2 Clinically Applicable Concepts of Fat Metabolism
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Abstract
This chapter explores surgically applicable anatomical, compositional, and diverse physiologic properties of adipose tissue and their effects on outcomes after body contouring procedures. Adipose is a complex, active endocrine organ. Eighty five percent of all adipose tissue in the human body is subcutaneous, arranged into apical, mantle, and deep layers. The deep layer is found deep to Scarpa’s fascia and is the target layer for liposuction. Adipose tissue is highly vascularized with low oxygen demand and high susceptibility to epinephrine in tumescent fluid. It contains a variety of cell types including a rich store of mesenchymal stem cells, adipocytes arranged into lobules, and supportive connective tissue. Now considered the largest endocrine organ in the body, adipose plays active roles in energy homeostasis, glucose metabolism, immune function, and hormonal regulation. According to the widely accepted “Lipostatic Hypothesis,” the total body number of adipocytes is set during adolescence. Centrally regulated autonomic processes work to maintain a set body weight. If these are overwhelmed by a chronic positive or negative energy balance, adipocytes will change size and eventually volume with resultant metabolic sequelae. Some studies suggest that after lipectomy procedures, the lipostatic mechanism can lead to compensatory fat growth in non-surgically resected areas, both subcutaneous and visceral, beginning 3 months postoperatively. Potential resulting metabolic changes may theoretically affect the patient’s overall health as a result. Finally, understanding the structure and biologic properties of the adipocyte will help guide surgical techniques to improve overall “take” after fat grafting procedures.

Keywords: Adipose tissue anatomy, lipectomy, obesity, fat homeostasis, fat biology, adipocyte, fat grafting

2.1 Introduction
While historically we thought that adipose was an inert tissue, capable only of energy storage, this over-simplified understanding is now a thing of the past. After extensive research in recent years, adipose is now regarded as a highly specialized, complex endocrine organ exerting widespread effects in virtually all organ systems. According to the American Society for Aesthetic Plastic Surgery, suction lipectomy has become the most common plastic surgery intervention, with almost 400,000 patients treated in 2015. Increases in this patient population further obligates surgeons of the adipose organ to master an understanding of its biology, which will in turn cultivate a deeper appreciation for liposculptural impact and afford improved results.¹

2.2 Anatomy of Adipose Tissue
2.2.1 Gross Structure
Adipose tissue exists throughout the human body providing the largest volumetric contribution to the connective tissue matrix. Total body fat in lean adults, of which 85% is subcutaneous and the remaining is visceral,
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...contributes approximately 8–18% of total body weight in males and 14–28% in females, and can reach up to 60–70% in obese patients.²

Markman and Barton were the first to investigate the gross anatomy of subcutaneous fat in a cadaveric study in 1987. Their findings are still commonly accepted and utilized today.³ There are three discrete layers of subcutaneous fat: apical (or Periadnexal), mantle (or superficial), and deep.

The apical layer is most superficial, located just beneath the reticular dermis, containing yellow-appearing fat and fibrous septa running perpendicular to the skin. Other structures are present including sweat glands, hair follicles, and vascular and lymphatic channels. All these structures are susceptible to damage by the liposuction cannula if this layer is not carefully avoided (▶Fig. 2.1). Traumatic injuries were more common when larger diameter cannulas were used (8–10 mm) with sequelae including seromas, hyperpigmentation, and even skin necrosis. These complications are rare in today’s era of 2–3 mm cannulas.³,⁴

Next is the mantle layer, located everywhere but the eyelids, nail beds, bridge of the nose, and penis, and containing small fat lobules packed tightly with closely-spaced septae. It serves as a shock absorber, helping the skin resist trauma by distributing pressure over a larger field. The thickness of this layer is consistent throughout the body and correlates with the “pinch test”, a depth gauge for the liposuction cannula which should be inserted just beneath this layer.³,⁴,⁵

Finally, the deep layer, situated just above the underlying muscle fascia, contains large, irregular, poorly organized fat lobules. It is separated from the mantle layer by a continuous fibroelastic membrane, the fascia superficialis (called Scarpa’s, Colles’, or Camper’s fascia in certain anatomic areas). This is...
target layer for liposuction. Its thickness varies by region based on genetics, diet, and sex, with distinct gender-specific distributions to consider during body contouring procedures. While females display a metabolically-favorable gynoid or peripheral distribution, with increased fat deposition in the gluteofemoral areas, men tend toward a metabolically-unfavorable android or central distribution with increased visceral deposition.\(^6\)

### 2.2.2 Cellular Components and Structure

A wide variety of cell types comprise the adipose organ, of which only an estimated 50% are actually adipocytes (\(\text{Fig. 2.2}\)).\(^2\) Other cells that intermingle with the predominant adipocyte, including preadipocytes, endothelial cells, smooth muscle cells, and fibroblasts, are essential to the structure and function of adipose. Stem cells also exist in quantities so rich that adipose is considered their largest known reservoir.\(^7\) Almost every cell type in normal circulation may be present: immune, mesenchymal, vascular, and nervous cells have all been identified in lipoaspirates.\(^2,7\)

The adipocyte is derived from a connective tissue line of cells resembling fibroblasts.\(^8,9\) Mesenchymal stem cells differentiate into spindle-shaped preadipocytes which increase their lipid droplet size, becoming more spherical, to develop into metabolically-active mature adipocytes.\(^8,9\) The mature adipocyte consists of a single, large, central lipid droplet surrounded by a peripheral rim of cytoplasm containing a visible nucleus and other organelles, all encased in a thin external membrane.\(^9\)

Adipocytes in subcutaneous fat are arranged into lobules supported by septa, a stroma of loose connective tissue, containing a dense capillary network. A high osmotic pressure gradient forces the cells into a tightly packed configuration within the lobule, each supported by a web of collagen fibers known as the extracellular matrix (ECM). The ECM, contiguous with the interlobular septa, connects each cell to the capillary network and also acts as a substrate for cell growth and proliferation.\(^4,7,9\) This high capillary density, along

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**Fig. 2.2** Variety of cell types that comprise adipose tissue.
with low O₂ demands, gives adipose the highest partial oxygen tension of all organs. The characteristic arrangement of adipose (cells compacted within rich microvasculature) and the high sensitivity of these capillaries to epinephrine allows for effective use of tumescent anesthesia and makes office-based liposuction a safe and bloodless operation.

2.3 Physiology of Adipose Tissue

2.3.1 Functions of the Adipose Organ

Until recently, scientific belief resigned adipose tissue to the simplistic roles of energy storage, heat insulation, and organ cushioning only. This all changed with the discovery of leptin by Friedman and colleagues in 1994 a ground-breaking milestone which sparked an eruption of scientific interest and subsequent knowledge that continues to evolve to this day. Adipose is now considered the largest endocrine organ in the body with known significant roles in lipid transport and synthesis, insulin sensitivity, and regulation of hemostasis, blood pressure, immune function, and angiogenesis.

Energy homeostasis is an important function of the adipocyte, which is unique in its ability to store the most amount of calories in lipid form, readily available for rapid release. At times of rest, adipocytes uptake circulating lipids (products of broken down ingested fat) and stored them as triacylglycerol droplets. When high metabolic demands increase sympathetic drive, adipocytes become stimulated via adrenergic receptors. This prompts hydrolysis of stored lipid and release of free fatty acids into the vasculature for use by other organs and tissues. Perilipins on the surface of intracellular lipid droplets act as gatekeepers, preventing excessive hydrolysis. In obesity, perilipin concentrations decrease, rendering the adipocyte fragile and prone to free fatty acid release.

Adipose also interplays with the endocrine system by releasing two hormones specific to and highly expressed in this tissue. Leptin exerts a direct effect on the hypothalamus, signaling satiety and decreasing food intake. Homeostatic hormones, such as cytokines, insulin, glucocorticoid, sex hormones, and catecholamines, modulate leptin's release, thus implicating it in various other roles including glucose metabolism, human development, and blood pressure.

Adiponectin is highly involved in the mechanism of insulin resistance by enhancing insulin sensitivity in muscle and the liver. It also promotes free fatty acid oxidation in tissues, thereby decreasing serum lipid concentration. In obesity, adipose maintains a constant inflammatory state, releasing cytokines that modify release of these hormones. Adiponectin decreases while leptin actually increases creating resistance in target cells. These alterations are implicated in the metabolic derangements and disease state associations (including atherosclerosis) associated with obesity.

2.3.2 Adipose Tissue Development, Metabolism, and Turnover

Adipose development begins in infancy with cell proliferation. The number of adipocytes continues to increase through puberty before leveling off in
adolescence and finally ceasing in adulthood. After this point, the total number of adipocytes in the body generally does not change. Lifelong obesity is therefore largely determined in childhood. Weight changes in adulthood generally result from adjustments in cell volume—hypertrophy and hypotrophy—rather than number.\textsuperscript{2,10,14} Adipocyte number is tightly controlled in a constant remodeling process that carefully balances the rate of adipocyte apoptosis/necrosis with adipogenesis.\textsuperscript{10}

Fat cell turnover begins with adipogenesis. The fully developed mature adipocyte averages 50–60 µm in diameter. Throughout its 10 year lifespan, the cell will continue to expand until reaching a maximum size governed by blood supply, about 150–160 µm. After this point, the cell will succumb to hypoxia and die. The dying adipocyte releases inflammatory factors that recruit M1 macrophages to surround the dying adipocyte, forming “crown-like structures”, and phagocytose the lipid droplets remaining from dead cells.\textsuperscript{2,10} These macrophages release more cytokines, in turn recruiting more cells and promoting angiogenesis and preadipocyte differentiation. In obesity, a higher rate of cell death overwhelms available resources and blunts fat turnover, precipitating accumulation of metabolically unfavorable fat over time.\textsuperscript{10}

The commonly accepted “Lipostatic Hypothesis” explains the mechanism of body fat maintenance. Weight fluctuations trigger centrally-regulated autonomic systems that adjust food intake and metabolic rate until the set weight is regained.\textsuperscript{10} Chronic energy imbalance can overwhelm lipostatic mechanisms resulting in significant weight change. Most patients seeking liposuction have unwanted fatty deposits amassed from a lifestyle favoring a positive energy balance state between diet and exercise. Adipocytes in this state will hypertrophy until a critical size is reached, about 170% of ideal cell size and determined by genetics and anatomic depot site. After this point, hyperplasia will begin.\textsuperscript{2} Cells in obese tissue are generally larger, their size correlating with insulin insensitivity.\textsuperscript{2}

In a state of negative energy balance, adipocyte size and volume reduces. Cells appear dramatically slimmed down with a paucity of lipid and increased adrenergic nerve fiber and vessel densities.\textsuperscript{2} Glucagon and epinephrine activate triglyceride lipase in stored adipose tissue to mobilize fatty acids, resulting in weight loss.\textsuperscript{4} This can vary by anatomic region: for example, in the gluteofemoral region of premenopausal region, there is decreased expression of adrenergic receptors with reduced lipolytic activity making this area is more resistant to weight loss.\textsuperscript{2}

In the fed state, serum glucose increases activating insulin which antagonizes glucagon. With rising glucose levels, the insulin-to-glucagon ratio will eventually favor insulin. At this point, glucagon levels decrease and fat can no longer be mobilized. This raises important points about diet and nutrition. An ideal diet should both restrict caloric intake and promote stored fat mobilization. A diet rich in refined carbohydrates produces glucose surges, stimulating peaked release of insulin which inhibits adipocyte catabolism. Conversely, a diet of fats, proteins, and complex carbohydrates (i.e., fruits and vegetables), which require prolonged digestion and absorption times, maintains lower postprandial glucose levels, thereby effectively promoting weight loss (▶ Fig. 2.3).\textsuperscript{4}
2.4 Biological Implications of Liposuction

2.4.1 Biological Effects on Cosmetic Outcome

Knowledge of lipostatic hypothesis begs us to question the implications of procedures like liposuction that reduce total body fat. While the current data are conflicting, it raises interesting points that should be included in preoperative conversations to ensure successful outcomes and manage expectations. Most lipectomy experiments have been conducted with animal models and generally show a compensatory increase in non-excised fat pads. Similar results were seen in human studies which claimed that compensatory fat growth after lipectomy manifested as breast enlargement. This may have been due to general weight gain and body fat redistribution in non-aspirated areas, but alterations in the androgen-to-estrogen ratio could also be a contributing factor.

A recent review summarizes data from human trials examining short- and long-term outcomes after liposuction. These results generally concur with the animal studies: postoperatively, patients experience an initial loss of fat mass and weight lasting up to 3 months. However, after 3 months body fat
restoration gradually begins and is usually complete in one year. Hernandez et al was first to evaluate anatomic fat redistribution in a prospective, randomized-controlled trial. Patients treated with liposuction of the thighs, hips, and/or abdomen were compared to an untreated control group. In the first 6 weeks, the treated group maintained a reduction in percent body fat and total fat mass. But over the next 6 months, the difference between the groups gradually decreased until none was seen at 1 year. Interestingly however, at 1 year, fat loss was actually retained in the thigh and hip regions while fat accumulated in abdominal regions, both visceral and subcutaneous, whether or not patients had actually received abdominal liposuction. Furthermore, the volume of visceral abdominal fat was significantly increased when compared both with postoperative volumes in the control group and with baseline volumes in the treated group.

Several proposed mechanisms explain fat restoration after liposuction. Some theorize that cells injured by the liposuction cannula release inflammatory cytokines that promote adipogenesis. Others suggest that the sudden shortage of stored energy triggers homeostatic mechanisms, inducing a compensatory adipogenic cascade. Based on this concept, Benetti et al investigated a strategy to improve long-term outcomes in a randomized-controlled trial. After undergoing abdominal liposuction, enrolled patients were assigned to either a training group, which maintained a vigorous thrice-weekly exercise schedule, or a non-training group. At 6 months, total fat mass decreased only in the training group, while visceral fat mass increased in the non-training group when compared both with baseline preoperative values in these patients and with results seen in the training group. Thus, assurance of successful liposculpture outcomes is ultimately due to a combination of the surgeon’s operation and the patient’s dedication to appropriate diet and exercise routines to maintain a negative energy balance.

2.4.2 Metabolic Effects of Liposuction

While cosmetic outcomes of liposuction are clearly seen, much debate has focused around whether there are also metabolic effects. It is well established that a central (abdominal) fat distribution is associated with significant increase in risk for cardiovascular disease and type 2 diabetes mellitus, while a gluteofemoral distribution may actually be protective against cardiovascular disease.

With this rationale, many have tested the hypothesis that surgical reduction of fat volume from certain anatomic regions may yield health benefits. However, results have been conflicting. A landmark study of obese patients undergoing large volume abdominal liposuction by Klein et al failed to show any significant differences after 10–12 weeks in multiple endpoints including insulin sensitivity and risk factors for coronary artery disease. Others have reported similar findings in both obese and lean patients.

Conversely, numerous other investigators suggest that significant health benefits do exist, especially in the obese population and after longer-term follow up. For example, Giugliano et al reported a decrease in insulin resistance and inflammatory cytokines with increased adiponectin and HDL in obese patients 6 months after large volume liposuction. Also noted was a correlation between the volume of fat liposuctioned and the degree of change in these
factors.\textsuperscript{1} Other studies, including one containing the largest reported cohort of obese women, showed not only similar improvements in insulin levels and sensitivity, but also decreased blood pressure and lipid levels, all at 3–4 months.

The reasons for such inconsistent results are unclear. One explanation may be that while most of the larger studies limited their treatment area to the abdomen, some smaller studies did not standardize treatment areas and included patients liposuctioned in multiple different regions. Only one study has examined patients undergoing liposuction to the gluteofemoral region alone. At 1 year, these patients maintained decreased fat in this region and also exhibited an increase in postprandial triglycerides, suggesting a detrimental effect of liposuction in this area. Other results further suggested that these metabolic derangements may be due to post-procedural mobilization of preexisting triglyceride stores.\textsuperscript{1}

Although all of the above information suggests wide variability in cosmetic and metabolic outcomes after liposculpting, general patient satisfaction remains reassuring. In fact, one survey reported an 80\% satisfaction rate after liposuction despite weight gain in 43\% of responders.\textsuperscript{16}

\section*{2.5 Biological Implications of Fat Grafting}

Considering the biology of the adipocyte, a cell with fragile structure, high sensitivity to hypoxia, and adaptive propensity for cellular turnover, it is no surprise that fat grafting presents so many challenges. Reported graft resorption rates range from as low as 20\% to as high as 90\%. The commonly accepted “Cell Survival Theory” states that the success of fat grafting depends directly on the number of viable adipocytes transplanted.\textsuperscript{18} Therefore, understanding the biological implications of the transplantation process can help surgeons to improve graft “take”. The adipocyte’s cellular structure (a large lipid droplet surrounded by a thin external membrane) makes it highly susceptible to rupture when introduced to the forces of negative and positive pressure and sheer stress during the process of fat grafting. Sheer stress during aspiration can be minimized by using larger cannulas (5 mm rather than 3 mm), which have been shown to improve viability and take.\textsuperscript{18,19} High suction pressures and centrifugation speeds (up to 5,000 g) do not appear to have much effect on cell survival.\textsuperscript{20} Many have studied the effects of stem cells, suggesting increased graft viability and take with a high stem cell concentration in the grafted tissue.\textsuperscript{11} However, others report that tissue processing that achieves the highest possible concentration of pure fat for injection has the greatest impact on graft take.\textsuperscript{21,22} Finally, sheer force generated during injection has been shown to significantly affect graft viability. Maintaining a low positive pressure by slow injection is most important, even more so than the diameter of the injection needle.

\section*{2.6 Conclusion}

Once a highly underestimated tissue, adipose is now appreciated as a complex, dynamic organ. Recent discoveries have placed the adipose organ at the center of much scientific intrigue. Our understanding of its properties is constantly evolving with the proliferation of scientific data that continues today. With deep understanding and appreciation for the dynamics of adipose tissue, surgical outcomes can only improve.
References