

Anatomical, Histological and Metabolic Differences Between Hypodermis and Subcutaneous Adipose Tissue

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Abstract

The development of treatments using stem cells has drawn the attention of researchers to fat deposits given the fact they represent an almost unlimited reservoir of such cells, which can be accessed through minimally invasive techniques. However, the standardization of these studies has been made difficult because of the controversies of nomenclature regarding the many components of adipose tissue. Despite their distinct and independent structures with different metabolic responses, the terms hypodermis and subcutaneous adipose tissue are many times used as synonyms. However, the correct distinction between these two layers, the knowledge of their behavior and an uniformity of these terminologies are of utmost importance.

Thus, the purpose of this study was to make a bibliographic review on the theme, aiming to show the anatomical, histological and metabolic differences between these two tissues and standardize their nomenclature.

Introduction

Autologous adipose tissue has an unlimited amount of stem cells that can be easily accessed by minimally invasive techniques, and recently have been widely studied and included in new technology development models.

A rising number of experimental studies has shown the neoangiogenic and immunomodulatory potentials of adipose stem cells, promoting their use in the therapy of ischemic and autoimmune diseases [1].

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Moreover, the so-called "subcutaneous adipose tissue" has become an object of increasing interest. Regardless of the terminology used by different authors, new surgical and non-surgical techniques for its removal have been proposed, which entails the need for a deep knowledge of its anatomy so that more rational and effective procedures can be performed [2].

Adipose tissue can be divided into visceral adipose tissue (VAT) and superficial adipose tissue (SAT), which in turn is composed of two distinct layers separated by a fibrous tissue called *fascia superficialis*. These two layers are called hypodermis or areolar adipose tissue (AAT) and subcutaneous adipose tissue or lamellar adipose tissue (LAT) and will be the theme for our discussion in the article below.

In the literature there are few studies of these deposits with recent publications.

SAT has an embryological origin in the mesoderm, and its functions are to store energy, to protect against mechanical impacts, to allow the mobility on deeper structures and to supply insulation. It also provides a cosmetic effect by shaping the body contour [3].

As shown by studies on the anatomy of the abdominal wall, the superficial adipose tissue is organized below the epidermis and the dermis as follows: hypodermis or areolar adipose tissue (AAT), a fibrous horizontal layer of connective tissue (*fascia superficialis*), and subcutaneous adipose tissue or lamellar adipose tissue (LAT) [2, 3, 4, 5]. Owing to the fact there is no unanimity among the authors concerning nomenclature in the literature, these will be the adopted terms to describe the layers in the current review [4].

The *fascia superficialis* is a membranous layer formed by multiple sublayers of fibroelastic tissue, which is composed of collagen bands distributed in different directions, with intersection points between them and fine irregular adipose cells islets located between the collagen fibers, resembling lamellae [3, 5].

Studies on the anatomical dissection of the abdominal wall show an apparently continuous and macroscopically well-organized distribution, with different thicknesses along the abdominal wall and thicker in the lower abdomen. This membrane merges medially with the linea alba, in the caudal direction with the inguinal ligament and with the bone prominences of the iliac crest. In the cranial direction, it continues towards the thorax [3].

Anatomical Differences Between the Hypodermis and Subcutaneous Adipose Tissue

Anatomical studies highlight the fact that the distribution of the hypodermis (AAT) and the subcutaneous adipose tissue (LAT) shows variations influenced by genetic factors, age, gender, physical activity practice and dietary habits. Such studies distinguish parts of the body with both layers and regions where only hypodermal tissue is present. The subcutaneous adipose tissue is composed of many fat layers, and it is present only in certain parts of the body. Variations in the anatomical distribution according to gender establish differences in the body contour, depending on the location of these accumulations, which can be found in the abdomen, flanks, trochanteric region, the upper third of the inner face of the thighs, knees and back of the arms.

Recent studies have revealed that both layers of the superficial adipose tissue (SAT) had different behaviors depending on the deposition site [6]. Hypodermic thickness was practically uniform around the trunk, whereas the subcutaneous adipose tissue tended to be thin in the anterior part, especially anterolaterally over the external oblique muscle, showing maximum thickness posterolaterally at the level of the flanks [3]. Besides, the thickness of both tissues varied according to the type of individual: in obese and normal weight subjects the thickness of the subcutaneous adipose tissue progressively increased in the T10-femoral head direction, whereas the thickness of the hypodermis increased in the same direction only in the obese group [3].

With the weight gain and the resultant adipocyte hypertrophy in adulthood, the hypodermis uniformly thickens throughout the tegument whereas the subcutaneous adipose tissue proportionally increases in volume, thus being responsible for the located accumulations [5]. Therefore, the meaning of "located body fat: first to gain, last to lose" can be more easily understood.

As to obesity, the distribution is almost indistinct and there may be an increase in size and/or number of adipocytes in both layers. Once obesity is established, weight loss will be followed by an increase in fat mobilization rate and a decrease in the fat synthesis rate in all tissues; however, the number of cells will practically remain unchanged⁶. In women, the decrease will be better expressed through the volume of adipose cells in abdominal fat than in femoral fat due to the fact the latter presents a lower mobilization rate [3].

Histological Differences Between the Hypodermis and Subcutaneous Adipose Tissue

Despite the clear distinction between the dermis and hypodermis, both of them are structurally and functionally integrated through not only a network of intersecting nerves and blood vessels but also the presence of epidermal appendages.

The hypodermis, or areolar adipose tissue, is arranged in vertical compartments, distributed perpendicularly to the most superficial layers of the skin. Its hexagonal structure is very similar to honeycombs, with uniform distribution throughout the superficial adipose tissue. Depending on the analyzed area, there may be a variation in thickness [3]. It is formed by fatty lobules interspersed with well-defined fibrous septa (*reticula cutis superficialis*) and oriented perpendicularly towards the surface, strongly anchored to the dermis, and connecting it to the fascia superficialis. Owing to the fact it is composed of elastic and collagen fibers, Sbarbati denominates it collagenic peri-adipocyte basket [1]. These septa serve as a passage to vessels and nerves from the subcutaneous adipose tissue, with compartments

well-vascularized by capillary vessels [3,4]. This distribution in septa pattern plays an important role in the preservation of cell integrity.

The hypodermis practically covers all the body. It is arranged in compartments that are parallelly distributed to the most superficial layers of the skin. The fat lobules are organized into single or multiple layers, depending on the fat content and the hypodermic thickness in each individual. There was no clear differentiation concerning the distribution in the caudo-cranial direction towards the thorax. It was observed that the structural pattern as well as the elastic properties were highly stable, returning to its initial position after distension in the compression test [3].

The subcutaneous adipose tissue, in turn, presents larger, flattened and less-defined fat lobules with less evident fibrous septa, and in general obliquely oriented and connected to the membranous layer of the deep fascia of the abdominal wall muscles [3]. Sbarbati et al describe this layer from the collagenic peri-adipocyte basket as incomplete, extremely fragile and finely adherent, with few vascular components, which apparently characterizes it as an area of high lipid deposition [3].

In the abdomen, where it has been mostly studied, the subcutaneous adipose tissue overlays the deep fascia and the abdominal muscles with significant variation in thickness. It is thinner, with adipose component reduction, in the adhesion layers of the fibrous areas [inguinal ligament, linea alba, and bone prominences]. Its thickness varied in adipose content and mechanical strength among the studied individuals. The oblique distribution of the septa, its limited elastic properties when stretched and its low resistance to compression explain the sliding of this tissue over the deep fascia [3, 5].

Metabolic Differences Between the Hypodermis and Subcutaneous Adipose Tissue

The anatomical, histological and metabolic differences of the visceral adipose tissue (VAT) and the superficial adipose tissue (SAT) as well as the distinc-

tions regarding endocrine regulation vary according to age, gender, ethnicity, nutritional ingestion and the autonomic regulation of energy balance [7].

Many studies propose a correlation between VAT and metabolic disorders, like insulin resistance [8] and the complications related to obesity [7]. However, after the recent division of the superficial adipose tissue into hypodermis and subcutaneous adipose tissue [9], the implications of these compartments and their metabolic differences have been thoroughly studied [10].

The hypodermis (AAT) is characterized by the hypertrophy of adipocytes and the low level of inflammatory cell infiltration. On the other hand, the subcutaneous adipose tissue (LAT) has an important inflammatory profile due to the more significant inflammatory cell infiltration [7]. Recent studies reveal that in morbidly obese patients the inflammation level in the subcutaneous adipose tissue (LAT) is related to the severity of hepatic diseases [11].

Kim et al observed that both compartments of the superficial adipose tissue have distinct functionalities [10]. The adipose cell differentiation in both sub-compartments do not only depend on precursor cell activity, but it most probably also suffers the influence from the extra-adipocyte environment, like vascularization, innervation, and remodeling of the extracellular matrix. It is important to point out that the subcutaneous adipose tissue (LAT) has a strong correlation with insulin resistance and metabolic deregulation [7, 9].

Regarding the abdominal adipose tissue metabolism, the amount of subcutaneous adipose tissue (SAT) is highly correlated with fasting insulin, especially in men [11]. Differences in lipogenic and lipolytic activities are suggested due to the fact that some studies demonstrated a thermal insulation role of the hypodermis (AAT) and a metabolic role of the subcutaneous adipose tissue (LAT) in swines [11].

Cancello et al also described a specific role of the subcutaneous adipose tissue (LAT) in hepatic com-

plications secondary to obesity, like nonalcoholic steatohepatitis (NASH). By contrast, the researchers highlight the fact that kidney diseases are probably associated with protein genes expressed in the hypodermis (AAT) [11].

Smith et al suggested that the adipose tissue biopsy should be considered a procedure to study the metabolism of adipocytes [12]. The cellular content of the adipose tissue includes a specialized population of cells [adipocytes] and the stromal vascular fraction composed of preadipocytes, multipotent stem cells, endothelial and vessel wall cells, macrophages, lymphocytes, eosinophils, neutrophils, mastocytes and hematopoietic progenitor cells.¹³ The inflammatory and noninflammatory actions of macrophages have been vastly studied; nevertheless, little is known about events involving resident stem cells in obesity [13]. Recently, a population of macrophages has been identified in human adipose tissue. The glycoprotein CD34 found in this population was considered similar to adipose stem cells, thus reinforcing the idea that inflammatory macrophages are present in the adipose tissue of obese individuals [13].

The accumulation of fat in obese patients causes insulin resistance and a risk of metabolic disorders. On the other hand, the subcutaneous adipose tissue may bring beneficial metabolic results, and its secretions are frequently studied. The effects of adipokines like adiponectin and leptin are very well known [14].

Walker et al evaluated the expression of proteins related to the metabolism of adipocytes by comparing both layers in obese and lean individuals and correlating them with the HOMA-IR index [7]. Biopsies were performed in order to analyze the metabolism of glucocorticoids and sensitiveness to insulin, and a positive correlation of BMI with HOMA-IR, insulin, leptin and levels of TNF-alpha was found. However, BMI had a negative correlation with adiponectin concentrations. Levels of GLUT-4, resistin, TNF-alpha were evaluated in the hypoder-

mis and in the subcutaneous adipose tissue, and results showed that among obese patients there was an increase in resistin and TNF-alpha levels and a decrease in GLUT-4 levels [7]. Specific adiponectin regulation in the hypodermis was more significantly observed, and in obese patients leptin and 11BHS1 levels increased whereas adiponectin levels decreased [7]. The conclusion was that both compartments are metabolically different and important in the development of obesity, and the hypodermis has its independent effects [7].

Additionally, adipose stem cells can regulate obesity through cytokine secreting functions. The endocrine function of the adipose tissue depends on adipocytes and vascular stromal cells. Adipocytes are the main source of leptin and adiponectin while inflammatory cytokines, like IL-6 and TNF-alpha, are secreted by vascular stromal cells, namely the pre-adipocytes and adipose stem cells. Therefore, adipose stem cells may be considered secreting cells of the adipose tissue in obese individuals [13].

The valuable effects on metabolism promoted by the subcutaneous adipose tissue can be exemplified by the increasing interest in adipose tissue transplantations, which may bring some light on its physiological understanding and the therapeutic benefits.

Discussion

Clinical Implications

Adipose stem cells have drawn the attention of researchers over the past 15 years due to the following factors: harvesting these cells has been made easily through liposuction approaches [11]; they form an important regenerating tissue; they represent a possible regulator of obesity owing to their secreting capacity [15].

Such cells are therapeutically applied in many areas given their expansion ability and their capacity to undergo in vitro differentiation into adipogenic,

osteogenic, chondrogenic, myogenic and neurogenic lineages [15].

In restorative therapies based on cell implantation, adipose stem cells are perfectly suitable due to their capacity of multilineage differentiation and self-renewal as well as the ability to repair, replace and regenerate tissues and organs injured by an agent or disease [15]. The structural morphology of the peri-adipocyte basket and the presence of rich microcirculation in stem cells make the subcutaneous adipose tissue (LAT) ideal as a donor area, especially in sites where the collagen basket is thin, like in the trochanteric region and in the inner part of the knees [1].

Many clinical trials have evaluated its effectiveness in treatments of conditions like types I and II diabetes mellitus, hepatic cirrhosis, intestinal fistulas, cardiovascular diseases and amyotrophic lateral sclerosis among others [15]. Adipose stem cells have shown to regulate cytokine production inhibition both in TCD4 and TCD8 lymphocytes, stimulating the production of anti-inflammatory cytokines [15].

Traditional liposuction treats the subcutaneous adipose tissue (LAT), avoiding the superficial layer (AAT), whose removal causes irregularities in the contour. On the other hand, the thickness of the hypodermis decreases with weight loss [5].

Cellulite, or gynoid lipodystrophy (GLD) is a pathology specific to women due to the anatomical characteristics of the hypodermis. In men, the fibrous septa are smaller and arranged in oblique planes with small fat lobules, whereas in women these lobules are larger with parallel septa. These conditions are present from birth; however, with the hormonal changes in puberty, a greater storage of fat occurs along with interstitial fluid retention, and the fat lobules become enlarged due to the hypertrophy of the adipocytes, secondary to vascular alterations [12, 16].

Conclusion

Adipose tissue is divided into two distinct layers, namely hypodermis (AAT) and subcutaneous cellular tissue (LAT). These layers have completely different anatomy, histology and metabolism.

A correct and standardized nomenclature for the respective layers is of utmost importance. When some researchers refer to subcutaneous fat or adipose layer without a precise anatomical or histological description, it is impossible to know to which tissue their observation is related [17].

Further studies will undoubtedly reveal previously unknown concepts of the pathophysiology of adipocytes and their ultrastructural and metabolic differences, which will lead to a better understanding of their behavior according to body site. As a result, health professionals will be able not only to better understand the dynamics of weight loss and located body fat but also establish more precisely a more suitable therapeutic approach.

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