The role of inflammation in adipocytolytic nonsurgical esthetic procedures for body contouring

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Background: The adipocytolytic non-surgical esthetic procedures are indicated for the reduction of localized fat and are effective in reducing local adiposity through the ablation of adipocytes with fast and lasting results, besides causing local inflammation.

Objective: This study aimed to characterize the adipocytolytic procedures and correlate the phases of the inflammatory process with the results obtained from such procedures, in order to clarify the role of inflammation triggered by the adipocytolytic procedures and its relation with the lipolytic process, with a focus on body shaping.

Methods: This work is an integrative literature review that presents a total of 72 articles published between 1998 and 2015, derived from the PubMed database, in order to establish a relationship between clinical and basic science research, assuming an important role in medical practice based on evidence.

Results: The results show that the adipocytolytic procedures are characterized by triggering inflammation arising from the disruption of adipocytes by interfering with the lipolytic signaling pathways in both acute and chronic phases of inflammation through the direct action of proinflammatory cytokines or catecholamines. Therefore, inflammation plays an important role in modulating the lipolytic process, influencing body shaping.

Conclusion: The inflammatory process assists the adipolytic process in all stages of inflammation, contributing to the reduction of body contouring.

Keywords: inflammation, body contouring, esthetic procedures, adipocytolysis

Introduction

Overweight is a body alteration that is independent of lean body mass; however, it is directly related to the adipose tissue. Overweight is a nonpathologic condition, although evolution can lead to obesity (body mass index $\geq 30$ kg/m$^2$), which increases the development of several chronic inflammatory diseases.1-4

Fat tissue is derived from a mesenchymal precursor and this differentiation may follow two routes to generate either unilocular fat tissue (white) or multilocular (brown). The maturation of these cells is dependent on the receptor activated by peroxisome proliferator-$\gamma$ and the transcription factor CEBP-$\alpha$. The white fat tissue has the function of energy reserves and endocrine secretion. The location may be visceral or subcutaneous, which is related to the localized fat.2,5-8 The lipid accumulation in adipocytes is controlled by insulin and prostaglandins; on the other hand, the breakdown and release of these lipids are regulated by noradrenaline, glucagon, adrenocorticotropic hormone and steroid hormones.2,6,9,10
Recent research has shown that adipose tissue is able to release cytokines, chemokines and adipokines, which participate in autocrine or paracrine signaling pathways, with effects in the adipose tissue as in other surrounding tissues (endocrine activity). These cytokines have many functions, among which we can mention immune modulation and even modulating the lipolytic process, in other words, mobilization of fat from the adipocytes. The chemokine-producing cells are adipocytes, preadipocytes and macrophages especially.9,11

The heterogeneous locations of the unilocular white adipose tissue when associated with overweight culminates in an esthetic disorder called localized fat or focal adiposity, which is currently rejected by the populations based on their cultural values.1–3 The increasing demand by the populations worldwide for body fat reduction methods stimulates the development of safer and more effective techniques and approaches in the field of esthetic medicine, with regard to surgical and nonsurgical medical interventions.1,12–14

The most commonly used medical approaches for weight loss, aimed at reducing the subcutaneous adipose tissue, are surgical (lipectomy), such as liposuction and abdominoplasty, among other procedures. However, the growing desire for weight loss among the people encouraged the emergence and improvement of techniques for nonsurgical body contouring, among which can be mentioned cryolipolysis, radiofrequency, phototherapy (laser and light), injectable lipolytic (mesotherapy), hydrodilipolasy, low-intensity focused ultrasound, high-intensity focused ultrasound, cavitation and others therapies. These techniques have the following advantages: they are usually painless, although it is a subjective aspect, lead to quick recovery, require little or no downtime, have few adverse effects and are safer. However, the surgical approaches for body contouring have increased the risk of death, infection, embolism, visceral perforation, seroma, nerve compression, swelling, anesthetic toxicity, scars and five surface irregularities, besides having high costs.12,13,15–20

Generally, diversified nonsurgical techniques suitable for the reduction of localized fat and applied in clinical practice have lipolytic action aimed at reducing the local adiposity.21

Lipolysis is the term given to the hydrolysis of lipids into their respective metabolites: fatty acids and glycerol. This process occurs in the adipocyte and is physiologically controlled by the enzymatic action of the hormone-sensitive lipase (HSL) and lipoprotein lipase. The HSL is intracellularly expressed in adipocytes, and its activation is dependent on catecholamines, natriuretic peptides, growth hormones, glucocorticoids and tumor necrosis factor-α (TNF-α) and inhibition is dependent on insulin. The lipoprotein lipase is synthesized in the adipocytes and transferred to the endothelial cells of blood capillaries (extracellular), and is responsible for the chylomicrons breaks arising from food and very-low density lipoproteins.6,21,22

The hypertrophy caused by increased lipid inclusion in the adipose tissue results in several metabolic consequences for the adipocytes. The physiologic lipolytic process induces other processes such as innate immune response activation and the activation of resident macrophages in the adipose tissue. Importantly, in the context of physiologic lipolysis, no inflammatory process is involved in the clearance of fatty acids, since these are unsaturated and do not trigger proinflammatory signaling pathways.11,21,24

On the other hand, saturated lipids are able to activate the endotoxin inflammatory pathway through the toll-like 4 receptor (TLR4) present in resident macrophages of the adipose tissue. The lipid clearance stimulates chemotaxis of monocytes arising from hematopoietic bone marrow in a directly proportional manner, through the production and release of monocyte chemoattractant protein 1 chemokine by the adipocytes and its effect on the chemokine receptor present in macrophages and monocytes. These monocytes differentiate into macrophages when infiltrating the adipose tissue and are activated by saturated fatty acids, firing endotoxin pathway. The endotoxin pathway culminates in the activity of the nuclear transcription factor NF-κβ responsible for transcribing proinflammatory genes that induce the production and release of TNF-α by the macrophages and is also able to stimulate the adipocytes to produce and release proinflammatory adipokines. Thereby, a vicious circle between the activation of macrophages and production of adipokines from the adipocytes is generated.11,21,24–26

Lipolysis is a physiologic process regulated by multiple signaling pathways and is the basis for the nonsurgical methods for the reduction of localized fat. These methods can be classified into noncytolytic methods and cytolytic methods (adipocytolysis).22,27

Nonsyctolytic methods are techniques to stimulate the mobilization of lipids by the adipocytes without affecting their functions or the integrity of their cell membranes. These techniques act as temporary metabolic enhancers, encouraging the breakdown of lipids into fatty acids and glycerol to be mobilized out of the adipocyte and their subsequent metabolism by the liver. The disadvantages of these methods are that their effects in the adipose tissue and body shaping tend to be transient. Such methods are associated with physiologic lipolytic signaling pathways.21,27,28
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The cytolytic methods, also known as adipocytolysis, are techniques to break or solubilize lipids through the partial or total ablation of adipocytes, destroying their plasma membrane. These techniques promote chemical or mechanical ablation, causing permanent changes in the adipocytes and promoting improvement in the body contouring and reduction in the body fat with extended long-term effect.21,27

Among the nonsurgical procedures that use adipocytolytic principles, we can highlight high-intensity focused ultrasound, ultrasound cavitation, radiofrequency ablation, ablative laser and mesotherapy (sodium deoxycholate). The cellular changes caused by such techniques on the adipocyte membrane are: rupture of the membrane by cavitation, thermal damage, poration of the membrane, lysis and membrane emulsification. All adipocytolytic procedures trigger local inflammation evidenced by the appearance of local adverse effects arising from permanent alterations caused in the adipose tissue.12,15,17,19,21,27,29–37

This study aims to characterize the adipocytolytic procedures and relate the phases of the inflammatory process with the results obtained from such procedures, in order to clarify the role of inflammation and its influence on the lipolytic process. This integrative literature review confronts the clinical data related to adipocytolytic esthetic procedures with basic science research data related to inflammation in the adipose tissue and its local effects, assuming an important role in medical practice based on evidence, in order to improve the understanding of adipocytolytic esthetic procedures and their effects on body contouring.

Methods

This study is an integrative literature review based on the model proposed by Whittemore and Knaf.38 The selection of articles gave a total of 72 studies published between 1998 and 2015, derived from the PubMed database, which were divided into two groups: clinical research studies (41 articles) and basic sciences studies (31 articles). Of the total studies, 53 are original scientific articles and 19 are literature reviews, as shown in Figure 1.

The classification of articles in the two groups was performed according to the methodology adopted for each study. If the article used clinical data as a research resource, the classification was “clinical research studies”. If the article used experimental data as a research resource, the classification was “basic science studies”.

The selection of the clinical research studies group was based on the following inclusion criteria: articles containing the search keywords “inflammation and adipose tissue” or “adipocyte cytolysis” or “adipose tissue reduction”. However, the articles that contain only surgical and/or nonadipocytolytic techniques, according to Rotunda21 and Mulholland and Kreindel,27 were excluded. This methodology aimed at selecting the articles strictly related to basic science data, with the focus on inflammation and damage in adipose tissue.

After the classification and selection of articles, the clinical research group was confronted with the basic research group, aiming to improve the understanding of adipocytolytic esthetic procedures and their effects on body contouring.

Results

Database analysis

The selected articles were counted and grouped into a contingency table, in which was analyzed the relationship between the nature of research, basic or clinical, and the type of publication, review articles or original articles. Fisher’s test for statistical analysis of contingency was performed, presenting a p value of 0.5706. This indicates there was no significant difference between the article groups, showing a homogeneous distribution of the articles in the testing groups, minimizing possible selection bias, as shown in Figure 1.

Characterization of adipocytolytic procedures

The adipocytolytic esthetic procedures were characterized by Rotunda21 and Salti et al39 as techniques to break the adipocyte membrane, releasing its cytoplasmic contents into the interstitial tissue. These techniques, according to Mulholland and Kreindel27 and Thuangtong et al,27 cause tissue changes and permanent injuries to the fat cells. These effects are achieved through cavitation, thermal damage, formation of pores in the plasma membrane and solubilization of plasma membrane.10,21,27,29,37,39 Figure 2 illustrates the differences between the noncytolytic mechanisms (Figure 2A) and the adipocytolytic mechanisms (Figure 2B).

Cryolipolysis is a technique that can reduce body measurements. Although its inflammatory mechanism is not completely understood, the basic science literature reports...
apoptotic cell death, in contrast to the clinical data that report the presence of an intense inflammatory process. Although cryolipolysis is an adipocytolytic procedure, there is no consensus in the scientific literature about the membrane disruption mechanism, as described by Rotunda.21,40–44

**Cellular changes and possible adverse effects**

Cellular changes in the adipose tissue, caused by adipocytolytic procedures, culminate in tissue damage due to cell death process undergone by adipocytes, which can be promoted by necrosis.45,46 In Table 1 are outlined the most widely used techniques for body sculpting through adipocytolytic procedures and their mechanisms, cellular changes and possible local adverse effects.

Analysis of Table 1 indicates that all possible local adverse effects derived from adipocytolytic procedures stem from the inflammatory reactions of acute and chronic nature, triggered by changes exerted on the plasma membrane of adipocytes, generating an immune response mediated by chemotactic inflammatory cells in septa and areas of subcutaneous fat lobules.35,36,47,48

**Inflammation derived from adipocytolysis**

Disruption of the cell plasma membrane in response to physical or chemical aggression derived from esthetics procedures,
leading to cell death by primary necrosis, results in the display and release of intracellular molecules not found physiologically in the extracellular environment. Such endogenous molecules are known as damage-associated molecular patterns (DAMPs) and are capable of activating TLR, advanced glycation end products receptor and ST2 receptors. In the specific case of adipocytes, saturated fatty acids present in their lipid content also act as DAMP, activating the endotoxin pathway through recognition by TLR4+ phagocytes such as macrophages residents of adipose tissue.11,23,24,26,46

Saturated fatty acids released by adipocytolysis induce macrophage activation, leading to the production and liberation of proinflammatory cytokines, such as TNF-α, which is also produced in the adipocytes and, hence, released by their disruption. This interaction occurring between lysed fat cells and macrophage activation is negatively regulated by the suspension of adipocytolytic stimulation, neutralization of DAMPs, anti-inflammatory cytokines produced and released by the adipose tissue, physical exercises, activating transcription factor 3 activation in the macrophages, downregulation of the MAFB gene and vitamin E.4,8,24,26,49

The macrophages, once activated by the presence of DAMPs and recruited by the release of proinflammatory cytokines originating from adipocytolysis, acquire proinflammatory phenotype characterized by macrophage polarization 1 (M1) and produce TNF-α, interleukin (IL)-6, nitric oxide, among others proinflammatory molecules. In turn, the release of proinflammatory cytokines originating from the damaged fatty tissue, combined with the release of proinflammatory cytokines derived from activated M1 macrophages results in the local induction of resistance to insulin, lipolysis stimulation and inhibition of adipogenesis, as previously shown by Grant and Stephens.22 In Figure 3 is illustrated the mechanism of macrophage activation phenotype M1, triggered by adipocytolysis and release of proinflammatory cytokines by both adipocytes lysates, intact adipocytes and also by activated macrophages.4,11,22,26,46

Adipose tissue macrophages have great significance in the initiation and regulation of the inflammatory process, since their polarization triggers dichotomous effects. The proinflammatory M1 polarization, also called the classical activation of macrophages, is responsible for mediating TH1-type immune responses, with insulin resistance effects, lipolysis stimulation and inhibition of adipogenesis in the adipose tissue. On the other hand, anti-inflammatory M2 polarization, also called alternative macrophage activation, is the polarization most commonly found in expanding adipose tissue, which is being

<table>
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<th>Table 1 Adipocytolytic procedures</th>
<th>Mechanisms</th>
<th>Cellular changes</th>
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<td>HIFU</td>
<td>Cavitation and thermal disruption</td>
<td>Disruption of plasma membrane</td>
<td>Pain, bruise, edema, dysesthesia and erythema</td>
<td>1, 14, 17, 18, 30, 31, 33, 47, 66–69</td>
</tr>
<tr>
<td>No thermal cavitation ultrasound</td>
<td>Cavitation</td>
<td>Disruption of plasma membrane</td>
<td>Mild pain</td>
<td>15, 18, 19, 46, 72</td>
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<tr>
<td>Radiofrequency ablation</td>
<td>Thermal damage</td>
<td>Damage to the plasma membrane</td>
<td>Transient erythema and little pain</td>
<td>1, 12, 14, 17, 27, 32</td>
</tr>
<tr>
<td>Laser ablation</td>
<td>Poration</td>
<td>Formation of pores in the membrane</td>
<td>Rare swelling or local erythema</td>
<td>1, 14, 18, 34, 73</td>
</tr>
<tr>
<td>Mesotherapy (sodium deoxycholate)</td>
<td>Solubilization and emulsification</td>
<td>Disruption of plasma membrane and emulsification</td>
<td>Pain, bruise, urticaria, panniculitis</td>
<td>21, 18, 20, 29, 35–37, 39, 48, 74–77</td>
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Abbreviation: HIFU, high-intensity focused ultrasound.
The above data suggest that acute inflammation arising from adipocytolytic procedures is directly related to the appearance of local adverse effects and acts by helping the lipolytic process objectified by the procedures of body sculpting. The adipocytolysis reduces the number of adipocytes in the subcutaneous adipose tissue due to lysis of membranes and consequent cell death by necrosis. It also stimulates lipolysis by reducing the local accumulation of lipids in intact neighboring adipocytes, since the proinflammatory cytokines of the adipocytolytic microenvironment act locally, thereby contributing to the reduction of localized subcutaneous adipose tissue and reduction of body measurements.

The local inflammatory consequences derived from the adipocytolytic process are: triacylglycerol accumulation in macrophages, formation of foam cells or giant cells, granulomatous panniculitis and high lipid efflux derived from adipose tissue with consequent drainage through the lymphatic system. In contrast, systemic effects of inflammation derived from adipocytolytic process are demonstrated in experimental models, such as alterations in liver enzymes with increased esterase choline activity, reduction in alanine aminotransferase and aspartate aminotransferase activities and changes in lipid profile with increased rate of serum triacylglycerol and free fatty acids. There is no evidence in the literature that identifies systemic changes in the inflammatory profile of the post-procedure blood.

**Repair tissue derived from adipocytolysis**

Once the acute inflammatory stimulus is completed, the TH1 type immune response clears the acute inflammatory process. M1 macrophages reduce the production of proinflammatory cytokines and begin to produce anti-inflammatory cytokines, returning to macrophage configuration commonly observed in individuals with growing adipose tissue: the M2 polarization.

The M2 macrophage polarization, also called alternative activation, is responsible for immunomodulation and tissue repair. It is characterized by the production of anti-inflammatory cytokines such as IL-10 and IL-1 and growth factors such as platelet-derived growth factor, transforming growth factor-β, basic fibroblast growth factor and vascular endothelial growth factor. M2 macrophages also produce arginase, an enzyme that inhibits the production of free radicals which are present in the polarization M1. This anti-inflammatory effect is achieved by modulating TNF-α, generating an increase in blood levels of IL-10 coupled to increased insulin sensitivity by the adipose tissue observed in humans.

M2 macrophages activate the acquired immune response TH2, presenting antigens and inducing the production of specific antibodies to complete the clearance of the remaining products of acute inflammation. The production and release of growth factors such as fibroblastic growth factor, for example, will stimulate the synthesis of extracellular matrix by the fibroblasts and also stimulate local angiogenesis by other factors. M2 polarization is induced by IL-4 and IL-13 in macrophages and their pathways culminate in the STAT6 transcription factor activation responsible for the production of catecholamines such as adrenaline and noradrenaline. These catecholamines, in turn, act on intact adipocytes through β3 adrenergic receptors, inducing phosphorylation of perilipins and activation of HSL, culminating in the physiologic lipolytic effect. According to Grant and Stephens and Nguyen et al., the lipolytic effects are also obtained by an alternative activation of macrophages (M2 polarization) through the release of these catecholamines induced by anti-inflammatory cytokines, constituting an indirect lipolytic effect, since the cytokines do not act directly on the adipocytes to induce lipolysis. In Figure 4 is illustrated the mechanism of M2 macrophage activation in the context of adipocytolysis and the release of growth factors and catecholamines by the macrophages.

The growth factors produced by M2 macrophages have local effects characterized by the appearance of a new stromal granular structure, rich in capillaries, resulting from intense angiogenic and fibroblastic stimulation in the adipocytolytic site. This new stroma is called granulation tissue, the main function of which is to serve as a structural basis for the internal cell growth in the adipocytolytic site, in addition to providing blood supply. Fibroblasts deposit fibrin, fibronecrist and hyaluronic acid in the adipocytolytic site for the connective granulation tissue formation, which is transitory and subsequently replaced by collagen matrix due to the transforming growth factor-β1 produced and secreted by the M2 macrophages acting on fibroblasts.

Approximately 1 week after adipocytolytic stimulation, fibroblasts assume the myofibroblast phenotype, presenting thin microfilaments in their cytoplasm and performing a contractile function. This function is essential to the contraction of the affected area and deposition of the collagen...
The replacement of granulation tissue by deposition of collagen matrix depends mainly on the action of metalloproteinases and culminates in the tissue repair process characterized by the presence of fibroblasts, responsible for the production of extracellular matrix and deposit collagen on the adipocytolytic site. The scarring collagen (type I and III) deposited in the adipocytolytic site forms fibers bonded intermolecularly by crosslinking that are more cohesive and resistant compared to fibers commonly found in adipose tissue (collagen VI). This fact contributes to the fibrotic process that, in turn, prevents cell proliferation and cell migration to the adipocytolytic area by steric hindrance, featuring a cohesive and acellular scar, able to promote the retraction of the area, helping in the process of body contouring and avoiding sagging skin, commonly observed in nonadipocytolytic weight loss process.

**Consequences of adipocytolytic procedures**

The adipocytolytic procedures may culminate in fibrosis which is derived from the tissue repair process, but can also lead to remodeling through the metalloproteinases activity and tissue regeneration process as a result of mesenchymal stem cell activity from the adipose tissue.

In regenerative case, the collagen deposited on the adipocytolytic environment is replaced by new adipocytes which will colonize the area, regenerating and generating not only by myofibroblasts’ participation, but also by the collagen type I and III deposition as a result of tissue repair process, in contrast to collagen type VI normally found in the fatty tissue.

The scarring collagen (type I and III) deposited in the adipocytolytic site forms fibers bonded intermolecularly by crosslinking that are more cohesive and resistant compared to fibers commonly found in adipose tissue (collagen VI). This fact contributes to the fibrotic process that, in turn, prevents cell proliferation and cell migration to the adipocytolytic area by steric hindrance, featuring a cohesive and acellular scar, able to promote the retraction of the area, helping in the process of body contouring and avoiding sagging skin, commonly observed in nonadipocytolytic weight loss process. Figure 5 illustrates the fibrotic process (tissue repair) in the adipocytolytic site and its contribution to the reduction of body contouring.
Discussion

This study aimed to characterize the adipocytolytic procedures, corroborating the classification suggested by Rotunda and Mulholland and Kreindel. These procedures demonstrate inflammatory reactions triggered by adipocytolysis. These inflammatory reactions are well discussed in the clinical literature, but little explored in the basic or experimental science literature.

The confrontation between the clinical data, related to adipocytolytic esthetic procedures, with basic science research data, related to inflammation in adipose tissue and its local effects, supports the hypothesis that the inflammatory process assists the adipocytolytic process in all stages of inflammation, either directly by the action of proinflammatory cytokines or indirectly through the release of catecholamines.

The scarcity of research in the scientific literature, relating the molecular basis of inflammation observed in esthetic procedures to their adverse effects and outcomes, affects the understanding of the mechanism of action of adipocytolytic techniques applied to esthetic medicine.

Although the scientific literature is generally favorable to this therapeutic approach for the treatment of localized fat, more clinical or experimental research is needed to validate the effective participation of inflammatory pathways in the lipolytic process triggered by adipocytolytic esthetic procedures.

Although this study is the first review to confront clinical and basic research about the adipocytolytic procedures, it is not possible to propose a mechanism of action to explain the influence of inflammation in adipocytolytic process. However, the present integrative review plays an important role in medical practice based on evidence, to improve the understanding of adipocytolytic esthetic procedures and their effects on body sculpture.

Conclusion

The inflammatory process generated by nonsurgical adipocytolytic procedures can improve the efficacy of these procedures by stimulating the lipolytic process. According to scientific literature, the inflammatory process assists the adipocytolytic process in all stages of inflammation, either directly by the action of proinflammatory cytokines or indirectly through the release of catecholamines.

Deposition of scarring collagen from the tissue repair presents more cohesive and resistant collagen fibers, preventing cell proliferation and cell migration to the adipocytolytic area by being capable of promoting the shrinkage of the area, helping the reduction process of body contouring and avoiding sagging skin commonly observed in rapid weight loss process.

The inflammatory process triggered by adipocytolytic procedures may result in tissue regeneration or fibrosis. In both cases, the deposit of lipids should be avoided through the practice of appropriate physical exercise and proper diet in order to avoid compensatory hyperplasia or hypertrophy of adipose tissue and to maintain the obtained results.

Disclosure

The authors report no conflicts of interest in this work.

References


