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REVIEW

Metabolic syndrome pathophysiology: The role of adipose tissue

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Abstract Several pathophysiological explanations for the metabolic syndrome have been proposed involving insulin resistance, chronic inflammation and ectopic fat accumulation following adipose tissue saturation. However, current concepts create several paradoxes, including limited cardiovascular risk reduction with intensive glucose control in diabetics, therapies that result in weight gain (PPAR agonists), and presence of some of the metabolic traits among some lipodystrophies. We propose the functional failure of an organ, in this case, the adipose tissue as a model to interpret its manifestations and to reconcile some of the apparent paradox. A cornerstone of this model is the failure of the adipose tissue to buffer postprandial lipids. In addition, homeostatic feedback loops guide physiological and pathological adipose tissue activities. Fat turnover is determined by a complex equilibrium in which insulin is a main factor but not the only one. Chronically inadequate energy balance may be a key factor, stressing the system. In this situation, an adipose tissue functional failure occurs resulting in changes in systemic energy delivery, impaired glucose consumption and activation of self-regulatory mechanisms that extend their influence to whole body homeostasis system. These include changes in adipokines secretion and vascular effects. The functional capacity of the adipose tissue varies among subjects explaining the incomplete overlapping among the metabolic syndrome and obesity. Variations at multiple gene loci will be partially responsible for these interindividual differences. Two of those candidate genes, the adiponectin (APM1) and the perilipin (PLIN) genes, are discussed in more detail.

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Introduction

The concept of metabolic syndrome (MetS) has been evolving for years, but with the recognition that obesity is becoming a major global health problem, this syndrome has experienced both dramatic increases in interest as well as conceptual evolution. The MetS was originally proposed as a set of clinical risk factors that could be potentially explained by a common pathophysiologic link, insulin resistance (IR) [1]. In 2002, the National Cholesterol Education Panel (NCEP) endorsed its clinical significance and defined the most widely used criteria to identify these high risk individuals [2,3]. However, despite the common use of these criteria by researchers and clinicians to classify individuals, they may not provide therapeutic insight due to the lack of options for treating the cluster, beyond those already used to treat the individual factors. Thus, the clinical utility of the syndrome has been criticized [4,5]. Furthermore, it has been suggested that the syndrome may not confer greater risk than that explained by each of its components [6].

Contemporary to the raise in interest towards understanding the MetS and its molecular basis, there has been a revolution on the perception of the adipose tissue, which has evolved from being identified as a mere deposit of fat to being recognized as a highly metabolically active organ and as a major orchestrator of the MetS pathophysiology. The adipose tissue is an endocrine organ, which deploys several active compounds that can be grouped under the name of adipokines [7–9]. In view of this knowledge and in order to improve the clinical definition for the MetS, the International Diabetes Federation has promoted a new definition, which requires central obesity as a diagnostic requisite [10]. However, this is not universally recognized [11]. In fact, there are several situations in which obesity and MetS do not share the same path. In this regard, there is clear evidence of lean patients with most of the MetS traits [12–14], and conversely of obese subjects who appear as metabolically normal, placing some reasonable doubts to the use of obesity as the central diagnostic criteria [5,11].

An additional caveat is that the different definitions aim to different objectives [15]: current clinical definitions have been useful for epidemiological quantification of the problem [16] but do create groups excessively heterogeneous to gather good pathophysiological information, and, as stated above, their clinical application is not clearly useful. The use of waist circumference

might also increase noise in the diagnosed groups because of the difficult standardization of its measurement [5] and the different meaning among populations [17], and its clinical use has encountered some criticism [18]. Other definitions focus on pathophysiology and use IR to diagnose individuals. In trying to bring new light on mechanisms, they are bound to the fixed frame of IR.

Pathophysiology and its paradoxes

Taking in consideration the varying definition and success of the MetS in the different fields, current and future efforts should be focused in improving our knowledge about the pathophysiology of the syndrome that should provide more effective therapeutic approaches [19] and more precise definitions, preferably based on measurements of single parameters instead of presence of criteria. In this regard, the initial hypothesis of IR and hyperinsulinemia as the common cause of the symptoms was and still is under scrutiny (Fig. 1). There are studies focusing on metabolically-obese lean individuals [20] or free of other risk factors (EGIR-RISC [21]) to investigate and understand whether and how IR may by itself be a risk factor for atherosclerotic cardiovascular disease (CVD).

In addition, other pathophysiological models have been proposed (Fig. 1), including the saturation of the adipose tissue and subsequent ectopic fat storage leading to lipotoxicity [22] and the unbalanced secretion of adipokines and other active substances by the adipose tissue [7–9].

The need to find additional explanations arises from the several paradoxes deriving from the current concepts of MetS and obesity. If adipose tissue were responsible of the syndrome, then one

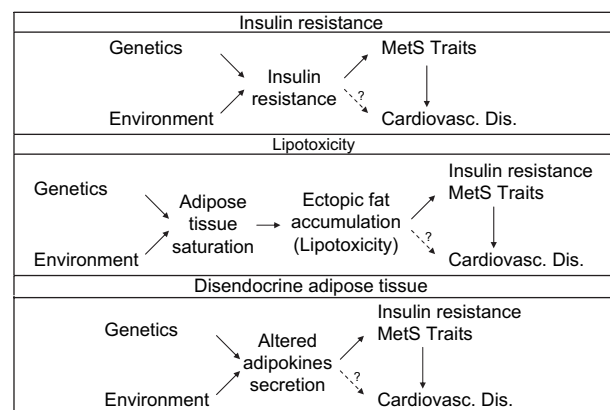


Figure 1 Disease models. Some of the pathophysiological models of the metabolic syndrome give limited explanations for observed facts.

should expect a stronger association between obesity and the other components of the cluster. However, most factor analyses show two different association paths: one involving obesity and hypertension and another one encompassing obesity–dyslipidemia–glycemic control alterations [23,24]. Besides, it seems that in diabetic patients, who supposedly have IR and hyperinsulinemia, the presence of the MetS is essential to their increased cardiovascular risk [25], and intensive glucose control does not substantially decrease it [26,27]. Furthermore, cardiovascular risk is more dependent on risk factors clustering than in obesity [11].

Another interesting aspect relates to the differences between men and women and between different areas of fat accumulation [28]. In some cases, fat in certain locations is apparently even protective against the MetS [29,30]. Thiazolidinedione treatment results in a paradoxical effect, improving insulin sensitivity while causing, on average, weight gain [31]. Moreover, animal models show similar paradoxes. This is the case of the knockout mouse for perilipin, a protein that stabilizes lipids in the adipocytes. This animal model displays reduced body fat and, paradoxically, an increased risk of glucose intolerance and peripheral IR [32]. Interestingly, in humans, common polymorphisms at the PLIN gene modulate the response of insulin sensitivity to changes in dietary saturated fat and carbohydrates [33]. Furthermore, chickens and mice inoculated with human adenovirus Ad-36 develop a syndrome of increased adipose tissue and paradoxically low levels of serum cholesterol and triglycerides [34]. Consistent with these observations, antibody-positive humans also had lower serum cholesterol and triglycerides levels.

Hypothesized model

Our aim is to integrate a collection of well known facts about the MetS and obesity into a novel perspective. Therefore, we propose a new model for MetS that might fit better with current evidence and be more conducive to classify groups of individuals for pathophysiological research.

Complex diseases of late onset usually result from a failure to maintain adequate homeostasis. This may be due to functional variation at the genetic level, environmental exposures or, most probably, the interaction between both. This is especially true for highly prevalent disorders that frequently are expression of counter regulatory processes and consequences of a displaced equilibrium.

In the following sections we will revisit the manifestations of the MetS from the perspective that they are derived from the lost of functional activities of the adipose tissue, thus defining it as an organ failure. Depending on the underlying cause a different range of manifestations may be seen. We will focus on the most common cause, a chronically inadequate energy balance and we will compare it to other situations that lead to MetS manifestations.

Adipose tissue functions

The functions described for white adipose tissue from classical physiology are: heat insulation, mechanical cushioning, and storage site for fat in the form of triglycerides. However, this view has been dramatically changed with the recognition of the adipose tissue as a key endocrine organ [7–9]. Adipose tissue secretes active endocrine, paracrine and autocrine substances in response to different stimulus. Some of them are mainly released by the adipose tissue (i.e., leptin) while others are shared with other systems (i.e., tumor necrosis factor- α ; TNF- α) thus interweaving its function in systemic whole-organism regulations. Data on stimulus, secreted substances and actions are still incomplete, and even worse, we lack an integrative frame to interpret their common regulation. Beyond these well accepted functional activities, there is a function that so far has received little attention and that might be key in the pathophysiological implications of the adipose tissue: buffering of lipids in postprandial periods [35].

Postprandial lipids buffering and energy balance

The current hypothesis considers that adipose tissue switches between two states: Avidly draining free fatty acids that come mainly from triglyceride rich lipoproteins during the postprandial period or gently releasing them during the fasting period. Switching between one state and the other is most probably regulated by a multifactorial system including substrate and hormone levels, but also the functional state of the adipose tissue itself. Any factors hindering the transition to a lipid accepting state will lead to failure of this function.

In this equilibrium, which determines the state of the switch, insulin levels certainly play an important role (just envision the situation in type 1 diabetes). Nonetheless if we disregard the many other factors that may affect the switch we will probably describe the whole equilibrium as the intensity of the response to insulin (Fig. 2A).

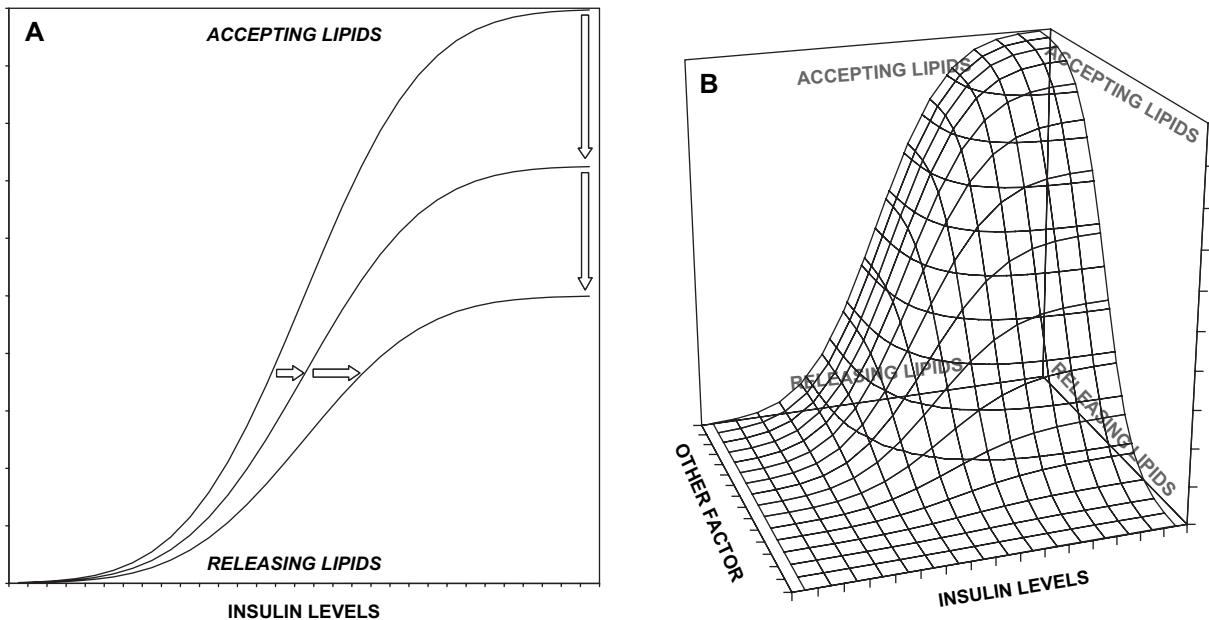


Figure 2 Multifactorial influences on the adipose tissue metabolic activity. Considering insulin as the only determinant of adipose tissue state (accepting/releasing lipids) might throw a partial interpretation of reality (A). Responses to insulin may be displaced to higher insulin levels or maximum response may be reduced in various situations that are called “insulin resistant states” (A). Taking into consideration that adipose tissue state is determined by multiple physiological factors simultaneously helps understanding that original causes might lay outside of the insulin action axis (B).

Different factors may cause displacement of the curve response to insulin (Fig. 2B), thus creating an observable “insulin resistance”. Describing this clinical condition that way suffers from being a partial phenomenological description of the situation and thus IR should not be a priori acknowledged as a crucial causal event (nor discarded as such). Consequently we will try to avoid this term, as it has acquired a connotation of causal issue in previous theories.

Glucose drainage in the liver and skeletal muscle depends on a similar equilibrium too, which is also mainly, but not entirely, regulated by insulin. Energy consumption in skeletal muscle cells is regulated competitively by the presence of substrates, mainly through the regulation of metabolic pathways, and to a less extent by competition for the same enzymes and upstream saturation of reactions: excess of glucose stops acyl-CoA transport into mitochondria through the increase of malonyl-CoA and conversely, long chain acyl-CoA inhibits insulin mediated inbound glucose transport at receptor (phosphorylation by protein kinase C), post-receptor levels or even at glucose hexokinase at the beginning of the glucose pathway [36]. Apparently palmitic acid is also directly capable of reducing insulin stimulated glucose uptake of cultured cells, reducing phosphorylation of Akt kinase and reducing downstream phosphorylations in the cascade [37].

Adipose tissue regulation

Adipose tissue has its own homeostatic cycle overlapping with that of whole body energy balance and storage. Regulatory mechanisms of these processes are also shared with the regulation of circulating energy-related metabolite levels (glucose and free fatty acids). Besides insulin and catecholamines as main players, adipose tissue lipolytic state is also governed by autocrine and paracrine signals, and possibly also intracellular signals depending on adipocyte repletion state (that could be represented by average adipocyte size). From this point of view, resistance to adipogenic actions of insulin may be seen as a homeostatic adaptation [38]. These interwoven complex regulatory cycles make it extremely difficult to isolate, study and describe the function of each system separately. However, there are hints suggesting that adipose tissue self regulation might depend on partially dedicated pathways [39] which could exert harmful whole body effects when activated.

Adipokines can be interpreted in this sense, showing homeostatic functions at different levels. With regard to those best characterized [9], leptin and adiponectin, homeostatic interpretations can be put forward to describe their actions.

Leptin can be considered as a signal emitted by adipose tissue to inform the whole organism that there is “enough energy for living”. It is

anorexigenic, reduces intracellular lipids and improves insulin sensitivity (by limiting food intake), inhibits glucocorticoids and enhances T₄, sex and growth hormones. Conversely, in the absence of functional leptin or its signal due to a defective receptor, patients suffer from morbid obesity and lack of sexual maturation and growth [9].

Adiponectin modifies metabolism in a way that free fatty acids are withdrawn from the circulation, mainly towards fat depots [40]. It also increases fatty acid oxidation in skeletal muscle but promotes preferentially glucose utilization. It also reduces hepatic glucose production [9], resulting in a global increase in insulin sensitivity. Expression of adiponectin mRNA increases as preadipocytes differentiate and circulating adiponectin concentrations are reduced in obesity, diabetes mellitus and/or in IR [40,41], decreasing apparently when adipose tissue is repleted. It is not influenced by meals or fasting. Adiponectin can be interpreted as an adipostat sensing adipose tissue mass [40]. More probably it could represent a self-regulatory signal for adipose tissue capacity indicating "energy storage space available in adipose tissue, it is not necessary to redirect fat to other destinations".

Beyond the maintenance of adipose tissue equilibrium, adipokines also exert effects in the whole organism, being also partially responsible for metabolic changes in the liver and muscles. So far, every time a new adipokine has been identified, an increase in its levels or a resistance to its signal was suggested as the cause of the MetS (i.e. adiponectin [41], resistin [42], visfatin [43], etc.). Instead of that approach, an integrated physiological view of the substances produced by adipose tissue may yield more comprehensive information for treating and monitoring the syndrome.

Recently, adipose factors have been found to regulate vascular tone [44]. It is possible that there is also a vascular self regulation of adipose tissue. Adipose tissue blood flow increases consistently when it is metabolically active, either accepting fatty acids during the postprandial period or releasing them during long-lasting exercise or long fasting periods [40]. It seems that basal adipose blood flow is maintained by a basal nitric oxide production while vasodilatation in these vascular beds depends on β -adrenergic signals [45]. The increase in blood flow following feeding occurs before the plasma peak of triglycerides and parallel to insulin concentrations, but insulin is not the local signal involved [46]. Still, this vasodilatation is at least partially β -adrenergic dependent [45]. Local signals from adipose tissue could be responsible or small vessels regulation, conducting

postprandial blood flow to those depots capable of accepting lipids.

Adipose tissue function failure

A failure of the adipose tissue function in taking up dietary fat (being permanently switched to releasing free fatty acids) might lead to an excess of lipid flux towards other tissues, during the postprandial period and even during the fasting period, and to a decreased clearance of triglyceride rich lipoprotein particles [47]. Simultaneously, the increased availability of free fatty acids stimulates the liver, packaging them in triglycerides that are released in apoB-containing lipoproteins. The interaction of these particles with HDL and LDL lead to the typical dyslipidemic profile [48]. On the other hand, circulating fatty acids and those released by lipoprotein lipase modify the energy draining paths in peripheral tissues, impairing glucose use, as described before [36,37]. Excess of triglycerides begin now to be recognized as independent risk factors of CVD [49–52] and could contribute to the increased incidence of cardiovascular events in this disorder. Thus, we should consider the classic diabetic dyslipidemia, recently re-coined MetS dyslipidemia, as the main clinical manifestation of the adipose tissue failure.

Causes of adipose tissue function failure

Adipose tissue failure can be secondary or primary. In untreated type 1 diabetes [53,54], the lack of insulin is responsible for the adipose tissue dysfunction and in the polycystic ovarian syndrome, hormonal influences impair anti-lipolytic signals [55]. In lipodystrophy the amount of tissue itself is reduced [56], whereas the most common case of failure is due to an excess of demands that cannot be met by the tissue. In this later case, the limits between primary and secondary vanish, as we deal with the demands/capacity ratio. While in an obese individual, the excessive demands may be clearly the cause of the syndrome, some genetic contexts have already been described that impair adipose tissue capacity and favor the appearance of this disorder with only minor dietary transgressions [33].

Depending on the underlying mechanism that decreases adipose tissue clearance of plasma lipids, the cluster of clinical abnormalities might differ, because they depend on different metabolic pathways and counter regulation occurs at different levels (Fig. 3).

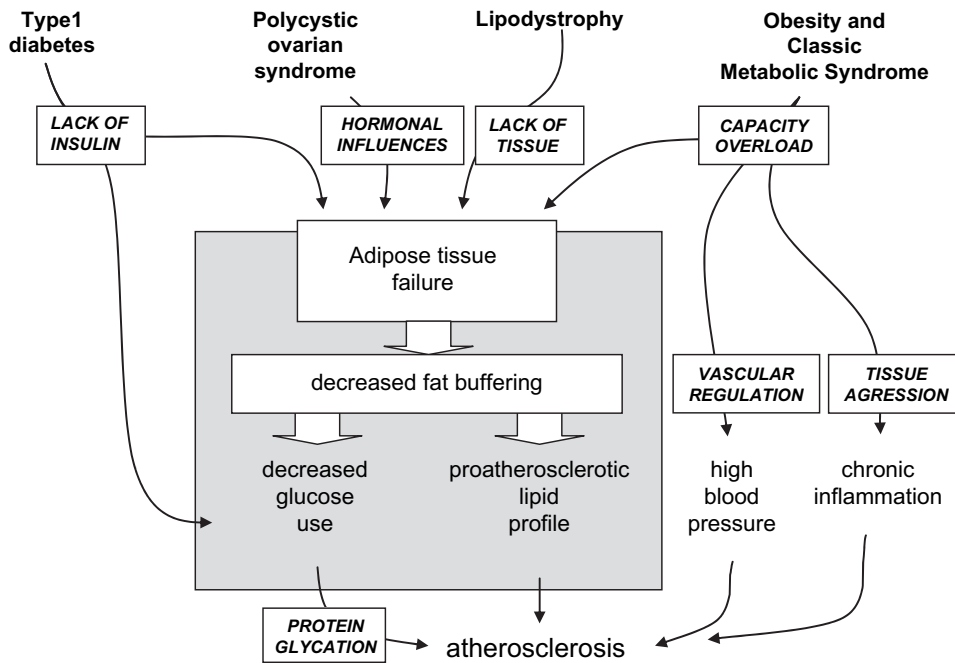


Figure 3 Causes of adipose tissue function failure. Several causes may differ in the final clinical manifestations.

Most problems in deciphering pathophysiology of the MetS arise from the fact that most symptoms appear together in most patients, making it extremely difficult to establish a causal order. It is even worse when patients with heterogeneous causes are taken together. We revise the most common cause and compare it with several other clinical situations with different origin and we try to explain these differences within our pathophysiological model.

Chronically inadequate energy balance

The most common situation of failure of the adipose tissue buffering function is in the context of the prototypic MetS in its current clinical definition. Excess of food, available in developed societies, creates a chronically inadequate energy balance (Fig. 4).

Etiology

The classical definition of function failure of an organ implies incapacity of the organ to meet the organism demands. This can be due to excessive demands, but also to an impaired buffering and storing capacity. One of the main periods of adipose tissue development occurs during the final months of gestation [57]. Hyperplasia of the tissue might have been impaired in patients with low weight at birth. This could explain why later on in life, the compensatory growth relies in abdominal fat accumulation [58] as a conserved depot and this early characteristic at birth is associated with the MetS and CVD in adulthood [59], as explained later on. Other genetic characteristics may also impair the adipose tissue capacity like proliferation limits [60] or variants of functional or structural proteins [33].

Still, it is reasonable to think that functional capacity (considering an average standard storing

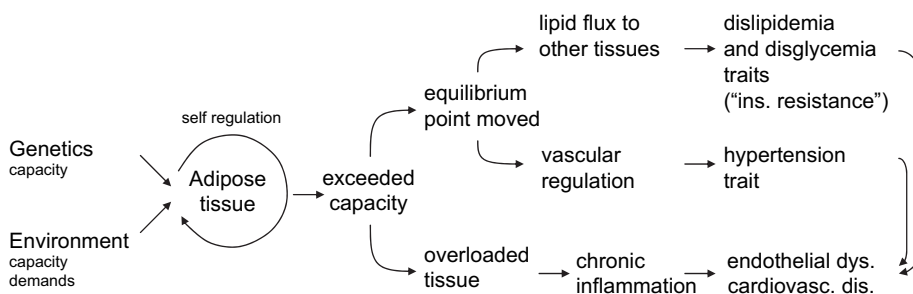


Figure 4 Adipose tissue failure in chronically inadequate energy balance. Our model fits here the manifestations of the most common type of metabolic syndrome.

capacity) is more likely to be reached among those who have more fat stored (overweight and obese), explaining the epidemiological association between the syndrome and obesity. Nonetheless, our approach explains the discrepancy between obesity and MetS, because it assumes that functional capacity is different among individuals.

Pathogenesis

Initially the excess of energy is sufficiently buffered and stored in adipose tissue, but some initial evidence of overload is already present. An increased production of apoB-containing lipoprotein particles that transport triglycerides to adipose tissue can produce an increase in LDL particles if adipose tissue achieves to maintain a fast conversion of the VLDL compartment to higher densities by extracting triglycerides from it. This way, newly secreted apoB can be rapidly shifted to the LDL-fraction [61]. We observed a remarkable transition of approximately 60 mg/dL increase in LDL-c for 20-year-old very fit lean men with optimal LDL-cholesterol levels (average body mass index 22.3 kg/m² and LDL-c: 74,5 mg/dL) after gaining an average of 12 kg of weight in 15 years [62]. This increase would be currently diluted in our population normal values, given that such high throughput towards adipose tissue is commonly seen and supported by the progressive weight gain with age [63].

Adipose tissue areas seem to differ in their main functions. All of them would share common properties and capacities but apparently, visceral fat is more active in terms of accepting and releasing free fatty acids [64,65]. This visceral fat is in a privileged situation for receiving fat input and releasing free fatty acids in a metabolically secured circulation. The liver processes the blood from this area [66] and thus the rest of the body is prevented from an excessive exposure to free fatty acids.

While massive energy storage takes place in subcutaneous adipose tissue, the buffering capacity of visceral adipose tissue is preserved, but when storage capacity of the former is exhausted, the visceral area is forced to take over and its buffering capacity is thus blunted. Individual and gender differences on subcutaneous fat capacity determine the moment in which energy starts to be stored in visceral fat [67]. Men, with an inferior subcutaneous fat storage capacity, determined by evolutionary requirements of reproduction biology [57], start to accumulate fat in the visceral depot far earlier than women [68]. So we may presume a sequential repletion of adipose depots that could explain the coincidence of increased visceral adiposity with the syndrome and the apparent

protection derived from subcutaneous (and mainly lower-body) increased deposits [29,30]. In fact, in obesity, whole body fat mass contribute to increased glucose uptake somehow compensating the "insulin resistance" effect [69]. Therefore, visceral obesity would be linked to the syndrome in a phenomenological but only partially causative way.

When adipose tissue capacity is surpassed by buffering demands, VLDL and similar particles conversion slows down and the patient shows the well known increase in triglyceride rich particles. Eventually, new surrogate storage depots are used for the excess of fat, like the liver and to a lesser extent skeletal muscle. Fatty liver disease further leads to steatohepatitis as a generic response of an overloaded system.

This approach is capable to explain the discrepancy between obesity and MetS, because it assumes that functional capacity is different among individuals, and also gives a reasonable interpretation of gender differences during women reproductive life. It also explains how it is possible that some increases of adipose tissue decrease the severity of the symptoms (i.e. virus induced).

Counter regulation

The multilayer nature of adipose tissue regulation implies that mechanisms at different levels are activated in order to keep adipose tissue homeostasis. At the same time, these might be responsible for an important part of the symptoms and potentially derive in the most harmful consequences of the situation.

Leptin, which is supposed to limit further fat storage by stopping food intake, is certainly raised in obese subjects. Similarly to the concept of IR, a situation of resistance to this hormone has been suggested as a possible cause of general obesity, but most probably the signal is overcome by external environmental and behavioral pressure instead of being the primary problem. In fact, addition of exogenous leptin achieved little improvement in their weight control or clinical situation.

After the first regulatory steps have been surpassed, a stressed tissue expresses a standard inflammatory response [70]. TNF- α and interleukin-6 are increased in obese patients. TNF- α is usually seen in cachexia-inducing states which to a certain extent may be seen as a search for recovery of balance. The response may be similar in other tissues accumulating fat (as a metabolic injury), like the liver, but in this case, chemo attractant factors are more powerful and can lead to steatohepatitis [71]. Chronic inflammation accounts for a misbalanced vascular and endothelial equilibrium and

probably contributes to the development of atherosclerotic disease, jointly with lipid disorders.

In obese patients, postprandial vasodilatation is blunted [46,72]. This could be related with impairment of insulin dependent vasodilatation, which is mediated mainly by nitric oxide. Nevertheless, as we mentioned before, vasodilatation depends on an adrenergic signal. Still, adrenergic tone is increased postprandially and even more in these hyperinsulinemic subjects but vasodilatation probably depends on one more step of signaling. Adipose factors regulating vascular tone [44] stop offering the lipid depot for storage during the postprandial period. Adiponectin levels decrease as blood pressure increases [41], which is consistent with this explanation and the interpretation of this adipokine shown above. The detailed mechanisms are not clearly established yet but it is a possible link to hypertension and other vascular alterations in the syndrome.

Similarities can be found between the MetS and other pathologies derived from overloaded organs that become insufficient (Fig. 5).

Other pathologies leading to adipose tissue failure

Some aspects of the prototypical MetS are not present when particular causes are involved. Some of the clinical characteristics described for the particular case of chronically inadequate energy balance depend on adipose tissue volume (adipokine production) and on regulatory responses of an overloaded tissue (vascular effects). Some of these characteristics depending on by-standing mechanisms do not appear in other similar pathologies. On the contrary, those symptoms dependent on fat storage failure, like dyslipidemia, apparent IR,

atherosclerosis and potential development of fatty liver disease are shared by all of them.

In type 1 diabetes, the lack of insulin is followed by the same typical dyslipidemia, due to the same mechanisms, but conversely, only 30% of people eventually develop hypertension [73]. Hypertension tends to develop after several years of the condition and usually reflects the development of diabetic nephropathy. The lack of insulin is itself responsible for the energy misuse in muscle, where uptake of both substrates, carbohydrates and lipids, is impaired. Insulin treatment, without an adequate dietary control, sometimes leads to an excessive fat deposition. The subsequent LDL cholesterol increase due to an important triglyceride rich particle conversion is thus often present [54].

In the same direction, lipodystrophies include dyslipidemia and IR in their presentation, but not hypertension. The intensity of the metabolic alterations depends on the extension of the affected tissues [56]. Levels of adipokines depend on the amount of remaining tissue. Leptin is low in lipodystrophy as the defect depends on absence of adipocytes. Its replacement helps the regulation of the energy intake and subsequently the metabolic control [56,74]. Other effects dependent on adipokines might not be present, but as autoimmune diseases, inflammatory markers might be raised due to other reasons. The tissue amount has certain importance. In fact, in common obesity, some amelioration of the syndrome has been reported after removal of visceral fat, probably due to a decrease in adipokines and inflammatory factors [75,76]. The improvement was partial and long term information is still not available. Adiponectin is also reduced in lipodystrophic subjects, and its administration reduced plasma glucose concentration, but independently of insulin levels [77]. The insulin sensitizing effect is

<u>Heart Failure</u>	<u>Adipose Tissue Failure</u>
<ul style="list-style-type: none"> • Overload: <ul style="list-style-type: none"> – (i.e.) High blood pressure • Function fails: <ul style="list-style-type: none"> – Pumping fails • Direct consequences (adaptation) <ul style="list-style-type: none"> – Tiredness and decreased activity • Counter regulation <ul style="list-style-type: none"> – Angiotensin, Catecholamines – Causes tachycardia... • Tissue suffering <ul style="list-style-type: none"> – Dilatation and fibrosis 	<ul style="list-style-type: none"> • Overload: <ul style="list-style-type: none"> – (i.e.) Dietary obesity • Function fails: <ul style="list-style-type: none"> – Buffering fails • Direct consequences (adaptation) <ul style="list-style-type: none"> – Substrate redirection (Insulin resistance) • Counterregulation <ul style="list-style-type: none"> – Insulin, Adipokines – Causes more obesity, dyslipidemia... • Tissue suffering <ul style="list-style-type: none"> – Chronic inflammation, atherosclerosis

Figure 5 Comparison of adipose tissue failure and heart failure. The reasoning applied is similar to that in other pathophysiological syndromes.

dependent on adiponectin capacity of reducing the plasma concentration of free fatty acids [77].

In the polycystic ovarian syndrome [78], hormonal influences could be changing the balance in the adipose tissue switch. In fact, a different mechanism has been suggested for impaired anti-lipolytic signals [55].

Molecular mechanisms involved

The state of the adipose tissue determining the direction of the lipid flow is dependent on cAMP intracellular levels. This messenger activates protein kinase A and 5' cAMP-activated protein kinase. Mainly protein kinase A phosphorylates the hormone sensitive lipase, activating it, and perilipin, which are proteins covering the lipid droplets of adipocytes, allowing translocation of the former into the lipid droplet [79].

An adrenergic signal, among others, via β -adrenergic receptors, increases the levels of cAMP. This is mediated by the coupling of the receptor with adenylate cyclase via the stimulatory G-protein [79].

Insulin receptor, on the contrary, activates phosphatidyl inositol kinase, and the increased levels of this second messenger, forces the action of protein kinase B-Akt that phosphorylates phosphodiesterase 3B that catabolizes cAMP leading to the anti-lipolytic action of insulin [45].

Very recently, some Fatty Acid-Binding Proteins (FABP) have appeared as a molecular link that limit adipose tissue when metabolically overloaded. FABP4 (aP2) and FABP5 (mal1) have to be present in leptin deficient mice to develop IR, type 2 diabetes and hepatosteatosis [39]. At the same time FABP deficient mice increased their weight even more than controls. Interestingly, FABP are also crucial in inflammation pathways [80], eventually activating kinases JNK and IKK. At the same time, these kinases phosphorylate the insulin receptor substrate, diminishing insulin signal transduction [81]. PPAR γ activation inhibits expression of nuclear factor κ B and promotes the expression of lipid-conserving genes in the adipocyte [82]. It is proposed that FABP sequesters some fatty acids that are actually ligands for PPAR γ activation [81].

Genetic factors

Variation at genes coding for proteins on the above described pathways might explain part of the clinical uncoupling between obesity and the MetS. Currently, SNPs on the adiponectin gene

have been widely studied in relation with MetS. Besides, the perilipin gene is emerging as a potential major player for obesity and other metabolic traits. Moreover, the later has also been shown to modulate the response of MetS traits to diet modifications [33]. Below we summarize some of the most relevant findings regarding these two important loci. Many other loci could be discussed, and their numbers are continuously increasing. A recent example is the association between *FABP4* and the MetS only among obese subjects [83]. However, space limitation precludes a comprehensive description of all the candidate genes for the MetS.

Adiponectin

Adiponectin plasma concentrations have been associated with each of the components of the MetS including insulin sensitivity and glucose homeostasis, obesity, hypertension and dyslipidemia. Once this was clearly established, a great emphasis was placed on determining the factors involved in its regulation. The existence of a genetic component of adiponectin levels was defined with heritabilities estimated in the range of 40–70% [84]. Several whole genome scans were carried out to identify specific loci and their results have not been consistent: Peaks on chromosomes 5 (close to D5S817) and 14 (between D14S608 and D14S599) in Northern Europeans [84], on chromosome 9p (between D9S168 and D9S925) in non-diabetic Pima Indians [85], on chromosome 15 (near GATA63A03) in Chinese [86], on chromosome 18 (near ACT1A01) in Japanese [86] and on chromosome 11 in Hispanic children [87]. Although some of the scans provided signals on Chromosome 3, where the adiponectin gene (*ADIPOQ*) is located, all of them were of minor intensity. More recent genome scans have linked 3q27 with adiponectin levels. However, whereas in the Amish population the link was explained by variation in *ADIPOQ* [88], in a Hispanic-American population it appeared to depend on variations of the *ADIPOQ* gene [89].

The region where *ADIPOQ* maps, 3q27, showed linkage with type 2 diabetes and the MetS. This has stimulated the search of variations of this gene related to adiponectin levels and to traits of the syndrome. The *ADIPOQ* gene contains three exons within a region of 17 kb and multiple genetic variations have been reported. Recently, Heid et al. [90] have published a detailed genetic architecture of this gene in Caucasians using 18 tag SNPs that revealed a complex two-block linkage disequilibrium (LD) structure. The associations between some of the *ADIPOQ* polymorphisms and MetS-related

phenotypes have been the subject of several recent reviews [91,92].

Whereas the relation between adiponectin plasma concentrations and the presence of the major metabolic disorders is well established, the evidence linking the *ADIPOQ* gene locus with adiponectin levels, metabolic syndrome traits and prevalence of CVD is still conflicting. The 276G>T (rs1501299) and 45T>G (rs2241766) SNPs have been the ones most studied, whereas other population specific SNPs have also revealed interesting associations.

The minor T allele at the 276G>T polymorphism in intron 2 has been significantly associated with higher plasma adiponectin concentrations with some level of consistency [91]. Still, in French Caucasian subjects from the IR Syndrome (SAFIR) cohort, no differences were found in adiponectin levels across 276G>T genotypes [93]. More discrepancies exist among studies examining MetS-related traits (obesity, hypertension, glucose levels, insulin resistance, dyslipidemias). Both alleles have been associated with metabolic profiles of increased risk in different populations, although a trend is emerging showing that homozygosity for the minor T allele tends to associate with better metabolic profiles. The 276T minor allele was significantly associated with lower fasting glucose and HOMA-IR in Korean subjects [94], with lesser T2DM risk in Japanese [95] and with lower risk of coronary artery disease among Italian [96] and American [97] diabetic subjects. Other studies carried out by Lacquemant et al. [98] in France and by Ohashi et al. [99] in Japan did not find significant association between the 276G>T polymorphism and risk of CVD. Conversely, Filippi, et al. [100], in a large case-control study, found that the 276G>T polymorphism was associated with lower adiponectin levels, worse clinical profile and increased coronary artery disease in Italian subjects.

This controversial situation is even more marked for the 45T>G polymorphism, consisting of a synonymous mutation in exon 2 (Gly15Gly). Although no significant association between the 45T>G polymorphism and adiponectin concentrations was reported in numerous studies, Berthier et al. [101] in Quebec and Vasseur et al. [102] in France reported a significant association between the G minor allele and lower adiponectin concentrations. Conversely, Heid et al. [90] found a significant association between the G minor allele and higher adiponectin concentrations in German subjects. With respect to the MetS traits, and presence of CVD, homozygosity for the major T allele seems to be protective [95,103], but there are also studies supporting the opposite conclusion [104].

Fumeron et al. [93] found that the G minor allele was associated with weight gain in a large cohort (SAFIR) of French Caucasians. Zacharova et al. [105] reported that in the STOP-NIDDM cohort the G minor allele was associated with weight gain, especially in men in the placebo group, and homozygosity for the T allele was associated with weight loss with acarbose, especially in women. However, others have not been able to replicate these findings [100,106].

The 45T>G and the 276G>T polymorphisms are found in negative linkage disequilibrium, which is higher in Caucasian populations. Statistically higher adiponectin concentrations have been found in association with the TT haplotype (having TT at both 45T>G and 276G>T polymorphisms) in comparison with the GG haplotype [107]. Accordingly, in Korean subjects [94], homozygous subjects for the TT haplotype showed significantly lower IR than did carriers of other haplotypes. Similarly, Menzaghi et al. [108] reported that, in non-diabetic subjects in Italy, carrying the TG haplotype was associated with higher mean fasting plasma glucose. The situation described for these two SNPs exemplify the controversial status of other polymorphisms in the adiponectin gene.

Overall, it seems that the locus may be related with a cluster of phenotypes spanning plasma adiponectin levels, abdominal obesity and risk of T2DM and coronary heart disease but this evidence is not unanimous [89]. The final outcomes might depend on very distant mechanisms of the homeostatic system. In fact, it is really difficult to capture differences in the highly regulated system described previously, keeping also in mind that there are other relevant factors (i.e., diet) that may modulate these associations. To illustrate this point, Berthier et al. [101] have suggested that the effect of the 45T>G polymorphism in different populations may be modulated by abdominal obesity.

Perilipin

In the late 1980s, Londos' laboratory first identified a heavily PKA-phosphorylated protein that was named as perilipin (*PLIN A*), resulting from its physical location surrounding lipid droplets [109]. Interestingly, *PLIN* was only found in adipocytes and in steroidogenic cells [110]. These cells [111,112] possess intracellular neutral lipid storage deposits that are metabolized by hormone sensitive lipase (HSL) in adipocytes and by cholesterol esterase in steroidogenic cells. As we described earlier, *PLIN A* plays a critical role in the hydrolysis of neutral lipids. The perilipin gene (*PLIN*) has

been assigned to the chromosomal location 15q26, near a previously reported susceptibility loci for obesity and insulin-dependent diabetes mellitus. This gene generates four different products (Perilipin A, B, C and D) due to differential splicing.

In agreement with functional studies in cultured cells, perilipin knock-out mice showed that the absence of perilipin results in leanness, increased basal lipolysis, enhanced leptin production, resistance to diet-induced obesity [32] and reversed obesity in a genetic model of obesity caused by leptin resistance [113]. They also present an increased risk of glucose intolerance and peripheral IR [32]. Increased leptin and metabolic disorders are consistent with demands surpassing the limits of a reduced functional range of the adipose tissue in accordance with our proposed model. These data suggest that the *PLIN* gene may have a role in modulating adipose tissue functions in humans.

We have investigated the association of various *PLIN* polymorphisms with measures of obesity, lipid metabolism and insulin sensitivity in independent samples of Caucasian and Asian subjects [114–118]. In normal subjects from a Mediterranean Spanish population [114] we have reported that *PLIN1*:6209T>C (rs2289487) and *PLIN4*:11482G>A (rs894160) polymorphisms, in introns 2 and 6, respectively, were significantly associated with lower body mass index in women. Carriers of the rare allele C at the *PLIN1* locus (6209C) weighed significantly less (-2.2 kg) than women homozygous for the wild-type genotype. The same was true for the rare allele A carriers at *PLIN4* (11482A). Moreover, the *PLIN4* variant was associated with significantly lower waist-to-hip ratio, plasma glucose, and triglyceride concentrations in these normal weight subjects. In addition, *PLIN1* and *PLIN4* variants were associated with a lower obesity risk in women [114]. Moreover, in this Mediterranean population, we have reported that the *PLIN4*:11482G>A polymorphisms interacts with a low-energy diet in determining body-weight [115]. Thus, obese patients who completed a 1-year low-energy diet treatment presented significant decreases in body weight (from 114.3 ± 3.9 kg at baseline to 105.5 ± 3.5 kg at 1 year) only in homozygosity for the G allele. Conversely, carriers of the minor A allele did not show significant changes in body weight [115]. It seems that the variant allele results in more resistance to both store and/or mobilize fat. Furthermore, *PLIN* variation also determines higher susceptibility to IR in Asian women when consuming a high-saturated fat, low-carbohydrate diet [33]. This confirms that under chronic dietary stress, the subjects with the variant allele present a worse metabolic response, proving

that in humans, this genetic variability is related with changes in adipose tissue functional capacity, which are only expressed when an excess of work stresses the system.

Conclusions

The model that we have proposed here addresses some inconsistencies of previous global explanations of the MetS. It has the advantage of providing a frame to incorporate future knowledge on the physiological function of the proteins before addressing their role in the disease. It has the limitation that so far there are no biomarkers that could report on the functional capacity and state of repletion of the adipose tissue. Adiponectin levels could belong to one of those sets of biomarkers. Additional development of functional tests on total capacity/functional residual capacity of individuals can result from current studies on postprandial fat curves and glycerol levels suppression by insulin doses.

The emphasis on functional capacity over amount of adipose tissue may resolve some of the current controversial definitions of the MetS such as the use of waist circumference and/or obesity as a necessary criterion for MetS diagnosis.

With respect to the treatment of the syndrome, this view suggests that while low fat diet may be effective in improving symptoms on some subjects, a low-energy diet would be the only etiological treatment. Treatment should focus on subjective perception of hunger as currently being addressed by Rimonabant, a cannabinoid receptor type 1 blocker used for management of multiple cardiometabolic risk factors [119]. Looking into future treatment possibilities we could hypothesize drugs capable of inducing lipolysis in a clinically and metabolically secured setting (perhaps apheresis) that could rehabilitate fat deposits, requiring diet care afterwards to prevent reappearance of the disease. We must reflect on the fact that current drugs, like glitazones, aim toward the opposite, getting adipose tissue to continue accepting more lipids beyond its own self-regulating limits. While this approach certainly achieves a symptomatic relief of problems we hope for the time when an etiological treatment of the syndrome is available.

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