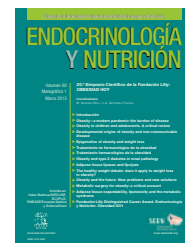


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20.º SIMPOSIO CIENTÍFICO OBESIDAD HOY

Adipose tissue expandability, lipotoxicity and the metabolic syndrome

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Whereas it is clear that obesity is a cardiovascular risk factor, the mechanisms linking expansion of the adipose tissue (AT) to these co-morbidities is uncertain. We think that inappropriate AT expandability and function is a key determinant of obesity-associated metabolic complications by initiating a lipotoxic proinflammatory cascade that affects essential metabolic organs. Thus, understanding the mechanisms that control AT expansion and function may provide therapeutic approaches to optimise adipose lipid deposition and prevent lipotoxic events. Similarly, understanding of the organ specific lipotoxic effector mechanisms may provide the rational for lipid related biomarkers as well as for personalised therapeutic advice to maintain energy homeostasis despite obesity.

Introduction

Obesity is emerging as one the most important public health problems. Despite the new scientific discoveries elucidating the mechanism controlling energy balance and implementation of governmental policies to control its development, the prevalence of obesity is progressively increasing. More worryingly, there is no indication that current strategies may solve the problem in the near future. This, together with the realisation that pharmacotherapy has failed to deliver a long term solution leaves us with a glum perspective for the future. Although obesity per se causes human sufferance and social stigma, it is its associated metabolic complications, including diabetes, cardiovascular events and its association with increased susceptibility to cancer and neurodegenerative diseases that is threatening to

become the second wave of the obesity tsunami. For this reason we think it is important to be prepared to minimise the impact of these upcoming devastating diseases.

When addressing the problem of obesity there are two fundamental questions. The first directly relates to the mechanisms of energy balance and more specifically aims to identify the mechanisms of their dysregulation leading to obesity. It is clear that obesity results from positive energy balance determined by a combination of excess food intake and decreased energy expenditure resulting in excessive nutrient availability which is deposited in the AT, a specialised organ for storage of energy and mobilisation of resources if and when needed. This is an apparently simple concept. In fact, it is easy to understand that obesity is the result of eating more than we spend and intuitively it may appear that the easy solution is to eat less and spend more. However, being simple does not equate to being easy. From accumulating genetic evidence it seems that multiple genetic defects affecting the central nervous system function and more specifically the mechanisms controlling food intake may be involved. It is also clear that the human genome has not changed in the last 50 years (period where the prevalence of obesity has markedly increased), and that important environmental factors related to nutrient composition and availability, sedentary habits, psychological stress and the involvement of complex systems of reward may play important roles. This, together with robust adaptive allostatic systems attempting to maintain a specific set point of energy balance and the evidence that defects in these systems preferentially result in activation of pathways that save energy, makes the control of energy balance an impossible task with the current available strategies.

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Solving this simple but difficult problem is likely to take longer than we may afford and for this reason, and while many other groups are investing their efforts in addressing the pathogenesis of the obesity problem, we feel that we need to focus on the second fundamental problem. This is to understand the link between the expansion of the AT that defines obesity and the development of cardiometabolic complications. At the present moment we do not understand why accumulating fat should cause diabetes, atherosclerosis, heart attacks or hypertension. More elusive is the link with a growing spectrum of pathologies associated to obesity, including specific type of cancers, neurodegeneration and even increased susceptibility to psychiatric disease. The realisation of the clustering of these pathologies in specific individuals cannot be explained by random association of events. In fact, it can be speculated that these pathologies may have some common pathogenic mechanisms that may exacerbate the genetic vulnerability recognised in some of these pathologies. This commonality has been recognised and has led to the integration of some of these pathologies under a common umbrella named the metabolic syndrome (MetS) (Fig. 1). There is a debate whether this concept represents a real pathogenic entity or not and whether it is of any use. In our opinion, this concept represents a good tool to help in the diagnosis and management of these patients and fuels research into the common pathogenic mechanisms of these concepts; however it is clear that its intrinsic heterogeneity decreases its usefulness until a better understanding of its specific nosological entities is refined.

Lipotoxicity as a link between obesity and metabolic syndrome

Integrating the knowledge that we and others have generated over the years, we consider the MetS as a toxic syndrome determined by a state of overnutrition. We think the manifes-

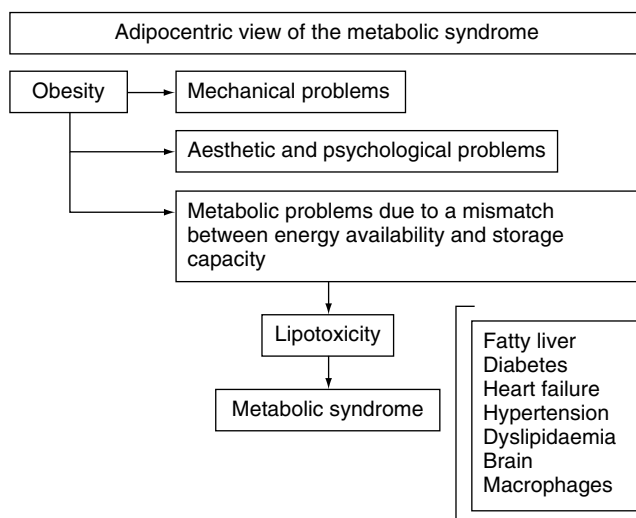


Figure 1 Adipocentric point of view of the metabolic syndrome. Concept of lipotoxicity induced by the mismatch between adipose tissue storage capacity and nutrient availability as the link between obesity and metabolic complications.

tations of the MetS are the result of a conflict between excessive nutrient availability in the form of lipids and/or other forms of complex nutrients accumulated in metabolically relevant organs different from AT, and the genetic make up of these specific organs that determine their genetic vulnerability/resilience to the nutritional insult. This may explain the puzzling observation that obese individuals develop heterogeneous forms of MetS and may justify the existence of individual phenotypes within the whole spectrum of the MetS. Our model of the MetS departs from the concept of lipotoxicity, defined as the toxicity associated to ectopic accumulation of lipid species in organs such as muscle, liver, heart, kidney, macrophages or even in the hypothalamus. However, when considering this lipotoxic model, there are some fundamental questions that need to be addressed. For example, it is unclear what determines the accumulation of lipids in these organs, how accumulation of lipids relate to the inflammatory phenotype typically associated with the MetS, and how the understanding of this model may be used to develop antilipotoxic strategies and useful biomarkers of metabolic risk.

Adipose tissue expandability and the MetS

The safest place to store energy is to accumulate it in the form of lipids in the AT, and organs designed to fulfil this storage mission. It is assumed that the AT can expand as much as necessary to cope with the demands of nutrient storage and in fact this may have been the case for many years when obesity was not a problem. However, now, when the prevalence of obesity is high, is when the AT is under more pressure to expand and when the genetic make up that enables AT expansion is most challenged. Thus, our point of view is that the problem of obesity associated complications may not be determined by the absolute fat mass but by the inability of the AT to fulfil its storage mission beyond a specific maximal threshold defined by genetic and environmental factors. Obviously, in those individuals with more positive energy balance, more fat mass and increased storage demands, it is more likely that the specific threshold for expansion and function may be surpassed. This will explain the epidemiological link between fat mass and insulin resistance. This concept of a specific individual threshold could also help to explain the outer layers, the clinical evidences that some very obese individuals maintain very healthy metabolic profiles despite the increased fat mass and conversely that some relatively leaner individuals have inappropriately unhealthy metabolic profiles. In summary, we think that the metabolic complications of obesity occur not because of the excess fat mass but the inability to further expand their AT and in some way become more obese.

What are the determinants of adipose tissue expandability? (Fig. 2)

If we depart from the concept of a threshold limit to AT expansion and function, a key question is what the determinants of this threshold are and whether we can predict the threshold. This is a difficult question because the

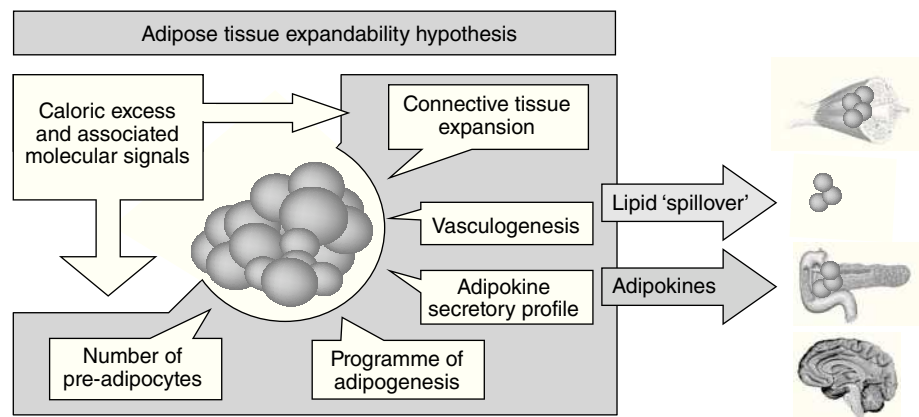


Figure 2 Factors controlling adipose tissue expandability and their link with peripheral metabolic complications.

threshold depends on intrinsic AT related factors that control storage capacity and their interaction with mechanisms controlling food intake and energy expenditure that define the AT demands. This means that the same AT storage threshold may or may not be associated with metabolic disease depending on the nutritional load determined by the balance between energy intake and energy dissipation.

With respect to the AT intrinsic factors, this threshold may be affected by the number of precursor of adipocytes and by the specific genetic programme that defines adipocyte differentiation and the capacity for membrane lipid remodelling. However, adipocytes are not the only type of cells present in the AT. Adipose tissue expandability and function may also be affected by the vascularisation acting as a limiting factor for nutrient availability, mobilisation of lipids and washing of toxic metabolites. Similarly the extracellular matrix may be an important determinant of the AT capacity for expansion. The AT also includes immune cells, such as macrophages and lymphocytes. The function of these immune cells in AT is debated but we and others have proposed that one of the physiological roles of AT macrophages is to clean up lipids spilled in the context of physiological dynamic mobilisation of lipids and also contributing to the remodelling of the AT required for physiological expansion of the AT under conditions of positive energy balance. However accumulation of macrophages in AT may also play a key pathophysiological role in the context of the MetS, particularly when pathologically overloaded with lipids (see below) and polarised towards an M1 pro-inflammatory phenotype. On top of these factors, environmental/nutritional components may also introduce an epigenetic component that may affect the threshold.

What is the role of Inflammation in the adipose tissue expandability model? (Fig. 3)

Obesity associated metabolic complications is associated with a state of subclinical chronic inflammation which has been identified as the pathogenic link between obesity and MetS. Indeed there is evidence that obesity induced insulin resistance is associated with macrophage infiltration in AT and qualitative and quantitative alterations in AT adipokine secreted proteins that contribute to inflammation. In our

opinion there is no conflict between the AT expandability model and the involvement of inflammatory mediators playing an important pathogenic role. It is clear that inflammation per se cannot be the cause of obesity and AT expansion. In some way this inflammatory response acts as a limit to the expansion of the AT by causing insulin resistance. Based on this we could comfortably assume that the inflammation occurs secondary to positive energy balance and increased AT pressure to expand. In this respect inflammation is an effector of the failure of the AT and may cause metabolic complications but it is unlikely to be the first hit initiating the inflammatory response in the context of obesity. It is also perfectly assumable that once AT inflammation occurs, this will elicit a second hit on the adipose systems preventing further expansion of the AT, further exacerbating the failure of the AT configuring a feed back forward vicious cycle. In summary we think the AT expandability model provides a valid intellectual framework to understand the MetS and its inflammatory reactivity on the basis of a primary defect in AT functionality beyond a maximal threshold of expansion.

Peripheral effectors of lipotoxicity induced MetS and their diagnostic/therapeutic implications

Once the AT fails to store fat effectively, the excess of lipids ends up in other metabolic organs which are not purposely designed for this storage function. This results in development of fatty liver, lipotoxic induced beta cell failure and skeletal muscle induced insulin resistance. Accumulating evidence also suggests that this lipotoxic effect may also lead to lipotoxic macrophages and inflammatory responses which altogether contribute to the MetS. Several related concepts are relevant to understand the lipotoxic process and to take diagnostic and therapeutic advantages. Specific mediators of the toxic effects of lipids have been identified. This includes specific reactive lipid pathways involving ceramides and or diacylglycerols that affect insulin signalling nodes and confer a state of insulin resistance. Ectopic accumulation of lipids also activate stress responses such as endoplasmic reticulum stress, autophagia, reactive oxygen species production, stress signalling cascades that ultimately

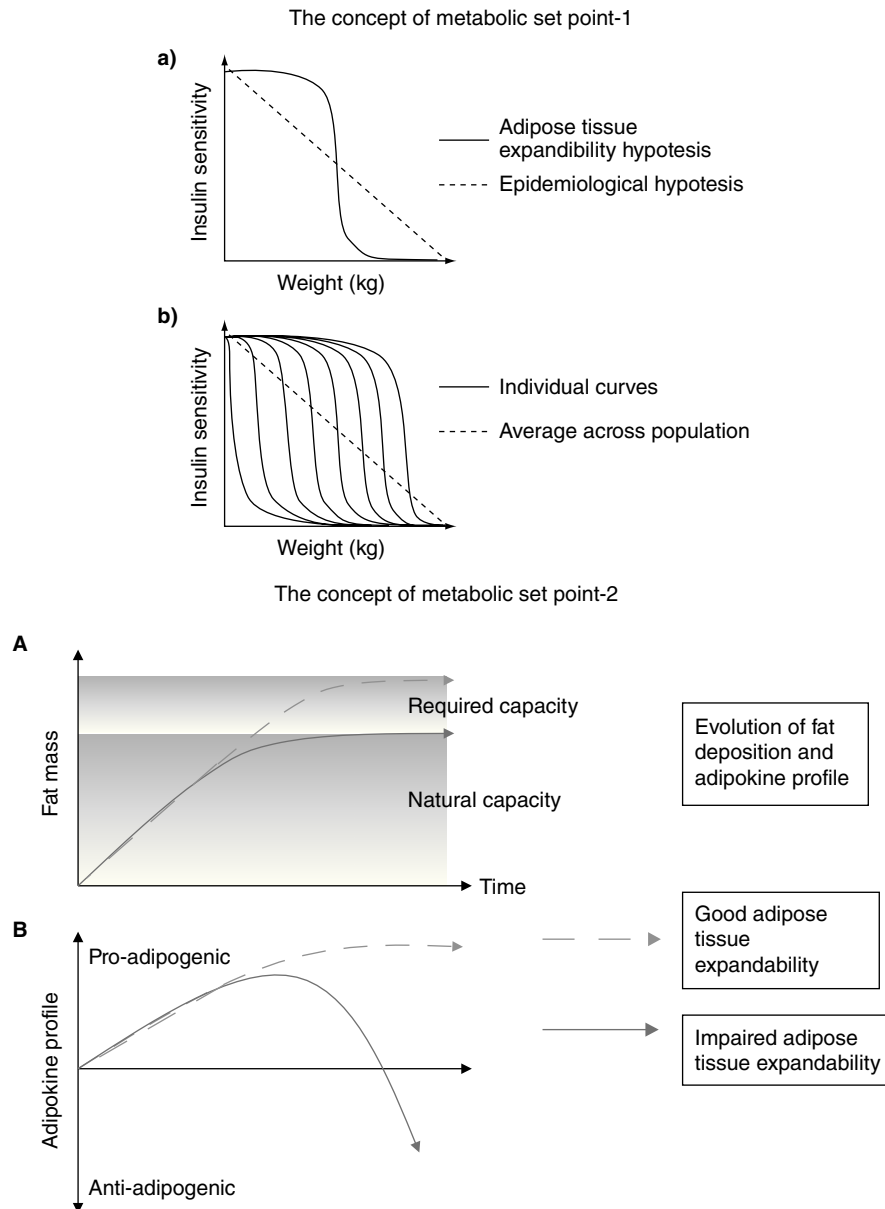


Figure 3 A) Concept of metabolic set point (I). Once an individual reaches their maximal adipose tissue mass, then metabolic complications ensue, suggesting that individuals would go from metabolically normal to metabolically compromised in a relatively small weight window. B) Concept of metabolic set point (II). Evolution of fat deposition and adipokine profile in individuals with adequate or impaired adipose tissue expandability.

cause cellular dysfunction and a specific phenotype depending on the targeted cell. On the basis of this knowledge, strategies targeting inflammatory/stress pathways have been suggested. In our opinion, the main problem with these strategies is that they tend to be too reductionists and fail to consider the more global nature of the toxicity problem as well as aspects such as redundancy, multiplicative, amplifying effects and adaptive compensatory responses that escape highly targeted strategies. The success of these targeted approaches requires identifying important hierarchical nodes of control that can affect global pathways. Alternatively, targeting of very late effectors in the toxic response is in our opinion unlikely to elicit a global beneficial effect. Thus to solve this problem it is fundamental to

understand the pathways involved in the lipotoxic reaction, their interactions and their hierarchy, a challenge that requires systems approaches.

Another aspect that may have potential therapeutic and diagnostic implications is the fact that the toxic effect of lipids may to a certain extent depend on the organ considered. This concept refers to the intrinsic characteristics of a specific cellular type with respect to how it handles lipids, its vulnerability and resilience to the toxic effects of lipids. If different organs/cells have different lipid networks this may justify their different vulnerability and the specificity of the disease phenotypes in the context of the heterogeneity of the MetS. Identifying these differences may provide some advantages: a) it may help to identify individuals at

higher and lower risk of developing specific pathologies; and b) it may help to design individualised therapeutic approaches that avoid their more vulnerable systems at the expense of making extensive use of their strongest adaptive systems.

A key challenge in clinical medicine is to identify those obese individuals that are more vulnerable or more resilient to metabolic disease before clinical evident signs emerge. This has enormous implications not only for the quality of life of these individuals but also for the budget of national health systems. In this respect finding diagnostic and predictive biomarkers is essential. Our model provides the rationale to consider a lipid related marker/signature a good candidate to identify those individuals in whose AT is failing and are developing organ specific lipotoxic insults. In an ideal scenario and assuming that there are truly organ specific lipid networks peculiarities, we can conceive that some of these signatures may not only inform of a global lipotoxic stress but may also inform about organ vulnerability, information which may be of enormous help for patient stratification and personalised therapeutic advice.

In summary, we think that inappropriate AT expandability and function is a key determinant of obesity associated metabolic complications by initiating a lipotoxic proinflammatory cascade that affects important metabolic organs. Understanding of the mechanisms that control AT expansion and function may provide therapeutic approaches to optimise adipose function and prevent lipotoxic events. Similarly, understanding of the organ specific lipotoxic effector mechanisms may provide the rationale for lipid

related biomarkers as well as for personalised therapeutic advice to maintain energy homeostasis despite obesity.

Conflicts of interest

The author declares that he has no conflicts of interest in this article.

Recommended references

- Carobbio S, Rodríguez-Cuenca S, Vidal-Puig A. Origins of metabolic complications in obesity: ectopic fat accumulation. The importance of the qualitative aspect of lipotoxicity. *Curr Opin Clin Nutr Metab Care*. 2011;14:520-6.
- Hagen RM, Rodríguez-Cuenca S, Vidal-Puig A. An allostatic control of membrane lipid composition by SREBP1. *FEBS Lett*. 2010;584:2689-98.
- Sørensen TI, Virtue S, Vidal-Puig A. Obesity as a clinical and public health problem: is there a need for a new definition based on lipotoxicity effects? *Biochim Biophys Acta*. 2010;1801:400-4.
- Tan CY, Vidal-Puig A. Adipose tissue expandability: the metabolic problems of obesity may arise from the inability to become more obese. *Biochem Soc Trans*. 2008;36:935-40.
- Vidal-Puig A, Unger RH. Special issue on lipotoxicity. *Biochim Biophys Acta*. 2010;1801:207-8.
- Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome--an allostatic perspective. *Biochim Biophys Acta*. 2010;1801:338-49.
- Virtue S, Vidal-Puig A. It is not how fat you are it is what you do with it that counts. *PLoS Biol*. 2008;6:237.