# Subcutaneous Tissue Histophysiology 66

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Between the dermis (syn: cutis) and the underlying bones, muscles, or fasciae lies a tissue of uneven thickness according to body sites and individuals, called subcutaneous tissue or subcutis (syn: hypodermis). The term "subcutaneous fascia" is sometimes used as a synonym for subcutaneous tissue, although this definition is the subject of current debate as outlined below. From an anatomical and physiological viewpoint, subcutaneous tissue contains two components which, although intricate, have different functions: the interstitial tissue and the adipose tissue.

## 1 The Interstitial Connective Tissue

### 1.1 Histomorphology

Subcutaneous interstitial connective resembles dermis in structure but is much looser. As such, it is a network of collagen and elastic fibers embedded in a ground substance made of a mucopolysaccharide gel sequestering a large amount of water and an additional small amount of "free" interstitial liquid (Brace and Guyton 1979). On its outer side, subcutaneous tissue is in direct contact with the dermis. The dermo-hypodermal junction is irregular, the dermis being attached to

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subcutaneous tissue by extensions (retinacula cutis). The deepest sweat coils (▶ Chaps. 27, "Infrared Densitometry for In Vitro Tape Stripping: Quantification of Porcine Corneocytes," and ▶ 1, "The Human Skin: An Overview") and the bulbs of the terminal hairs in anagen phase are located in subcutaneous protrusions into the dermis. In some parts of the body, the subcutaneous tissue contains a thin layer of muscle, the subcutaneous muscle or panniculus carnosus. In humans, this muscle is only present in the neck and testis, while in most mammals this subcutaneous muscle covers most of the trunk. In humans (and also in pigs), there is one of more thin membranous layers (stratum membranosum) within the subcutaneous tissue that in some parts of the body separates subcutaneous tissue into two distinct zones: a fatty superficial layer (Camper's fascia) and a thinner, more membranous deeper layer (Scarpa's fascia).

There is some debate on the correct nomenclature of the membranous layers within subcutaneous tissue, with some referring to it as "subcutaneous fascia," while others have argued that this term should be used to designate the entire subcutaneous tissue and the membranous layer (s) designated as a "membranous layer(s) within the subcutaneous fascia" (Abu-Hijleh et al. 2006; Benjamin 2009; Lancerotto et al. 2011).

The loose structure of subcutaneous tissue makes it a path for blood and lymphatic vessels and nerves going to or coming from distant body sites; their course is short on the trunk and the cephalic areas and long on the limbs because of the elongation and deformation of the metameres during intrauterine limb growth. Additionally, the subcutaneous tissue holds a specific nervous structure, the Pacinian corpuscle, which acts as a mechanical pressure detector, as well as free nerve ending, especially in the part of subcutaneous tissue adjacent to perimuscular fasciae (Corey et al. 2011; Hoheisel et al. 2011; Tesarz et al. 2011). Finally it contains the subcutaneous adipose tissue which is an organ in itself.

Subcutaneous tissue is much more compliant than both dermis and perimuscular fasciae (Iatridis et al. 2003). Since it is situated between these less compliant structures, subcutaneous tissue is responsible for much of the deformation, or strain, that develops within non-muscle soft tissues as a result of externally or internally generated mechanical forces.

## 1.2 Interstitial Pressure

The interstitial pressure in the absence of mechanical stress has been studied in animals using a capsule with holes which has been inserted in the subcutaneous tissue and left in place until the end of the traumatic inflammation. Within the capsule, the pressure is negative and approximates 6 Torr (1 Torr = 1 mmHg (in honor of Torricelli)) (Brace and Guyton 1979). There is recent evidence that connective tissue fibroblasts actively participate in regulating interstitial fluid pressure and transcapillary fluid flow. A defining characteristic of areolar connective tissue is its loose collagen mesh filled with polyanionic glycosaminoglycans that bind large quantities of water. Reed et al. demonstrated that tension exerted by fibroblasts via integrins onto the collagen network restrains the loose matrix from excessively swelling by preventing osmotically active glycosaminoglycans from becoming maximally hydrated. One can thus think of areolar connective tissue as a meshwork with pores partially occupied by cells (fibroblasts) that hold on to the sides of the pores, keeping the mesh within a certain average pore size that prevents swelling (Reed and Rubin 2010; Wiig et al. 2003). During acute inflammation, loss of integrin-mediated cell-matrix tension results in a rapid drop in interstitial fluid pressure (becoming much more negative), causing a large rise in transcapillary fluid flux and the formation of edema.

## 1.3 Molecular Transfer Function

Insofar as blood capillaries run through the subcutaneous interstitium, exchanges and molecular transfers can occur. They are passive and regulated by the diffusion laws (Fick's laws). The

following formula applies to the passage from the blood capillaries toward the interstitial tissue:

$$J = K_f(P - p) - (\pi_d - \pi)$$

where J (moles $cm^{-2}\ h^{-1}$) is the flow, P and p are the perfusion and oncotic pressures in the capillary, and $\pi_d$ and $\pi$ the electrostatic and osmotic pressures in the ground substance. These exchanges apply especially to water and small molecules. However the capillary wall is not completely impermeable to proteins, resulting in a slow and continuous flow of large molecules into the interstitial tissue where the concentration in proteins reaches a quarter to three quarters of the plasmatic concentration (Renkin and Crone 1996). These proteins are first captured by the lymphatic capillaries and then drained toward the central veins (40–72-h cycle) (Renkin and Crone 1996). In case of edema, the distance over which metabolic exchanges have to be made is increased, which favors the occurrence of decubitus ulcers.

## 1.4 Shape Preservation

One of the major functions of the connective tissues is to preserve the overall shape of soft tissues (Scott 1975). The same applies to the subcutaneous connective tissue, which keeps the skin closely round the relief of the muscles and underlying bones. This function is secured by the gel nature of the ground substance and its hydration. In case of extracellular dehydration, the subcutis turgor decreases and loses its elasticity: the lower recovery of skin when it is raised is a sign frequently used in medicine. During aging the GAGs content decreases, inducing the laxity of the tissue.

## 1.5 Mechanical Function

The "looseness" of subcutaneous tissue allows the skin to be lifted up and moved laterally. Where the subcutis is absent (e.g., in a grafted area), the skin cannot be moved and is very fragile on friction. Limb movements also need skin sliding over joints and consequently subcutaneous shear. The looseness of areolar connective tissue layers within subcutaneous tissue also allows for some amount of "internal" gliding relative to stiffer adjacent membranous fascia layers (such as the subcutaneous membranous fascia layer mentioned above and perimuscular fasciae). In humans and animals, shear strain between subcutaneous connective tissue layers can be measured with ultrasound elastography.

Until recently, the stiffness of connective tissue was thought to be determined by the material properties of the extracellular matrix. It is now apparent that, at least in rodents, fibroblasts within "loose" areolar connective tissue play an active role in regulating the tension of the tissue. When the tissue is stretched, fibroblasts expand by actively remodeling their cytoskeleton (Langevin et al. 2005). This change in fibroblast shape is accompanied by the extracellular release of ATP and results in a drop in tissue tension (Langevin et al. 2011, 2013b). Whether similar tension regulation also occurs in humans remains unknown but could be important for adjusting interstitial fluid pressure and transcapillary fluid flow and prevent swelling when the tissue is stretched during body movements (Langevin et al. 2013a).

The deformability of subcutaneous tissue is anisotropic as moving the skin is easier in a specific direction. On the other hand, the filling of the subcutis by adipose tissue contributes to skin being permanently stretched. On the body sites subjected to high or prolonged external pressures, the adipose tissue forms a cushion which distributes the force on a larger area. Physiological body pressure sites (soles, buttocks) are provided with a thick fat (or muscular) mattress. The loss of adipose layer on the metatarsal heads is associated with thickened stratum corneum and callus formation. Subcutaneous fat-deprived people are prone to decubitus ulcers and pressure sores (type 1 pressure sore). However overweight people also are likely to develop such wounds. A lower mechanical resistance of subcutaneous tissue to shearing forces facilitates excessive sliding

of skin over bones when in semirecumbent position and results in endothelial damage of vessels crossing the fascia and their further occlusion and thrombosis. This is the most current mechanism of type 2 decubitus ulcers (Exton-Smith 1983).

## 2 The Subcutaneous Adipose Tissue

Humans, as aquatic mammals, are endowed with a subcutaneous adipose layer over their whole body (Vague et al. 1974), even in conditions of great thinness. Subcutaneous fat is absent on a few areas only: the eyelids, nose, ear pinna, and male genitalia. This adipose layer is in general thicker in females. It is one of the two components of the total fat mass, the other one being the deep adipose tissue. In addition to the well-developed cells, both contain a fraction of immature adipocytes that may grow upon endocrine stimuli and lead to obesity. The subsequent metabolic problems apply especially to deep adipose tissue.

### 2.1 White Adipose Tissue: Morphology

Adipocytes are voluminous cells (Table 1) compacted in lobules separated by thin connective tissue septa where run vessels and nerves. Each lobule has its own arteriole (Sudan and Payan 1974). The cells, round or deformed by mutual pressure, have a more or less regular diameter (about 50 μm). They harbor an enormous single lipidic vesicle devoid of membrane (Sudan and Payan 1974) and on the periphery a pushed away thin ring of 0.2–0.3-μm-thick cytoplasm containing a flattened nucleus. The adipocyte is surrounded by a regular and continuous basal membrane and a loose connective tissue (interstitium). The latter is made not of bundles but of isolated collagen fibers. It contains, very close to the cells, vessels without pericytes and an amyelinic nerve network. Neither naked axons nor contact with adipocyte membrane is found. Some fibroblasts, mast cells, and macrophages are visible (Sudan and Payan 1974), as well as a few adipoblasts, which are oblong cells with abundant cytoplasm and one or several small lipidic vacuoles. Adipogenesis is still possible in adults (Sudan and Payan 1974).

Adipocyte volume, as measured with Sjostrom and Bjorntrop's technique (Sjostrom et al. 1971), is usually larger in the subcutaneous tissue than around internal organs. It also shows a great variation according to body sites and sex (Fried and Kral 1987), being larger on the hips than on the shoulders in females and children and generally smaller in males (Table 1). Weight loss induced by sport reduces the adipocytes size, not their number.

### 2.2 Body Fat Mass and Subcutaneous Fat

Body fat mass decreases in males after the age of 13, whereas in females it still increases until adulthood (Table 2) and then keeps higher than in males over the whole life span (Table 3). In both

**Table 1** Adipocytes mean volume (nl) (mean ± 2 sem) (Vague et al. 1984)

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Shoulder | Hip | n | Shoulder | Hip | n |
| 5–9 | 046 ± 0.05 | 0.66 ± 0.07 | 17 | 0.50 ± 0.07 | 0.59 ± 0.07 | 9 |
| 10–14 | 0.42 ± 0.06 | 0.42 ± 0.06 | 24 | 0.48 ± 0.05 | 0.67 ± 0.09 | 17 |
| 15–19 | 0.37 ± 0.05 | 0.37 ± 0.05 | 22 | 0.50 ± 0.06 | 0.75 ± 0.09 | 25 |
| 20–29 | 0.39 ± 0.04 | 0.39 ± 0.04 | 42 | 0.49 ± 0.04 | 0.81 ± 0.05 | 53 |
| 30–39 | 0.39 ± 0.05 | 0.39 ± 0.05 | 22 | 0.47 ± 0.06 | 0.76 ± 0.08 | 21 |
| 40–49 | 0.42 ± 0.05 | 0.42 ± 0.05 | 27 | 0.47 ± 0.06 | 0.71 ± 0.07 | 20 |
| 50–69 | 0.42 ± 0.06 | 0.42 ± 0.06 | 13 | 0.51 ± 0.07 | 0.71 ± 0.08 | 14 |
| 70–91 | 0.46 ± 0.09 | 0.46 ± 0.09 | 13 | 0.53 ± 0.06 | 0.59 ± 0.06 | 22 |

sexes, it increases with age up to the 60s. Until the age of 15, in both sexes, fat is predominant on the lower part of the body. The same applies in women until the age of 50, at which time the fat increases in the upper part of the body, together with the body fat mass. In males, from puberty to old age, the fat is mostly located in the upper part of the body (Rebuffé-Scrive 1988; Vague et al. 1984; Table 4). This distribution is also found in obese subjects who are classified in two main categories: gynoid type if the subcutaneous fat accumulation is found mainly on the hips and thighs and android type if it is located preferentially on the upper part of the trunk and the abdomen. Android type obesity is associated with visceral deposits and an increased risk of arterial occlusive disease. Chubby cheeks are positively correlated with visceral obesity (Levine et al. 1998), as shown by computed tomography, but not with the subcutaneous fat thickness.

**Table 2** Fraction of fat tissue in body weight (%), as measured from content in triglycerides (France 1970–1980) (mean ± 2 sem) (Vague et al. 1984)

| Age group | Male | n | Female | n |
|---|---|---|---|---|
| 5–9 | 14.0 ± 1.8 | 17 | 17.8 ± 2.2 | 9 |
| 10–14 | 13.3 ± 1.8 | 24 | 19.5 ± 2.0 | 17 |
| 15–19 | 11.4 ± 1.2 | 22 | 25.0 ± 1.8 | 25 |
| 20–29 | 11.0 ± 1.2 | 42 | 26.3 ± 1.9 | 53 |
| 30–39 | 11.1 ± 1.2 | 22 | 26.8 ± 2.2 | 21 |
| 40–49 | 12.0 ± 1.3 | 27 | 27.7 ± 2.4 | 20 |
| 50–69 | 12.2 ± 1.6 | 13 | 27.0 ± 3.2 | 14 |
| 70–91 | 10.8 ± 1.6 | 13 | 16.6 ± 2.3 | 22 |

## 2.3 Energetic Function

The adipose tissue's main function is to serve as the most important energy store of the organism. In normal conditions, it represents 10 % of the body weight or 40 days of energy expenditures, stored in the lipidic vesicle in the form of triglycerides (Black and Cunliffe 1998). In spite of histological appearance, the adipose tissue is very active: its metabolic rate is identical to that of the kidney, half that of the liver (Jungermann and Barth 1996).

After a meal, the chylomicrons of the circulating VLDL are hydrolyzed by the lipoprotein-lipase at the endothelial surface of the capillaries, and their fatty acids are captured by adipocytes, where, in the endoplasmic reticulum, they are transformed into triglyceride. Insulin stimulates fatty acids and glucose capture, together with fatty acids and triglyceride synthesis within the cell.

Releasing energy from adipose tissue consists in triglyceride hydrolysis into fatty acids by triglyceride-lipase (within the adipocyte endoplasmic reticulum), an event triggered by

**Table 3** Body composition data pooled from studies in the USA and in the UK, obtained by DEXA. BMC: Body Mineral Mass (Wahner and Fogelman 1994)

| Age group (years) | BMC (g) | | Fat mass (g) | Lean mass (g) |
|---|---|---|---|---|
| | n | Mean ± sd | Mean ± sd | Mean ± sd |
| Females | | | | |
| 20–29 | 111 | 2,537 ± 424 | 19,556 ± 7,836 | 39,506 ± 4,787 |
| 30–39 | 94 | 2,580 ± 428 | 18,270 ± 7,951 | 39,538 ± 4,385 |
| 40–49 | 60 | 2,639 ± 353 | 23,284 ± 9,353 | 40,120 ± 3,976 |
| 50–59 | 143 | 2,400 ± 352 | 22,373 ± 6,932 | 38,057 ± 4,861 |
| 60–69 | 52 | 2,240 ± 350 | 23,124 ± 6,581 | 38,549 ± 4,063 |
| 70–79 | 25 | 2,256 ± 374 | 24,162 ± 7,369 | 38,082 ± 4,691 |
| Males | | | | |
| 20–29 | 6 | 2,827 ± 747 | 14,757 ± 6,986 | 56,954 ± 5,069 |
| 30–39 | 33 | 3,078 ± 441 | 15,273 ± 3,755 | 56,036 ± 5,263 |
| 40–49 | 53 | 3,199 ± 459 | 16,790 ± 4,516 | 57,007 ± 6,101 |
| 50–59 | 59 | 3,265 ± 449 | 18,894 ± 5,011 | 58,150 ± 6,276 |
| 60–69 | 42 | 3,158 ± 383 | 18,079 ± 4,849 | 57,473 ± 5,484 |
| 70–79 | 24 | 3,144 ± 358 | 17,538 ± 5,310 | 55,255 ± 4,527 |

**Table 4** Arm/thigh ratio of subcutaneous fat. Arm as well as thigh fat were assessed by a fat/muscle ratio: mean skin fold thickness from four circumferential sites (anterior, posterior, medial, lateral) divided by limb perimeter at the same level Lever and Schaumburg-Lever (1983)

| Age group | Males | n | Females | n |
|---|---|---|---|---|
| 5–9 | 0.84 ± 0.06 | 17 | 0.78 ± 0.04 | 9 |
| 10–14 | 0.85 ± 0.06 | 24 | 0.70 ± 0.05 | 17 |
| 15–19 | 1.04 ± 0.08 | 22 | 0.70 ± 0.06 | 25 |
| 20–29 | 1.16 ± 0.09 | 42 | 0.76 ± 0.05 | 53 |
| 30–39 | 1.19 ± 0.07 | 22 | 0.78 ± 0.08 | 21 |
| 40–49 | 1.16 ± 0.04 | 27 | 0.78 ± 0.08 | 20 |
| 50–69 | 1.14 ± 0.08 | 13 | 0.72 ± 0.08 | 14 |
| 70–91 | 1.09 ± 0.04 | 13 | 0.90 ± 0.10 | 22 |

glucagon and catecholamines. Oxidation by the peripheral tissues of these fatty acids may represent 80 % of the basal consumption of oxygen. Inside the adipocyte, lipolysis is facilitated by activation of β receptors (formation of cyclic AMP) (Mauriege et al. 1988), the contrary occurring when α receptors are activated. Cyclic AMP is destroyed by phosphodiesterase, but the latter is inhibited by theophylline (1.3 dimethylxanthine), hence the use of this product and caffeine (1.3,7 trimethylxanthine) as lipolytic. However the intensity of the response varies with body sites and sex; it depends on the relative proportion of β and α receptors. α2 receptors outnumber β receptors in the subcutaneous adipocytes, whereas they are found in similar quantities in the omental adipocytes (Mauriege et al. 1987). In females, the subcutaneous adipocytes of the gluteal and femoral areas have more α than β receptors and are larger than in males (Richelsen 1986). The lipoprotein-lipase activity is also higher (Fried and Kral 1987). It would be increased in situ by estrogen or progesterone injection (Rebuffé-Scrive 1987; Rebuffé-Scrive et al. 1985).

In addition to the release of fatty acids, other lipids, and metabolites, adipose tissue secretes several hundreds of identified bioactive factors (adipokines) including leptin, adiponectin, aplin, and vaspin that influence local adipogenesis, immune cell migration into adipose tissue, and adipocyte metabolism and function, as well as regulate metabolic processes in the brain, liver, muscle, vasculature, heart, and pancreatic β-cells (Cao 2014). Leptin (LPT), a 167-amino-acid protein, is secreted by adipocytes as soon as the lipid supply is sufficient. LPT inhibits the hypothalamic center for hunger and reduces the synthesis and release of the neuropeptide Y, which increases food intake, reduces thermogenesis, and increases insulin blood level. In short, LPT regulates the feeding habits, the metabolic level, the autonomous nervous system control, and the energetic equilibrium. LPT blood level is a reflection of body fat mass. For a similar BMI, it is much higher in women (testosterone would inhibit LPT synthesis and secretion). In obese subjects, the efficiency of the LPT is reduced and hyperleptinemia is observed. A lipid-rich diet would facilitate the resistance to LPT (Friedman 2000).

Adipoblasts can differentiate into adipocytes and therefore increase the fat mass when they mature. This transformation would require the action of plasminogen, after the fibronectin matrix which surrounds the adipoblast has been degraded by the plasma kallikrein (Selvarajan et al. 2001).

Although visceral adipose tissue was for decades considered a major culprit in development of the metabolic syndrome, recent evidence indicates that subcutaneous adipose tissue, especially on the trunk, also can be involved in the development of insulin resistance. Decreased adipocyte differentiation leading to adipocyte hypertrophy and spillover of free fatty acids can lead to local inflammation as well as ectopic fat deposition in other tissues such as liver and pancreas (Patel and Abate 2013).

## 2.4 Thermal Function

The subcutaneous adipose tissue contributes to the thermal insulation of the organism. The fatty areas (gluteus, outer sides of the arms, and thighs in children and women) are usually the coldest ones. The thermal inertia of fat is low: $22–32.10^{-5}$ $cal^2.cm^{-4}.°C^{-2}.s^{-1}$, whereas that of the skin without subcutis is higher than 90 $cal^2.cm^{-4}.°C^{-2}.s^{-1}$ (Houdas and Guieu 1977). This property is most useful to protect the inner organs (the core) in hot as well as cold environment, a

situation that should have been endured by many primitive humans.

## 2.5 Aesthetic Function

The body distribution of the subcutaneous adipose tissue is an essential component of the male and female morphology: predominance on shoulders and thorax in males and hips and buttocks in females. In the latter, the relief of the limb muscles is lightly marked, as it is masked by the adipose tissue. On the face, adipose tissue reduction preceding skin hyperlaxity is often the first sign of aging: in cases of obesity, the chubby cheeks maintain a barely wrinkled aspect on the face longer. Filling is a technique used in cosmetic surgery to compensate for a reduced adipose tissue. In infants under a year, the subcutaneous adipose tissue thickness, especially in the face and limbs, gives the child a typical morphology. It is likely to be an energy reserve before the start of a period where growth, standing, and exercise will be simultaneously acted.

## 2.6 Brown Fat

Brown fat has long been known for its thermogenic functions in hibernating animals. The morphology of their adipocytes is very specific because of the multilocular distribution of the adipose vesicles (Lever and Schaumburg-Lever 1983). It was, until recently, thought to be vestigial in humans and present mainly in fetus and newborns. However, the role of brown and "beige" fat is now being reexamined with the new understanding and knowledge that adipocytes within white adipose tissue can be induced to become thermogenic, especially after cold exposure (Lee et al. 2014; Peirce et al. 2014).

## 2.7 Conclusion

The subcutis is an area of the body that has received comparatively little attention, compared with the skin and underlying muscles. The anatomical continuity between the subcutaneous connective tissues, especially the membranous layers, and the fasciae enveloping muscles, is recently being appreciated from the points of view of biomechanics and sensory perception. There is no doubt that further incorporation of subcutaneous tissue into our understanding of the cutaneous, adipose, and musculoskeletal systems will inform our understanding of whole-body physiology.

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