insulin resistance. On the contrary, CB₂ receptors are mainly located at immune tissues and blood cells. These receptors are usually located in the areas responsible for modulating energy balance, feeding behaviour, hepatic lipogenesis, and glucose homeostasis [285]. Endocannabinoid system stimulation promotes metabolic processes that lead to weight gain, lipogenesis, insulin resistance, dyslipidemia, and impaired glucose tolerance [286, 287].

Rimonabant, a CB₁ endocannabinoid receptor inhibitor, showed not only to reduce excess body weight in obese subjects, but also a range of both central and metabolic peripheral effects [288], including decreased blood pressure in hypertensive patients, improved insulin sensitivity and dyslipidemia, also decreasing the prevalence of metabolic syndrome [289]. Rimonabant produced significant improvements in blood glucose control beyond what would be expected from its effects on weight loss [290]. So, metabolic and inflammatory benefits are not totally dependent on weight reduction and could be due to its direct action on abdominal fat or through neuroendocrine factors enabled or disabled by the drug [291]. The same argument has led to the use the topiramate not only as an anti-obesity drug, but also as an oral anti-diabetic drug, as discussed below.

Rimonabant, the first and only specific endocannabinoid inhibitor, was approved as an adjunct to diet and exercise for the treatment of obese or overweight patients by the EMEA in 2006. However the FDA never approved its use in the US due to
concerns on serious adverse events. A meta-analysis reported that the 20 mg of rimonabant was associated with an increased risk of adverse events including psychiatric and nervous system adverse events [292]. As a result, in 2009 the EMEA withdrew the market authorisation for rimonabant in the European Union [293].

**Orlistart**

As explained above, the release of FFAs due to excessive fat accumulation at adipose tissue is one of the key inductors of pathogenesis in obese patients. One of the strategies of the anti-obesity pharmacology consists of the reduction in energy uptake by partially inhibiting the hydrolysis of dietary triglycerides into absorbable FFAs, thus decreasing lipid absorption in the gut by 30 percent [294]. In this category of drugs lies orlistat, a gastrointestinal lipase inhibitor that was firstly approved by the FDA for the treatment of obesity in 1999. The main advantage of these pharmacological agents is to avoid systemic-side effects, since they bind lipid molecules in the intestinal tract.

Orlistat is a synthetic drug derived from a natural lipase inhibitor. It does not directly act on appetite as sibutramine, but rather decreases fat absorption. This is achieved by binding to pancreatic lipase, the main enzyme that hydrolyses triglycerides [295]. The long-term efficacy of orlistat (120 mg three times daily) for weight loss has been demonstrated in several clinical trials with following periods from 2 to 4 years [296]. Additional evidence has been observed in several systematic reviews in adults [297] and a systematic review with 2 short-term studies in adolescents [298].

In average, the use of orlistart leads to around 5 to 10 % weight reduction in 50-60 % of patients after 12 months of treatment [17]. Moreover, in a trial assessing orlistat in the prevention of diabetes in obese subjects (the XENDOS Study), the risk of developing T2DM in obese subjects with impaired glucose tolerance was reduced [299]. Besides, this drug counts with an added value: several studies have evaluated the effects of orlistart on inflammatory markers in obese patients. Treatment with orlistart for up to 1 year showed a significant reduction of CRP levels [300]. For this reason, despite the modest weight loss achieved by orlistart, it is important to highlight that it confers some beneficial effects on cardiovascular
risk, including plasma levels of LDL-cholesterol, blood pressure [301] and glycemia [299], as well as improving insulin resistance [299].

However, orlistart also produces relevant side effects, as the rest of anti-obesity drugs. Its main side effects include gastrointestinal disturbances such as abdominal pain, dyspepsia, flatulence, diarrhea and steatorrhea [295, 301]. Besides, it has been also related to severe liver injury [302]. After receiving 32 reports of serious liver injury in patients taking orlistat between 1999 and October 2008, including 6 cases of liver failure, the FDA carried out a safety review. In May 2010, these facts led to a label revision and the addition of a warning of severe liver injury.

Until 2012, when topiramate in combination with phentermine was approved by the FDA, orlistat was the only drug for weight loss that remained in the market.

Several new anti-obesity drugs are under research as monotherapy (Table 3) or in combination (Table 4). While these new drugs arrive to market, we are going to analyze the use of topiramate in the treatment of obesity as cardiometabolic disease.

**Table 3:** Novel obesity treatments in Phase II and III trials

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Drug Name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT2C agonist</td>
<td>Lorcaserin (ADP-356)</td>
<td>Arena</td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>Pramlintide</td>
<td>Amylin Pharmaceuticals</td>
</tr>
<tr>
<td>CB1 receptor antagonist</td>
<td>CP 945598</td>
<td>Pfizer</td>
</tr>
<tr>
<td>CB1 receptor antagonist</td>
<td>Taranabant</td>
<td>Merck</td>
</tr>
<tr>
<td>CB1 receptor antagonist</td>
<td>AVE 1625 Surinabant</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td>Y2 receptor agonist</td>
<td>PYY3-36</td>
<td>Amylin, Nastech</td>
</tr>
<tr>
<td>Y4 receptor agonist</td>
<td>TM30339</td>
<td>7TM Pharma</td>
</tr>
<tr>
<td>Histamine Agonist</td>
<td>Betahistine</td>
<td>Obecure</td>
</tr>
</tbody>
</table>

**Table 4:** Novel combination obesity treatments in clinical trials

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Drug Name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion + Naltrexone</td>
<td>Contrave</td>
<td>Orexigen</td>
</tr>
<tr>
<td>Bupropion + Zonisamide</td>
<td>Empatic (Excalia)</td>
<td>Orexigen</td>
</tr>
<tr>
<td>Pramlintide + Leptin</td>
<td></td>
<td>Amylin</td>
</tr>
</tbody>
</table>
Topiramate

Background

Topiramate (TPM) was serendipitously discovered in 1979 by Maryanoff and Gardocki when they were working on a new anti-diabetic agent [303]. TPM is a broad-spectrum anticonvulsant with useful neurological effects that derive from multiple central nervous system mechanisms of action. It is a “neurostabilizer” that attenuates the excitability of brain neuronal pathways. TPM is approved in many countries worldwide as monotherapy and adjunctive therapy for the treatment of epilepsy in adult and paediatric patients [304].

Besides its well-known antiepileptic properties, this drug is also used for prevention of migraine attacks [305, 306], and may have a potential role in the treatment of movement disorders [307]. Furthermore, TPM has been proposed to treat bipolar disorder [308], and due to its effects on stabilizing mood and reducing impulse control problems, as a treatment for obese patients with binge eating disorder [309-311]. So, it has been also associated with significant reductions in binge frequency, binge per day frequency, weight, body mass index and obsessive-compulsive scores. Moreover, it has also been used in patients with bulimia nervosa [312, 313], and even in patients with alcohol dependence and for tobacco abuse [314].

![Topiramate chemical structure](image)

**Figure 13**: Topiramate chemical structure. Systematic (IUPAC) name: 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate.

Pharmacology of Topiramate

Topiramate, a sulfamate-substituted monosaccharide derivative of the naturally occurring sugar monosaccharide D-fructose (Fig. 13), is structurally different
from other antiepileptic drugs (AEDs). It has a unique combination of actions at various receptor sites and ion channels. TPM enhances γ-aminobutyric acid (GABA)-mediated chloride flux at GABAA receptors [315], blocks the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of the glutamate receptor [316, 317], and there is also evidence that specific actions are taken on GluR5-kainate-receptors (Fig. 14) [316].

**Figure 14:** Topiramate activities at receptor sites (GABAA receptors and kainate/AMPA subtype of the glutamate receptor) and ion channels (voltage-activated sodium (Na) channels, high-voltage-activated calcium (Ca) currents, potassium (K) conductance). Inhibition of carbonic anhydrase (CA) isoenzymes (subtypes II and IV).

TPM is rapidly absorbed and its bioavailability after oral consumption is greater than 80%, reaching maximum plasma levels 1.3-1.7 hours after oral administration [315, 318]. TPM pharmacokinetics is dose proportional, reaching a steady state in 4-8 days in patients with normal renal function [319]. The extent of protein binding of TPM is around 15%. When administered as monotherapy, TPM is not extensively metabolized, with 50-80% of the drug being excreted unchanged in the urine [320], with an elimination half life of 19-23 hours.

TPM is not an inhibitor *in vitro* of the cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 [315, 321]. Therefore, no interactions involving changes in the pharmacokinetics of TPM are expected due to enzyme inhibition [322]. Moreover, predominantly renal elimination and low protein binding minimize the potential for clinically relevant
interactions with other drugs. However, described TPM interaction with other drugs (e.g., low-dose oral contraceptives, digoxin, hydrochlorothiazide, metformin, pioglytazone and risperidone) may require adjustments of TPM or the concomitant therapy or routine monitoring of clinical response. In patients taking oral contraceptives, it is important to consider that their efficacy may be reduced due to a decrease in circulating estrogens.

**Topiramate: Mechanisms of Action and Metabolic Effects**

Several potential mechanisms have been proposed to explain topiramate-induced weight loss, although the underlying mechanism remains still unclear. Studies in animal models suggest that the potential mechanisms of TPM-induced weight loss include decreased caloric intake and reduction in body fat gain [323]. During clinical trials in epilepsy, subjects taking TPM reported loss of appetite and hunger reduction [324-326] related to an increase in energy expenditure, even though the objective measurements of appetite may not be reduced during weight loss [327]. Regarding energy expenditure, TPM may decrease energy storage and usage efficiency, and thus increase energy consumption [328], theoretically by increasing thermogenesis [329].

With regard to adipocyte function, TPM may inhibit an adipocyte enzyme, the so-called “mitochondrial carbonic anhydrase isoenzyme V” [330], and through this mechanism, inhibit the lipogenesis catalyzed by this enzyme [331]. TPM is also involved in the decrease of lipoprotein lipase (LPL) activity in white adipose tissue (WAT). This is a relevant fact regarding the potential pathogenicity of increased levels of free fatty acids (FFAs), what at the same time reduces lipogenesis [332]. On the contrary, TPM may increase lipoprotein lipase activity in brown adipose tissue [333], which may promote thermogenesis and lipoprotein lipase activity in skeletal muscle, supporting the potential for substrate oxidation [332, 334]. In addition, TPM may increase adiponectin levels [334], which favourably affects several peripheral physiologic processes related to metabolic disease. However, the effect of TPM on leptin in humans is controversial [332, 335].

The main potential mechanisms proposed to explain TPM-induced weight loss are summarized in the Fig. 15.
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Figure 15: Anti-obesity topiramate proposed mechanisms of action. Topiramate enhances γ-aminobutyric acid (GABA)-mediated chloride flux at GABAA receptors, which may decrease night-time and deprivation-induced feeding and it blocks the kainate/AMPA subtype of the glutamate receptor, so it may reduce compulsive or addictive food behaviour. Topiramate may also increase levels of neuropeptide Y (NPY) in the hypothalamus and increase levels of hypothalamic corticotropic-releasing hormone (CRH), which may have catabolic activity. Thus it may have CNS effects which result in alteration of caloric balance. In the adipose tissue, topiramate inhibits lipogenesis, through the inhibition of mitochondrial carbonic anhydrase and also decreasing lipoprotein lipase (LPL) activity in white adipose tissue. TPM may decrease energy storage and usage efficiency, and thus increase energy expenditure, theoretically by increasing thermogenesis. Another effect of Topiramate is the increase of adiponectin levels and the decrease of leptin levels.

Efficacy and Tolerability of Topiramate as Anti-Obesity Drug

Early on, even at the time of its approval (in 1996 in the USA) as an antiepileptic drug, TPM was reported to promote dose-related weight loss [336]. Since then, clinical trial data have supported TPM as having weight loss effects [335, 337-345]. However, TPM does not have a regulatory for weight reduction [346], even though some clinicians have used it “off-label” for this purpose.

In a meta-analysis [347] of randomized controlled trials (3320 individuals), patients taking TPM lost around 5 kg of additional weight as compared with placebo. In addition, dosage and treatment duration were related to the efficacy of TPM to promote weight loss. Several factors have been studied as predictors of weight loss
related to TPM intake. Among them, the baseline BMI and the duration of treatment appears to be the most closely related, whereas the role of gender and daily dosage is uncertain [327, 351-359]. With regard to the duration of TPM treatment, the weight loss occurred most frequently during the first months of treatment (4 to 6 months) and continued for at least 1 year [335, 348-350]. On the other hand, mixed results have been reported on the role of daily dosage. While some studies did not find a direct relationship between weight reduction and TPM dosage [351, 352], data from other studies support that the extent of the loss is directly related to final dose [325, 353]. As for gender, some results that suggested a greatest BMI decrease in females [351] have not been confirmed in other studies that did not find differences between adult males and females [354].

Several studies have been conducted to assess the safety of TPM for weight loss in obese subjects [337, 350]. The most frequent adverse events were related to the central and peripheral nervous system, including somnolence, paresthesia and memory loss, and were dose-related, occurring early in treatment, and they were usually resolved spontaneously. [350].

Efficacy and safety of TPM as an anti-obesity drug have been also tested in patients with T2DM [338, 355-357]. In a clinical trial, overweight/obese diabetic patients under diet and exercise alone or in combination with metformin were randomized to 175 mg/day of TPM or placebo [355]. Patients in the TPM group lost 6.0 kg vs. 2.5 in the placebo group, which respectively represented 5.8% and 2.3% of their baseline weight. Patients under TPM treatment showed a significant reduction in haemoglobin A1c from baseline (0.9% vs. 0.4% in the placebo group), along with reduced blood pressure and urinary albumin excretion. Adverse events were predominantly neuropsychiatric or related to the central and peripheral nervous system.

**Topiramate in Combination Therapy for Weight Loss**

Up to date, TPM alone does not have an indication for weight loss. However, a combination of TPM controlled-release with phentermine, known as Qsymia® (Vivus, Inc., CA, USA), has been recently approved (July 2012) in the US for the treatment of obesity [32].
Phentermine is among the oldest approved anti-obesity agents, indicated as an adjunct to appropriate nutrition and physical exercise for short-term (up to 12 weeks) treatment of obesity [358]. Due to its generic status, it is the most commonly prescribed appetite suppressant [358].

The combination of TPM and phentermine has shown synergistic potential for safe, effective and sustained weight loss [287, 302] (Fig. 16). Lower doses of both agents also improve the intolerances and toxicities associated with higher doses of each one [359]. This fixed-dose combination is presented as a once-a-day single capsule of phentermine hydrochloride, which is readily absorbed to provide therapeutic effects early in the day, added to controlled release TPM, which provides persistent weight loss throughout the day.

![Figure 16: The combination (phentermine plus topiramate controlled-release) leads to greater changes in body weight from baseline than each agent alone or placebo. Source: A Study Comparing Multiple Doses of VI-0521 With Placebo and Their Single-agent Constituents for Treatment of Obesity in Adults. Vivis, Inc. ClinicalTrials.gov Identifier: NCT00563368.](image)

Several clinical trials involving thousands of patients have demonstrated that the combination of phentermine and topiramate is effective in promoting weight loss and also in improving adiposopathy-associated metabolic diseases [358-363]. The weight loss achieved with combination therapy is greater than using either agent alone [364]. In a 1-year placebo-controlled clinical trial, phentermine plus topiramate combination in addition to lifestyle modification demonstrated clinically meaningful weight loss [362]. Moreover, when compared to placebo, combined treatment has been associated with favourable changes in
cardiometabolic and anthropometric parameters (e.g., HDL-cholesterol, blood pressure and waist circumference), also improving haemoglobin A1C levels in overweight and obese subjects with type 2 diabetes [365].

**Cardiometabolic Implications of the Regular use of Topiramate**

As discussed earlier in this chapter, the relentless rise in the prevalence of obesity predicts an exponential increase in the incidence of obesity-related cardiometabolic and non-cardiometabolic complications. A vigorous therapeutic strategy is needed to prevent and treat obesity-related comorbidities, thereby avoiding disability and premature death [366]. TPM actions on obesity should be evaluated not only by weight loss, but also according to the obesity-related comorbidities. If obesity is considered as a cardiometabolic disease, it should be mandatory to study not only the classical cardiovascular risk factors and cardiovascular events, but also the metabolic aspects related to insulin resistance, metabolic inflexibility and endoplasmic reticulum stress and adipokines, as well as inflammation, oxidative stress and endothelial biomarkers.

a) Classical Cardiovascular Risk Factors and Cardiovascular Events

TPM in combination with lifestyle measures, besides a demonstrated weight loss, may lead to a reduction in newly diagnosed type 2 diabetes mellitus as well an improvement in lipid profile and a reduction in blood pressure, and therefore a lower cardiovascular risk. However, data about these targets are sparse. In a study conducted in women with cryptogenic epilepsy receiving TPM, it was associated with lower HDL-cholesterol levels, which may increase vascular disease [367]. This important aspect of lipid metabolism should be clarified. Several studies have shown a beneficial decrease in total cholesterol and triglycerides, but also accompanied by a decrease in HDL-cholesterol [333, 335, 350, 368]. The influence of weight loss on LDL-cholesterol levels is poor, so limited reduction can be expected. In animal models, TPM has been reported to lower triglycerides and circulating free fatty acids [369, 370].

With regard to type 2 diabetes mellitus, a significant reduction in haemoglobin A1c from baseline has been reported in patients under TPM treatment [286], along with reduced blood pressure and urinary albumin excretion [338, 355-357].
Glucose tolerance, as measured during the oral glucose tolerance test, has been also observed to improve in obese subjects treated with TPM, but it may be secondary to weight loss [335]. However, although several studies in animal models have associated TPM with an increase in insulin sensitivity, enhancing insulin action in the adipose and muscle tissues [332, 368], this findings have not been confirmed in humans.

b) Metabolic Aspects Related to Insulin Resistance, Metabolic Inflexibility and Endoplasmic Reticulum Stress

Animal testing data show that TPM improves insulin resistance (IR) independently of weight loss [332, 368]. Recently, the potential hepatic molecular mechanistic cassette of the anti-insulin resistance effect of TPM has been reported [371]. The study demonstrated that IR acts at hepatic molecular level and that the TPM-mediated insulin sensitivity is ensued partly by the modulation of hepatic insulin receptor isoforms, activation of tyrosine kinase, induction of GLUT2 and elevation of adiponectin and adiponectin receptors, in addition to its known effects on improving lipid homeostasis and glucose tolerance [371].

In humans, IR, as measured by the HOMA index, was reduced after 20 weeks of treatment with an average dose of 100 mg TPM/day in patients with migraine [372]. Similarly, in premenopausal women with cryptogenic epilepsy taking TPM, a significant improvement in insulin resistance was found, although it was surprisingly accompanied by a HDL-cholesterol reduction when the expected effect should have been just the opposite [367]. With regard to MetS or IR syndrome -abdominal obesity, glucose intolerance, elevated triglycerides, low HDL-cholesterol and hypertension- in subjects under TPM treatment, most of the available data derive from studies carried out in epileptic patients [373]. There are no specific studies about insulin resistance, metabolic inflexibility and/or endoplasmic reticulum stress in obese subjects under TPM treatment.

c) Adipokines

In a study conducted in rats, TPM improved glucose homeostasis and lipid profile, as well as raised adiponectin levels in a dose-dependent manner [371].
In humans, TPM has shown to significantly reduce leptin levels from baseline in patients with migraine [372] and epilepsy [352]. In both types of patients, adiponectin as well as the leptin/adiponectin (L/A) ratio were also increased. The observed changes in leptin and adiponectin have also a positive cardiovascular profile, in addition to the metabolic improvements. However, other studies have not found a similar leptin reduction. So, in a prospective study carried out in patients with different types of refractory focal epilepsy who received TPM as adjunctive treatment, no significant reductions in serum leptin levels were observed [374]. Just like in the aforementioned study, no changes in leptin were found in premenopausal women with cryptogenic epilepsy [367].

d) Inflammatory Biomarkers

As previously described in this chapter, obesity is an established determinant of C-reactive protein (CRP) in adults [208, 375] and children [208-210, 376].

In a study evaluating the association between weight change and clinical markers of cardiovascular risk in subjects taking TPM or amitriptyline as migraine-preventive treatments, individuals from both treatment groups were divided into three groups: the 'major weight gain' group gained > 5% of their baseline body weight at the conclusion of the study; the 'major weight loss' group lost > 5% of their baseline body weight; and the third group had < 5% of weight change [377]. Those who gained weight presented significantly higher values of CRP, mean diastolic blood pressure, heart rate, haemoglobin A1c, total cholesterol, LDL-cholesterol and triglycerides than those with major weight loss. However, both groups experienced decreases in systolic blood pressure and HDL-cholesterol. Authors concluded that weight gain during migraine treatment is associated with deterioration of cardiovascular disease risk markers [377]. Nevertheless, no specific data are available on the effect in those just taking TPM.

Furthermore, although no particular studies linking CRP and TPM have been reported, a reduction in weight and body fat mass has been positively associated with lower plasma CRP levels [375]. In addition, the CRP response to lifestyle modifications, as well as drug treatment, may be genetically regulated. So, genetic variants on the CRP locus and other loci may be responsible for the interindividual variability of plasma CRP concentrations, which could have
important implications for the development of more personalized preventive and therapeutic approaches to reduce cardiovascular disease in obese patients [378].

A study evaluating the effect on lipids and C-reactive protein of switching from enzyme-inducing antiepileptic drugs (carbamazepine or phenytoin) to TPM [379] showed that this therapy change resulted in a decrease in serum CRP around 50%, as well as a significant improvement of lipid profile. According to the authors, this finding provide evidence that CYP450 induction rises CRP levels and serum lipids, including LDL-cholesterol, and these effects are reversible upon deinduction [380]. Low-dose TPM appears not to induce the enzymes involved in cholesterol synthesis [379].

On the other hand, interleukin-6 (IL-6) and TNF-alpha (TNF-α), two adipokines with proinflammatory actions on both vascular and fat tissue, should be considered of paramount importance in obese subjects undergoing medical or surgical treatment, especially TNF-α because of its implication in insulin signaling impairment [381]. In animal models, a significant decrease in TNF-α have been observed in male rats when treated with TPM in a dose-dependent manner [371]. In humans, cytokines play an important role in obesity. IL-6 and/or TNF-α were unchanged in small samples of migraine patients receiving TPM therapy [372, 382].

e) Endothelial Biomarkers

Just one study assessing the relationship between TPM and endothelial biomarkers has been conducted in subjects suffering from migraine, obese and non-obese [372]. In this study, circulating vascular endothelial growth factor (VEGF) increased during the first 2-4 week followed by a continuous decrease. The role of increased VEGF concentrations prior to these metabolic changes is not clear and might, hypothetically, involve a centrally mediated effect of TPM on body weight regulation.

Our Preliminary Experience with TPM: Effects Upon Weight Loss and Inflammatory Markers (Adiponectin and IL-6)

Up to date, we have carried out two studies on the use of TPM as an anti-obesity agent. The results have not been published, but the work was presented at the
In a first pilot trial, we aimed to assess the efficacy and tolerability of TPM when used as a weight loss agent in a sample of middle-aged overweight patients at moderate-high cardiovascular risk, who had been resistant to a lifestyle change for at least 6 months. Dosage was titrated upward by weekly increases of 25 mg/day over a 7-week period (according to Rosens tock [355]) and continued afterwards up to a target dose of 150-200 mg/day during the maintenance phase. Significant reductions in body weight (5.48 ± 4.12 kg; p < 0.001), BMI (2.0 ± 1.46 kg/m²; p < 0.001) and body fat (2.7 ± 3.3 Kg, p = 0.002)) from baseline were observed in the sample population (n = 42). 9 out of 10 patients lost more than 5% of their initial body weight, and almost 2 out of 10 lost more than 10%. With regard to tolerance, 6 out of 10 patients suffered adverse events, being paresthesia the most frequent one (36% of the whole sample). Only 5 of the 42 patients abandoned the treatment, 4 of them due to moderate adverse events and only 1 due to inefficacy of treatment after a period of 6 months.

In a second phase, we aimed to assess the potential beneficial effects of TPM on metabolic factors and subsequently on cardiometabolic disease, usually associated to obesity. With this scope in mind, we also measured inflammatory markers such as IL-6 and adiponectin at baseline and after 9 months of treatment.

Subjects who were non-responders to lifestyle changes in usual clinical practice were treated with TPM in addition to lifestyle change measures (n = 15). In order to control the true potential TPM effects on haemodynamic, metabolic and biomarker parameters of TPM independently of the achieved weight reduction, these subjects were matched by sex and age with patients retrospectively selected who were responders to life-style changes with a clinically significant weight reduction (over 5%).

Main results of the study are summarized here. Subjects under TPM treatment showed significant weight loss, accompanied by a reduction in BMI and fat mass. In fact, 53.3% showed a weight reduction > 7%. These subjects also significantly reduced haemodynamic parameters, particularly systolic diastolic and mean blood
pressure, whereas in the control group only relevant changes were observed in diastolic blood pressure. With regard to metabolic changes, haemoglobin A1c was significantly reduced in subjects treated with TPM but not so in the control group. Moreover, a downward trend was appreciated with regard to triglycerides in both groups, although it did not reach statistical significance. Regarding biomarkers, subjects under TPM treatment showed significant changes in IL-6 and adiponectin levels, unlike the life-style responder control group. Finally, drug tolerance was good overall and there were no patient withdrawals from the study. The most frequently reported side effects include paresthesia (35.7%) and insomnia (14.3%).

Our study confirms previous results [355] regarding the effectiveness of TPM as an anti-obesity drug in patients with moderate to high cardiovascular risk. In fact, it goes even further, obtaining an improvement in circulating cytokine levels (i.e. adiponectin and IL-6), which are related to vascular inflammation and pro-inflammatory activity of visceral fat and/or of the SVF (Stroma-Vascular Fraction - consisting of macrophages, endothelial cells, progenitor cells and leukocytes).

The effects of TPM on lowering blood pressure, IL-6 and adiponectin levels were not observed in subjects who achieved weight reduction based on recommended lifestyle changes given in usual clinical practice. This may suggest a favourable effect of the direct action of the drug, and not a weight-loss dependent effect. Patients under TPM treatment showed a more favourable cytokine profile, which underlines the probable anti-inflammatory effect of TPM. The effect of TPM on cytokine levels might be explained by its action at any of the following sites [315, 383]: GABA-activated chloride channels, inhibition of excitatory neurotransmission, kainate and AMPA receptors, or GluR5 kainate receptors. Thus, it is possible that some of these mechanisms may play a major role in the activity of macrophages and/or adipocytes. For example, TPM induced enhancement of GABA-activated chloride channels could interfere with autonomous nervous system functioning and, in turn, have major implications in the regulation of peripheral metabolism. So far, the only antiobesity drug that had demonstrated a peripheral metabolic effect was rimonabant, due to its action as a CB1 receptor blocker [384-386].

Despite of important limitations to our study, such as small sample size or the inclusion of a retrospectively selected control group, we believe these do not
question the validity of our findings and observed tendencies, which should encourage the development of new prospective studies to clarify the mechanisms by which a drug, without granted peripheral action, could improve cytokine levels, and all the implications derived from this.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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