ORIGINAL ARTICLE

Adipose tissue infiltration in normal-weight subjects and its impact on metabolic function

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Discordant phenotypes, metabolically healthy obese and unhealthy normal-weight individuals, are always interesting to provide important insights into the mechanistic link between adipose tissue dysfunction and associated metabolic alterations. Macrophages can release factors that impair the proper activity of the adipose tissue. Thus, studying subcutaneous and visceral adipose tissues, we investigated for the first time the differences in monocyte/macrophage infiltration, inflammation, and adipogenesis of normal-weight subjects who differed in their degree of metabolic syndrome. The study included 92 normal-weight subjects who differed in their degree of metabolic syndrome. Their anthropometric and biochemical parameters were measured. RNA from subcutaneous and visceral adipose tissues was isolated, and mRNA expression of monocyte/macrophage infiltration (CD68, CD33, ITGAM, CD163, EMR-1, CD206, MerTK, CD64, ITGAX), inflammation (IL-6, tumor necrosis factor alpha (TNFα), IL-10, IL-1b, CCL2, CCL3), and adipogenic and lipogenic capacity markers (PPARgamma, FABP4) were measured. Taken together, our data provide evidence of a different degree of macrophage infiltration between the adipose tissues, with a higher monocyte/macrophage infiltration in subcutaneous adipose tissue in metabolically unhealthy normal-weight subjects, whereas visceral adipose tissue remained almost unaffected. An increased macrophage infiltration of adipose tissue and its consequences, such as a decrease in adipogenesis function, may explain why both the obese and normal-weight subjects can develop metabolic diseases or remain healthy. (Translational Research 2016;■:1–12)

Abbreviations: ATMc = adipose tissue monocytes/macrophages; MH = metabolically healthy; MU = metabolically unhealthy; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; MHO = metabolically healthy obese

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AT A GLANCE COMMENTARY

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Background

Discordant phenotypes study is crucial in the fight against obesity. Discordant phenotypes help to the understanding of obesity pathophysiology. Metabolically healthy obese individuals have paid a huge attention, whereas their lean counterparts have not received as much attention. This manuscript deals for the first time with the differences in macrophage infiltration between metabolically healthy and unhealthy normal-weight subjects, finding a greater infiltration in subcutaneous adipose tissue of metabolically unhealthy normal-weight subjects.

Translational significance

The importance of the visceral adipose tissue paradigm is revised. Subcutaneous adipose tissue fails before visceral adipose tissue, even before of an overweight/obesity degree, indicating body mass index is not the most relevant variable for metabolic function.

INTRODUCTION

Obesity has been related to a process of low-grade inflammation or metainflammation[1] leading to chronic activation of an innate immune response.[2] Adipose tissue has been recognized as a key regulator of energy balance, playing an active role in lipid storage. The inflammatory response is one of the main factors associated with obesity-related complications. A key feature of obesity-induced inflammation in the adipose tissue is the recruitment of immune cells, specifically macrophages.[3] Obesity is associated with increased macrophage infiltration in adipose tissue.[4] Thus, although the adipocyte is the defining cell in the adipose tissue, contributing to the production of inflammatory molecules, it appears that macrophages also contribute substantially to the inflammatory signals induced by obesity.[4] Furthermore, macrophages can release factors that impair adipogenesis, thus predisposing to adipocyte hypertrophy and its consequences.[5] This is the case in obese patients with metabolic disorders, in whom a decrease has been demonstrated in the lipogenic capacity of the stromal mesenchymal cells from the adipose tissue.[6] Thus, the content of adipose tissue monocytes/macrophages (ATMs) appear to contribute critically to the metabolic syndrome and other complications of obesity.

A paradoxical but common finding in the obesity clinic is the identification of individuals who can be considered "inappropriately" healthy for their degree of obesity, with a degree of adipose tissue inflammation similar to that of normal-weight subjects,[7] known as metabolically healthy obese (MHO) individuals. The opposite phenomenon, normal-weight individuals who have metabolic disorders usually associated with obesity, was first suggested by Ruderman et al,[8] although previous studies suggested that normal-weight individuals with the metabolic syndrome were not rare in the general population.[9,10]

Adipose tissue located in the viscera (VAT) is considered to be functionally and metabolically different from that found in the subcutaneous depot (SAT).[11,12] Traditionally, VAT has been associated with the risk of metabolic and cardiovascular disease.[13,14] Inflammatory cells such as macrophages are known to be more prevalent in visceral fat compared with subcutaneous fat.[15] Macrophage functions are shaped in a very tissue- and signal-input specific manner, allowing these cells to develop extremely specific functional programs. Accepting higher complexity of macrophage activation opens new avenues toward understanding and modulating these cells in disease settings.[16]

The factors determining "healthy" vs "unhealthy" in normal weight and obesity remain ill defined. Discordant phenotypes are always interesting to provide important insights into the mechanistic link between the adipose tissue dysfunction and associated metabolic alterations.[17] In this study of VAT and SAT, we investigated for the first time the differences in monocyte/macrophage infiltration, inflammation, and adipogenesis of normal-weight subjects who differed in their degree of metabolic syndrome.

MATERIALS AND METHODS

The study included 92 normal-weight subjects (body mass index [BMI] $\leq$ 25), classified according to their degree of metabolic syndrome, as defined by the Adult Treatment Panel IV criteria, into the 2 groups: metabolically healthy normal-weight (MH) subjects with 2 criteria or less for the metabolic syndrome; and metabolically unhealthy normal-weight subjects (MU) who fulfilled 3 or more criteria for the metabolic syndrome. Patients were excluded if they had cardiovascular disease, arthritis, acute inflammatory disease, infectious disease, renal disease, or were receiving drugs that could alter the lipid profile or the metabolic parameters at the time of inclusion in the study. The study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki. All participants gave their written informed consent and the