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ORIGINAL ARTICLE

Gluteal femoral subcutaneous and dermal adipose tissue in female

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Abstract

Background: During the sexual maturation, gluteal femoral adipose tissue is subjected to numerous modifications, not observable in other regions, in particular in women and less in men. Other authors described this region, but they used imaging techniques having lower resolution, than MRI proposed in this study. High resolution imaging techniques might provide important and more detailed information about the anatomy of gluteal femoral region.

Methods: This study has been performed using 7T-magnetic resonance imaging and ultrastructural analysis in order to provide accurate description of the subcutaneous adipose tissue and dermis of gluteal femoral region. In this study specimens harvested from cadavers and form living patients have been analyzed.

Results: The results showed the presence of three layers: superficial, middle, and deep, characterized by different organization of fat lobules. High resolution imaging showed the adipose papilla that originates from dermis and protrude in subcutaneous adipose tissue. Adipose papilla is characterized by a peculiar morphology with a basement, a neck and a head and these elements represent the functional subunits of adipose papilla. Moreover, ultrastructural study evidenced the relationship between adipocytes and sweat glands, regulated by lipid vesicles.

Conclusions: This study provides important information about subcutaneous and dermal fat anatomy of gluteal femoral region, improving the past knowledge, and move toward a better understanding of the cellulite physiopathology.

KEYWORDS
7T-magnetic resonance imaging, adipose papilla, collagen septa, fat layers, fat lobules

1 | BACKGROUND

Subcutaneous white adipose tissue (sWAT) may represent the most extended tissue of the body and its relationship with a lot of pathologies has been largely demonstrated, such as obesity, metabolic disorders and insulin resistance.[1–4] In the scientific literature adipose tissue is one of the best characterized tissues and its morphology and cellular composition are well described.[5–7] sWAT characterization attracted numerous researchers for multiple purposes. For example, in plastic surgery sWAT is largely used as a source of regenerative niches.[8–10] The more recent studies demonstrated that the adipose tissue is characterized by different morphology and cellular compositions in relationship with the site of harvesting and the stem population of sWAT was attractive for its regenerative potential.[11–13]

In the past, also our research group classified the subcutaneous adipose tissue of different regions such as abdomen, trochanter, breast, face, foot.[13–19] Numerous authors focalized their attention, particularly, on the face adipose tissue,[7,13] distinguishing numerous compartments, characterized by different morphology, specific cell composition and different connective fibers organization.[14,15] Our studies confirmed that also in other regions, subcutaneous adipose tissue is compartmentalized and organized following a characteristic architecture, depending by the function of these regions.[13,18,20]

For example, the foot fat pad presents two different types of adipose tissue, the first characterized by thin connective septa and by large fat lobules, the second, on the contrary, is characterized by thicker connective septa and smaller lobules. In particular, the region with large lobules has cushioning function, while the more fibrous region has structural and mechanic function.[18,19]

A similar organization was described, by our research group in the trochanteric area or in Bichat fat pad.[13,21,22] In the trochanteric fat pad, it is possible to observe a subcutaneous adipose tissue characterized by strong and thick collagen septa, due to the mechanic stimulation received during walking or during sitting.[18] The Bichat fat pad resembles visceral fat. In fact, it is characterized by very thin collagen septa, by collagen organized in a basket-like structure that envelops the mature adipocytes and by cluster of unilocular adipose cells. It is a soft adipose tissue.[13]

Only recently, some papers focused the attention on the dermic adipose tissue.[21–23] Dermic layer is very complex, and its organization is related to the presence of skin appendages and to sweat and sebaceous glands.[24,25]

Among all the regions mentioned before, basing on our knowledge, the gluteal femoral district present peculiar characteristics and could be interesting to evaluate the composition of this region, particularly in female. These regions are in strong relationship with the sexual maturation and the pubertal phase.[26–28]

Moreover, the differences between the male and female were described in the past literature by different authors and were related to the different hormone sensitivity.[26–28] In female the gluteal area represents a symbol of fertility and this the region correlated with the reproduction, and to cultural and ethnic differences.[29,30] For these reasons, it is one of the body regions more subjected to aesthetic surgery or to different types of aesthetic treatments.[31,32]

Gluteal femoral area became the focus of different studies concerning a modification observed on the skin that assumed orange peel aspect, characterizing cellulite or edematous sclerotic panniculitis.[33–35]

Recent study by Conti et al, demonstrates that the orange peel aspect is due to a pathology associated to peculiar aspects of stem component of the tissue, confirmed by data obtained from proteomic analysis of cellulite affected subcutaneous adipose tissue.[20] Cellulite is a highly interesting pathology, since the enormous of people affected; indeed, it involves in more than 90% of women. Anyway, even today the number of papers regarding the characterization of the area affected by cellulite is poor.[20,33–40]

Independently from cellulite, the anatomy and morphology of gluteal femoral area are still lack of knowledge.[41,42] Published study described the anatomy and connective fibers organization of this area with different techniques, such as ultrasound and x-ray characterized by lower resolution than 7T-MRI, described in this study.[43] The lower resolution could impact on the interpretation of collagen septa distribution. With MRI it is possible to describe the collagen septa organization in more detailed manner, but also in this case, high resolution is necessary and the spectrometer operating at 1.5T or at 3T, do not guarantee always a good interpretation of collected data.[44] These studies were mainly finalized to the development of a methods able to deeply investigate and, then, to treat cellulite. In general, all the authors agreed on the necessity to remodel the adipose tissue lobules and connective septa. Some studies proposed a very unusual description of subcutaneous adipose tissue anatomy, evidencing a different distribution of connective septa among female and male.[36–44] The female connective septa were described with parallel orientation, while in male was proposed a crossing distribution of the connective structure.[41,42] With the cellulite progression, parallel connective septa caused a pressure on adipose lobules, that protruding on the skin, causing the orange peel aspect.[41] The actual treatments for cellulite focused on the remodeling of subcutaneous adipose tissue and of the connective septa, are based on this description.[37,45]

The resolution that characterized these past studies could be not sufficient to have really resolving methods. For this reason, our research group employed very high-resolution magnetic resonance imaging, operating at 7 Tesla, to study the anatomy of subcutaneous adipose tissue in gluteal area, with the aim to improve the knowledge about morphology and ultrastructure subcutaneous adipose tissue, with particular attention to the dermal adipose tissue, considering that this region is characterized by a peculiar morphology, probably due to hormones influence.

2 | MATERIALS AND METHODS

2.1 | Samples

For this studies 10 cadavers and 5 living patients were employed.

Ten biopsies of gluteal femoral area were surgically collected from cadavers, provided by ICLO Teaching and Research Center, in Verona. Caucasian female ranging between 35 and 45 years old and having a BMI of 26±2 were selected. Biopsies of $2\times2\,cm^2$ were cut in three portions (Figure 1) and preserved at −20°C for the subsequent imaging analysis.

In addition, also five peritrocanteric femoral area samples were harvested from the right side of respective five Caucasian females. They were subjected to liposuction for aesthetic purposes. Patients ranging between 30 and 45 years old and had a BMI of $26\pm2\,kg/m^2$. In all patients, cannula entry sites large enough for the cannula to enter were made in the skin with a 15 blade scalpel. The entry hole was made at the level of the anterior superior iliac spine. Klein modified solution was injected into the donor site.[46] The volume of infiltrated solution was the same for each side and was injected using a blunt Lamis infiltrator (Byron Medical, Inc. Tucson, Ariz). After 15 min from the infiltration, the fat graft was harvested through the same incisions made previously.[46] The harvesting canula was 3 mm in diameter and 23 cm in length, with a blunt tip (Byron Medical).

Aspiration of the superficial adipose compartment was performed in accordance with the distribution of adipose tissue, specific for each patient trying to avoid the interruption of Scarpa's fascia. After liposuction, a small amount of fluid was let back into the tissue and was allowed to drain slowly until the end.

Samples were immediately embedded in buffered formalin at 4% and sent to our University for the ultrastructural examination.

The exclusion criteria were as follows: BMI over 30 kg/m2; smoking; metabolic disorders such as glucose intolerance, diabetes, hypertension, thyroid dysfunction, and dyslipidaemia; unstable body weight in the last 6 months prior to the commencement of the study; current use of medications including antidepressants, appetite suppressants, thyroid hormone medication, orlistat, topiramate, diuretics, anti-inflammatory, or antibiotics; and previous liposuction surgery.

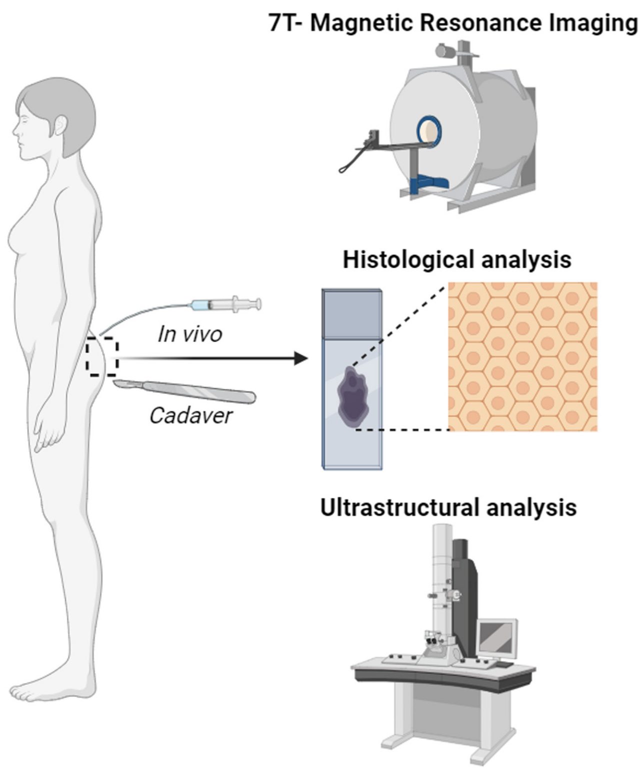

FIGURE 1 Experimental plan design and gluteofemoral adipose tissue harvesting.

2.2 | Histology

Specimens of gluteal femoral area, harvested from cadavers, were surgically collected form right gluteal area and had dimensions of $2\times2\,cm^2$. Samples were immediately were fixed in buffered formalin at 4% for 1 h and then dehydrated using a gradient of ethanol (from 70% to 100%) and embedded in xylene 100% for 1 h. Successively specimens were embedded in pre-warmed paraffin and cut, using a microtome in order to obtain section of 5 μm thick. For the histological evaluation, slices were stained with hematoxylin and eosin and the image acquisition was done using a bright field optical microscope, Olympus BX-51 (Olympus, Tokyo, Japan) equipped with a digital camera (DKY-F58 CCD JVC, Yokohama, Japan) and connected with a PC endowed with Image-Pro Plus 7.0 software. Slides were gently cleaned with ethanol, then placed on the microscope slides holder and acquired.

2.3 | Transmission electron microscopy (TEM)

Sample of gluteal femoral region, of living patients, harvested with liposuction, were fixed with glutaraldehyde 2% and were post-fixed in 1% osmium tetraoxide (OsO_4) in aqueous solution for 2 h, dehydrated in graded concentrations of acetone and embedded in Epon–Araldite mixture (Electron Microscopy Sciences, Fort Washington, PA, USA). The semi-thin sections (1 mm thickness) were examined by light microscopy and stained with toluidine blue. The ultra-thin sections were cut at 70 nm thickness and placed on Cu/Rh grids with Ultracut E (Reichert, Wien, Austria), stained with lead citrate and observed using an FEI Morgagni 268D electron microscope (FEI Company, Eindhoven, the Netherlands).

2.4 | Scanning electron microscopy (SEM)

Specimens of gluteal femoral region of living patients, harvested by liposuction were fixed with glutaraldehyde 2% in 0.1 M PB, post-fixed in 1% osmium tetraoxide (OsO_4) in the same buffer for 1 h, dehydrated in concentrations of acetone, critical point dried (CPD 030, Balzers, Vaduz, Liechtenstein), fixed to stubs with colloidal silver, sputtered with gold by an MED 010 coater (Balzers), and examined with a FEI XL30 scanning electron microscope (FEI Company, Eindhoven, the Netherlands).

2.5 | 7 T Magnetic resonance imaging (MRI) and 3D reconstruction

Magnetic Resonance Images of $n=10$ samples of gluteal femoral adipose tissue, harvested surgically from cadavers, were observed using a Bruker Biospin spectrometer (Bruker Biospin MRI GmBH, Ettlingen, Germany) operating at 7T, with a strength of 040G/m and equipped with 3.5cm i.d. transmitter/receiver birdcage coil. The samples were positioned inside the coil and the region of interest (ROI) was selected in order to collect the whole image of the sample with all the details of epidermidis. The acquisitions were performed using T1-weighted RARE sequences at high resolution with the following parameters: TE=7ms, TR=2800ms, field of view=22×8mm, number of averages=16, flip angle 180 degrees, slice thickness 0.350mm and matrix size 256×128 pixels. 3D images were acquired using a T1-FLASH sequence with the following parameters: TE=8ms, TR=50ms, field of view=22×8×28mm, number of averages =1, flip angle 20 degrees, slice thickness 0.5mm and matrix size 320×128×128 pixels.

At the end of acquisitions, on MRI slices, the length of each papilla was determined manually in all samples.

3 | RESULTS

3.1 | MRI

sWAT of female gluteal femoral area was showed in Figure 2. High resolution magnetic resonance imaging showed the first macroscopic aspect of gluteal femoral region: the organization of fat lobules in three different layers identified as superficial, middle and deep (Figure 2). More specifically, the distribution of fat lobules followed a peculiar scheme (Figure 2): large fat lobules were located in superficial and deep layers, while the middle layer appeared characterized by smaller fat lobules. These were surrounded by thin collagen septa, (Figure 2B, white arrows). With the role to envelop the fat lobules, but also to separate the layers of them (Figure 2B). Moreover, it was possible to detect the adipose papilla that originate in the superficial layer, protruding in dermis. As showed in Figure 2A, the adipose papilla was characterized by a peculiar morphological aspect. It was possible to detect a basement (Figure 3A), originating directly from the superficial layer of subcutaneous adipose tissue, a neck Figure 3B that represented the protruding portion and a head Figure 3B, located in the reticular dermis. The head of adipose papilla was characterized by ovoid shape with very thin extensions in dermis, that represents a derma domain characterized by lower signal intensity in comparison with adipose tissue (Figure 3B). Moreover, in dermis, the heads of adipose papillae appeared distributed in a very homogeneous scheme, as showed in the Figure 4. Two sequential transversal sections of gluteal femoral sample were reported. The heads were characterized by ovoid shape and resulted dispersed, regularly in dermis (Figure 4A,B).

3.2 | Histology

Histology performed on cadavers biopsies of female gluteal femoral area, reflected the same aspect of dermis and subcutaneous tissue observed in MRI (Figure 5). Primarily, it is possible to confirm the presence of three different layers of subcutaneous adipose tissue (Figure 5A), and the structure of adipose papilla, visible at higher

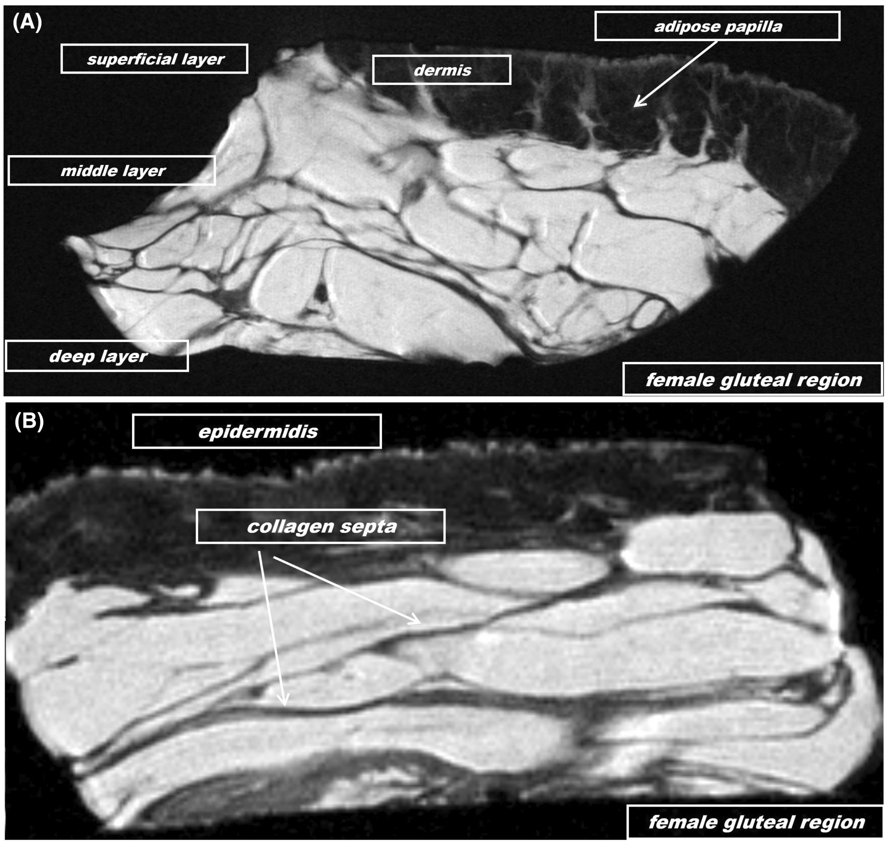

FIGURE 2 It shows the high resolution 7T-MRI of gluteal femoral area in cadavers in which is possible to distinguish the three layers: superficial, middle and deep (A). Superficial and deep layer are characterized by large fat lobules surrounding by thin collagen septa, while middle layer is composed by small fat lobules. Layers were separated by thick collagen boundless (A and B, white arrow). (B) Adipose papilla is observable. It originates from superficial layer and protrude in dermis (B, white arrow).

magnification (Figure 5B). It is also observable the thick collagen septa that separate the three layers (Figure 5A). Histology confirmed the origin of adipose papilla from superficial layer and the protrusion in dermis (Figure 5B), assuming a peculiar morphology characterized by a basement, neck and a head. The different portions of adipose papilla were separated by thin collagen septa and appeared characterized by mature unilocular adipocytes (Figure 5B). In the Figure 6 was possible to appreciate semi thin sections, stained with toluidine blue, in which axial section of sweat gland (SG) and mature adipocytes (MA) were visible.

In these sections, mature unilocular adipocytes and sweat glands were embedded in a dense collagen matrix.

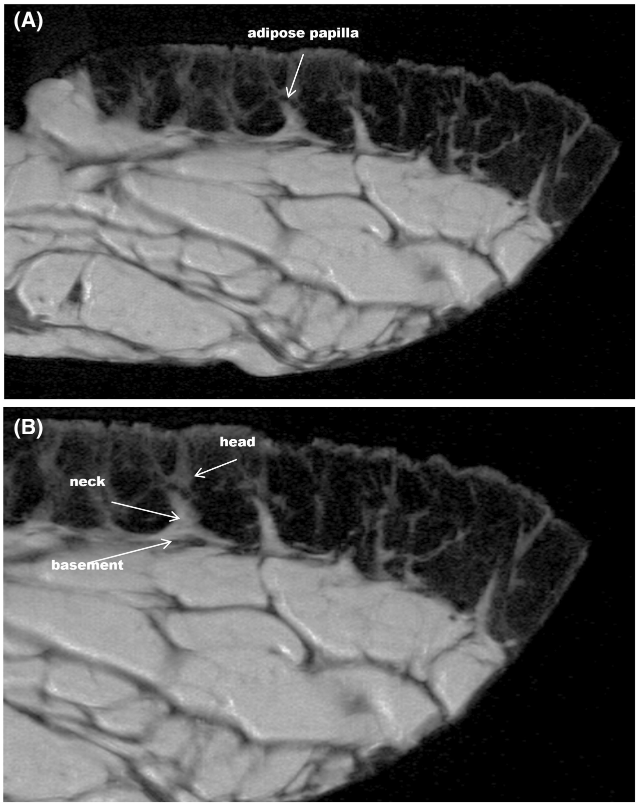

FIGURE 3 7T-MRI of adipose papilla showed the three functional subunits: basement that originates from superficial layer of gluteal femoral area, neck that protrude in dermis and head (A). Heads of adipose papilla were characterized by protrusion with a signal intensity lower than fat and higher than collagen (B, white arrows).

3.3 | TEM

Ultrastructural analysis, performed on living specimens, evidenced the relationship among adipose mature unilocular cells (MA) and sweat glands (Figure 6A and 6B SW). Ultrathin sections evidenced the presence of mature adipocytes very close to the sweat gland and of numerous lipid vescicles (Figure 6C, LV) dispersed in the extracellular matrix. It is also visible the membrane of adipocytes lipid vesicles, and it could be a feature of activated cells (Figure 6D).

3.4 | SEM

In the Figure 7 scanning electron microscopy showed the aspect of gluteal femoral area at low magnification, in which is possible to recognize epidermidis, papillary and reticular dermis, and hypodermis (Figure 7A). Papillary dermis, imaged at higher magnification, evidenced the presence of adipose papilla, strictly connected with the hair and hair bulb, characterized by mature unilocular adipocytes surrounded by very dense collagen matrix (Figure 7B). Adipose papilla had origin from the hypodermis and protruded in reticular dermis (Figure 7B, white arrow). In addition, SEM of gluteal femoral area of living female, showed the thin collagen fibers enveloping mature unilocular adipocytes (Figure 8A,B) and the presence of very small vescicles in the extracellular space among the adipocytes (Figure 8C).

4 | DISCUSSION

In the past, description of gluteal sWAT was performed by different research groups using, principally, ultrasound, histology, and

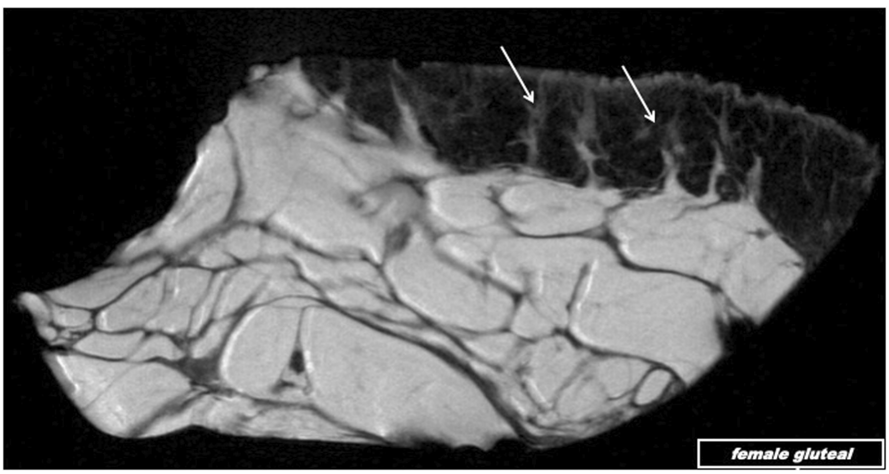

FIGURE 4 Transversal slices of gluteal femoral area, showed particular organization of adipose papilla heads. They are organized in a regular structure, in which heads appeared homogeneously dispersed. It can be see the protrusion of adipose papilla form superficial layer of gluteal femoral area (white arrows).

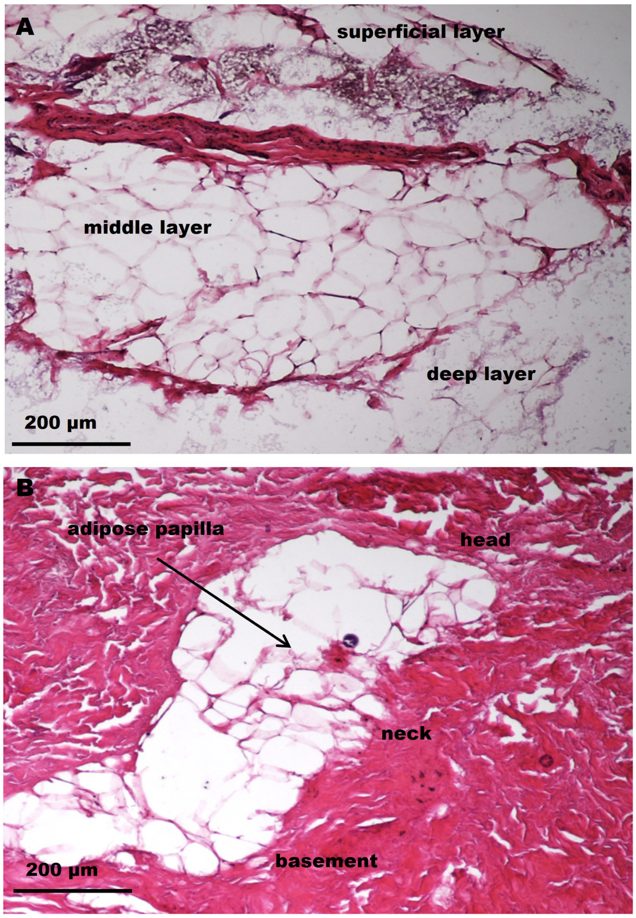

FIGURE 5 Histological evaluation of gluteal femoral area evidenced the division in three layers separated by thick collagen boundless (black arrow). Gluteal femora area is characterized by mature unilocular mature adipocytes (A) imaged at 10× magnification. Histology of adipose papilla, imaged at 20× magnification shows the three functional subunits, separated by thin collagen septa (panel B). Scale bars are reported in each panel.

MRI with low resolution.[41–44] One histological study published by Numberger and Muller, performed with patients affected by cellulite and on cadavers, showed the existence of peculiar component of subcutaneous adipose tissue of female.[41]

In female, collagen septa were described as perpendicular to dermis and it determinate the formation of a structure called "standing fat-cell chambers." From this chambers papillae adiposae project in the corium. These papillae break up in the region or the *stratum reticulare* of the corium, surround hair bulbs, sweat glands and blood vessels, that resulted protected from pressure and sharing forces.[41,47] When a pressure was applied, the chambers modified their shape but not volume. Moreover, the standing fat-cell chambers were defined as elements of skin, in the junction region of the corium and subcutaneous tissue can change the appearance of the skin surface. Further description of sWAT was proposed also by Rayan and Curri that compared the anatomy of gluteal area in correlation with the body fat distribution.[48] They observed patients with gynoid or android phenotypes. They described the female adipose tissue organized in large and rectangular lobules, distributed in parallel to each other. In their study male adipose tissue was described as organized in smaller fat lobules and with diagonal disposition of collagen septa.[48] Also, in this study the images did not clarify the explanation of fat lobules distribution.

In addition, Querleux provided more recent description of sWAT of the gluteal area in women selected for different body mass index (BMI) and focused the attention of the differences among areas affected by "orange peel" aspect and areas free from dimpling. In this study, MRI performed at 1.5 Tesla, was employed.[44,49] Described results showed no marked differences among area affected by cellulite and control area. Probably because the dimpling affected regions are too close to the region free from "orange peel" aspect. The acquisitions were performed only axially and, in this manner, it was possible to observe only the distribution of fat lobules, but it was not possible to appreciate differences between regions characterized by cellulite and region without it.[44,49,50]

In the present study, the existence of adipose papilla had been confirmed by ultrastructural analysis, that described the presence of a complex, or functional unit, formed by sweat gland adenomere and mature adipocytes. Histological and ultrastructural images evidenced that adipose papilla is composed by a basement, having a direct origin from the superficial lobules of the subcutaneous fat, a neck that is the protruding portion and an oval-shaped head, characterized also by radial extensions, diffuse in the reticular dermis.

Moreover, the present study focuses the attention, primarily, on sWAT of gluteal area not affected by cellulite or other pathologies, in order to provide new anatomical model of this region. The employment of high-resolution MRI improves the knowledge about the distribution of fat lobules, collagen septa, and adipose papillae in gluteal region.

The imaging of specimens, collected from cadavers, at 7T using 3D acquisitions, allows to collect detailed and fascinating information. This study describes the distribution of septa, and consequently of fat lobules, that appear more detailed, if compared to previous studies. Moreover, the sWAT and dermis appear directly connected, without the interposition of membranes.

Further important aspect of this study is the description of three layers in gluteal femoral female sWAT. Indeed, it is possible to observe that there is a gradient of fat lobules distribution, because in the superficial and deep layers it is possible to observe large fat lobules, while in the middle layer smaller lobules are present.

This new anatomical knowledge can represent an important aspect on which to base the treatment of cellulite, such as subcision.[50,51]

In fact, current subcision protocols have always referred to adipose tissue distribution based on images with less definition respect to high-resolution MRI.[50,51] Surely this new anatomical conception of adipose tissue will allow us to modify the current approach in the treatment of the area affected by cellulite.

Moreover, another important feature is the description of adipose papilla, that originates directly from the superficial lobules of sWAT and protrudes for long distance in dermis, reaching sweat, sebaceous glands and hair bulbs. This peculiar structure resembles mammary glands, in which mature adipocytes are surrounded

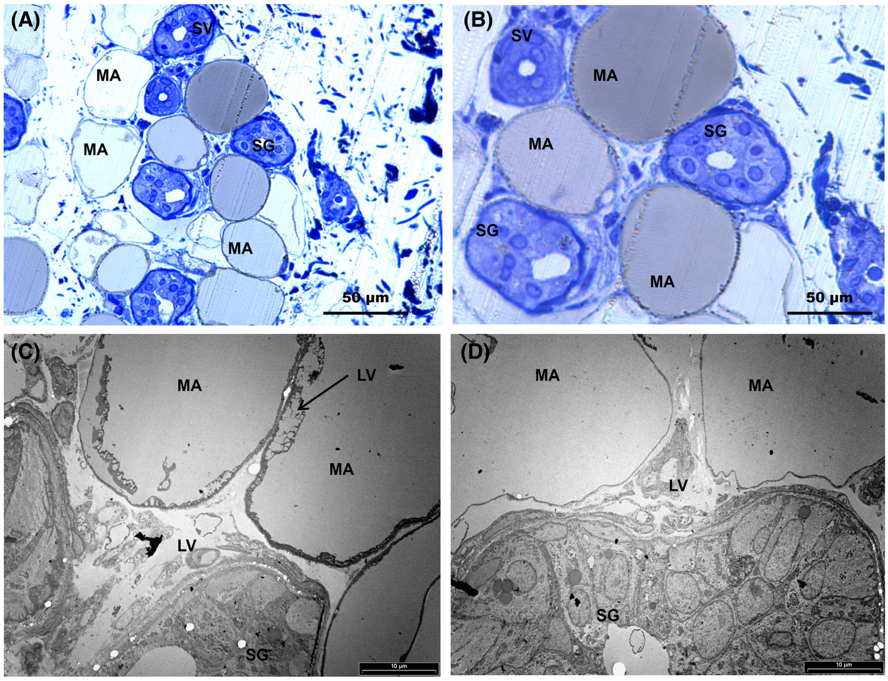

FIGURE 6 Semi thin sections of gluteal femoral area evidenced the relationship between mature unilocular adipocytes (MA) and sweat glands (SG) (A and B), embedded in a dense collagen matrix. Images have been acquired at 10× magnification. Ultra-thin section of gluteal femoral area, showed in (C), evidenced high magnification of sweat gland (SG) and mature adipocytes (MA), showing also the presence of numerous lipid vesicles (LV) in extracellular matrix and on adipocytes membrane. It is also visible the membrane of adipocytes lipid vescicles (D), and it could be a feature of activated cells. Scale bars are reported in each panel.

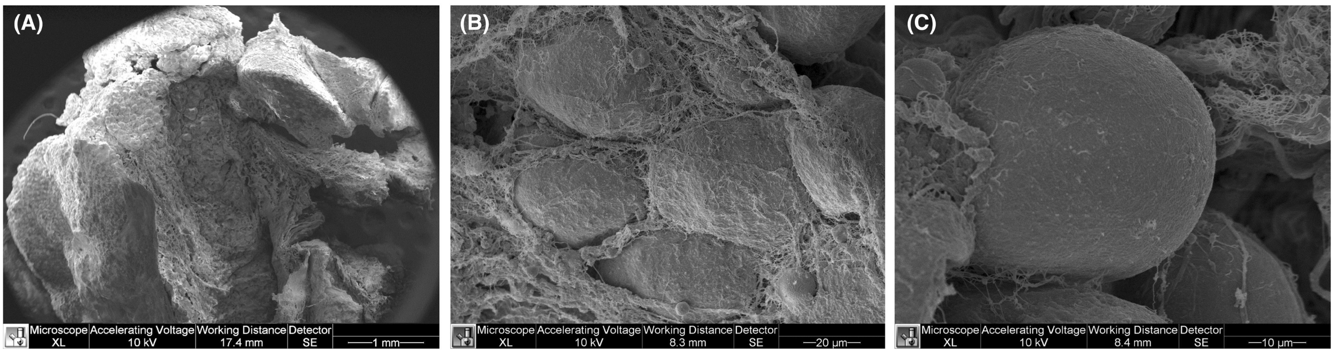

FIGURE 7 SEM analysis shows the organization of gluteal femoral area, in which epidermidis, papillary dermis, reticular dermis, hypodermis, or subcutaneous tissue are recognizable (A). It is possible to observe the high magnification of adipose papilla, associated to hair, that protrude in reticular dermis (B and C). Scale bars are reported in each panel.

by sebaceous glands. This aspect could evidence the hormone sensitivity that characterize this area in the female. In addition, adipose papilla is the demonstration of continuity among dermis and subcutaneous adipose tissue, because it represents the element of direct connection between the two compartments, due to the origin of adipose papilla from sWAT and the protrusion in reticular dermis. In this manner we can affirm that adipose papilla represents the main anatomic structure by which, the two compartments establish an active communication. This bioactive communication could be modified during the development of skin pathologies, such as cellulite, determining deep modifications of the normal subcutaneous adipose tissue anatomy and structure. Bioactive communication is characterized by vesicular trafficking, detectable in TEM, based on the lipid vesicles produced by mature unilocular adipocytes.

Surely, a deep investigation about the content of these vesicles is necessary, in order to determine the main actors in the communication between sweat glands and adipocytes. Recent published study of our research group, analyzed this crosstalk and biochemical alterations, occurring in dermis when subcutaneous adipose tissue is modified by cellulite development.[20] Consequently, to the acquisition this innovative data set, the present study leads to a deep revision of the anatomical descriptions of gluteal sWAT and stimulate the investigation of the crosstalk between adipocytes and sweat glands, in the absence of pathologies. For many years our research group has been studying adipose tissue in various body areas through the application of high definition tissue and intratissue imaging.[13,17,20,52–57]

This is allowing us to study the ultrastructure of the gluteal femoral area even better, with the aim of developing increasingly effective nonsurgical cellulite treatments.

The past anatomic models proposed parallel distribution of septa in female and crossed distribution in male.[41–44] These descriptions were not supported by high resolution imaging techniques, or by ultrastructural analysis. The differences among histology and ultrasound-based

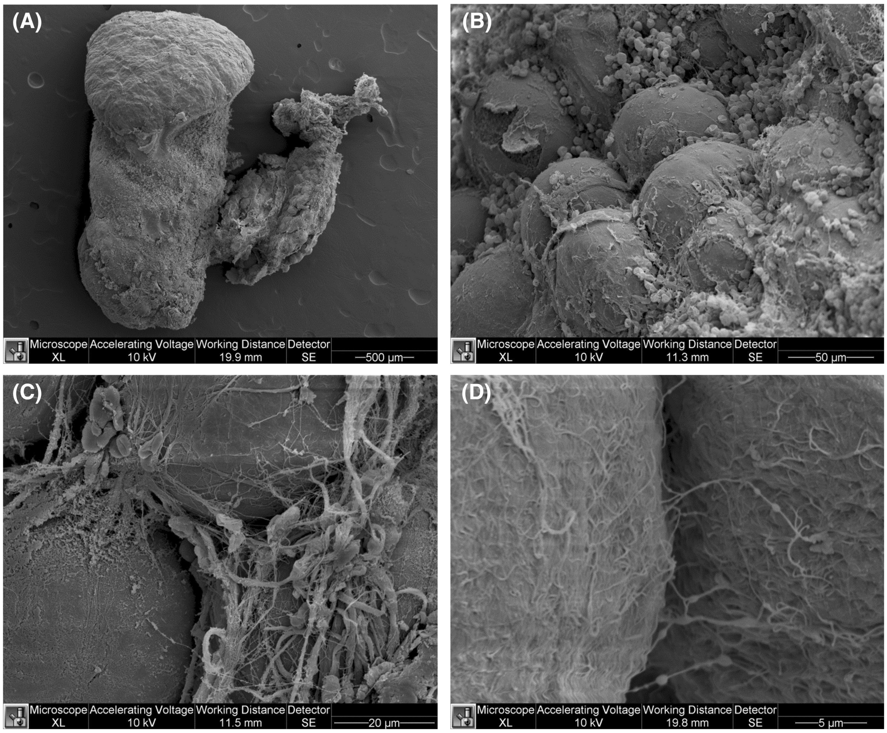

FIGURE 8 Adipocytes of adipose papilla, imaged at high magnification, appear enveloped by numerous collagen fibers (A) that cover the fat lobules. Matura adipocytes are surrounding by thin collagen membrane, that connect single adipocytes (B, C, and D). Scale bars are showed in each panel.

studies, and high resolution magnetic resonance imaging, depend also by the possibility to obtain more detailed images, that allows to have accurate description of gluteal region, in term of lobules distribution and presence of adipose papilla.

Moreover, the past studies were focalized on the anatomy of gluteal femoral area usually affected by cellulite, without comparison with gluteal region without morphological modifications.[50] The study of the anatomy of dermal and sWAT, without cellulite, is fundamental for the understanding of different pathologies (e.g., lipedema and localized adipose depots). Actually, both surgical and not surgical techniques for cellulite treatments proposed collagen septa remodeling. The new data set, described in the present study, acquired using 7T-MRI, put in evidence widely different characteristics of female sWAT, and these data could represent a new chapter in the study of cellulite or lipedema affected gluteal femoral area.

4.1 | Limitation of the study

Some limitations of this paper must be pointed out. The sample population is small, only women with a specific range of BMI and age. We do believe that further studies with larger series including patients with a different sex, BMI and age is necessary to confirm our conclusions.

5 | CONCLUSIONS

High resolution imaging suggests that the anatomy of gluteal femoral region might be deeply revised. The architecture of the subcutaneous adipose tissue of gluteal femoral region appeared widely different from the past models. Moreover, the study underlines the interconnection of sWAT with reticular and papillary dermis, due to the study of a peculiar functional unit: the adipose papilla. Probably, more accurate studies on adipose papilla are necessary in order to better comprehend the morphology of gluteal femoral area and the communication between mature unilocular adipocytes and sweat glands, that could represent the main actors during female hormonal maturation and during the development of different sWAT pathologies.

Furthermore it would be interesting to concentrate more on the study of adipose tissue's anatomy of the gluteal femoral area, increasing the knowledge acquired so far and, in parallel, developing surgical and nonsurgical techniques based on the novelties found, abandoning the techniques based on antiquated knowledge.

AUTHOR CONTRIBUTIONS

Conceptualization, G.C., N.Z., P.C.P., M.R., and A.S.; methodology, G.C, N.Z., L.Q.S, A.B, R.O, and A.S; software, G.C., N.Z. and A.T; validation, P.C.P., F.D.F., M.R., A.S. and G.C.; formal analysis, D.A., A.S., E.L.I.; investigation, A.C., S.V, F.D.F. and G.C.; resources, M.R., N.Z., P.C.P.; data curation, G.C, L.Q.S, N.Z., A.N., and S.V.; writing—original draft preparation, G.C., R.O., N.Z. and A.C.; writing—review and editing, L.Q.S., A.B., E.L.I., R.A., and. A.N.; visualization, G.C., A.S., P.C.P., N.Z. and F.D.F; supervision, M.R., A.S. and P.C.P.; project administration, G.C, N.Z., L.Q.S, R.O., A.C., A.N., S.V. and A.S; funding acquisition, N.Z. F.D.F, M.R. and P.C.P. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Our institutional ethics committee (Authorization Committee for Human Research (CARU)) approved the study design (protocol 2/2019).

INFORMED CONSENT

A written informed consent was obtained from all patients in the study.

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