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RESEARCH PAPER

Local fat treatments: classification proposal

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ABSTRACT
The poor understanding of the real, intimate action mechanisms behind any aesthetic procedures is a huge problem for many Aesthetic physicians. In addition, nomenclature of and regarding any procedure has become a true barrier when speaking about medical knowledge in the Aesthetic Medicine field since marketing and science often collide one another. Medical procedures for localized fat reduction are very different from each other and it is, at least, inaccurate to refer to all of them plainly as "fat reduction methods." A specific classification has become urgent and its categories should be able to imply what each method entails. For this classification proposal, "reversibility," "membrane disruption or inflammation," and "action selectivity," have been the selected criteria.

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Introduction and Background

From time immemorial, humans have strived to develop methods that would help them reduce the unwanted accumulation of adipose tissue in their bodies. There are multiple ways to act on the regulation of the body's adipose tissue content, including: intake control, central nervous system regulation, energy expenditure, endocrine system regulation, and direct fatty tissue removal. In the past 25 years, the treatment of obesity has improved due to multiple new resources and advances. We have witnessed the flourishing of bariatric surgery, intra-gastric balloons, lap bands, and countless diets. However, few methods have succeeded in effectively reducing localized adiposities.[1]

It all started almost a century ago, when invasive experiments and treatments for the removal of localized fatty tissue from the human body started to emerge. Those "interventions" were actual fatty tissue ablations (e.g. Dujarrier's 1926 report.[2] or Schrudde's 1972 work with uterine curettes.[3] The procedures in those years were a far cry from current practices, in terms of results as well as in terms of risks and techniques. The results were uncertain, to say the least, and complications —frequently very serious— were rampant. Non-invasive truly successful methods have been even fewer.[1]

Today, aesthetic physicians have to deal with different paradigms around the world. Ideas, beliefs, intellectual property and patents often get entangled. Nomenclature of and regarding any procedure has become a true barrier when speaking about medical knowledge peer transmission.[4] The more popular a treatment becomes, the greater the inaccuracies when it comes to talking or writing about it. This has happened to liposuction and mesotherapy, among others, and of course it is now happening with local fat reduction techniques as a whole. The issue of inconsistent terminology pervades aesthetic medicine and is often associated with the lack of time or interest to study or to achieve knowledge on anything beyond the strict scope of each person's sub-specialty.

Fat Elimination Mechanisms

Although adipocytes have some particular features, they are capable of reproducing just like any other type of cell. An increase in the number of adipocytes (or any other cell) is called hyperplasia.[5] In addition, adipocytes are also capable of increasing in content and therefore in size. An increase in the size of adipocytes (or any other cell) is called hypertrophy.[6]. The processes opposite to hyperplasia and hypertrophy are hypoplasia and hypotrophy, respectively.

The adipose tissue disorders of the great majority of aesthetic physicians' patients will be associated with adipocyte hypertrophy. Normally, we will treat a minority of patients with disorders associated to adipocyte hypotrophy or atrophy. Localized adiposities are an abnormal accumulation of fat in usual anatomical locations or an ectopic accumulation.

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Depending on their origin, these collections of fat will consist in hypertrophic and/or hyperplasic adipose tissue. Adipocyte hypoplasia is not an adipose tissue disorder very frequently treated in aesthetic medicine practices.

Lipolysis

Lipolysis is a natural chemical, molecular and reversible metabolic process. It takes place constantly in our bodies and is strictly regulated. Lipolysis is a central pathway for the disposal of energy and for the regulation of the metabolic state of the body. When specific receptors are stimulated, a cascade-type pathway is activated, where several intermediate enzymes are phosphorylated and undergo changes until they eventually stimulate any lipase.

Lipases acting on TAGs release fatty acids and glycerol.[7] Three lipases act in human triglyceride fatty acid breakdown, releasing one fatty acid from the triglyceride molecule at a time: adipose triglyceride lipase (ATGL, rate-limiting enzyme) 8 hormone-sensitive lipase (HSL)[9] and monoglyceride lipase (MGL), that finally releases the glycerol molecule and the third FFA.[10] Those released fatty acids which are not re-esterified into TAGs may be involved in β-oxidation, outside adipose tissue. β-oxidation can be described as a sequence of 4 basic reactions where a fatty acid loses 2 carbon atoms in the form of an acetyl CoA molecule. β-oxidation takes place after fatty acids have been activated by the enzyme acyl CoA synthetase and involves a sequence of 4 reactions: a) oxidation of the fatty acid by acyl CoA dehydrogenase, whose final product is trans-Δ2-enoyl-CoA (FAD mediated); b) hydration, catalyzed by enoyl CoA hydratase, whose final product is L-3-hydroxyacyl CoA; c) oxidation reaction catalyzed by the enzyme L-3-hydroxyacyl CoA dehydrogenase, whose final product is 3-ketoacyl CoA (NAD+ oxidation); and d) cleavage, where one molecule of acetyl CoA is separated from the remaining (shortened) acyl-CoA, catalyzed by enzyme β-ketothiolase. Each new round of β-oxidation extracts a new molecule of acetyl CoA from the β-oxidized fatty acid, and thus, it is shortened.

Acetyl CoA can follow several metabolic pathways[11] based on external stimuli and on the body's energy and structure requirements. Such pathways typically include: a) entering the tricarboxylic acid cycle (Krebs cycle) to be fully oxidized and produce energy through ATP, GTP and $NADH^{+}$; b) generating ketone bodies (ketogenesis) through acetoacetyl CoA and hydroxymethylglutaryl CoA to export energy to peripheral tissues; c) re-synthesising fatty acids; or d) taking part in the synthesis of ketogenic or "non-glucogenic" amino acids.

Adipocytolysis

Adipocytolysis, unlike lipolysis, is predominantly a physical, cellular, and irreversible process. Actually, it is rather a consequence than a process itself. From the molecular point of view, there is no catalytic activity mediated by any enzyme, nor is there any metabolic change. This phenomenon is generally unspecific, though different procedures may show highly different degrees of specificity. Adipocytolysis means the destruction of the adipocytes[12] not of its lipids There are different ways of killing these cells and, at least, we should be able to distinguish between traumatic and non-traumatic approaches.

Lipexeresis

Lipexeresis is the removal of fatty tissue by mechanical removal in situ.[3] It involves surgical −and therefore, invasive− techniques which have nothing to do with the physiological mechanisms of lipolysis or with adipocytolysis. Such techniques are divided into 2 distinct subgroups: lipectomies and liposuctions.

Lipectomies are surgical procedures by which adipose tissue is removed directly. Although liposuctions are surgical procedures as well, they are less invasive. Their main feature is fatty tissue removal by means of suction through a cannula.

Classification Proposal

The actions of medical procedures for localized fat reduction are based directly or indirectly on one of the 3 mechanisms discussed above. But they are different in terms of their means of application, adverse effects and contraindications, among others. In addition, their alternative indications, limitations, expectations, results, and protocols are different as well. In general, their features are so different that they often only share the fact that they are used for the purpose of removing localized body fat. It is inaccurate to refer plainly to "fat reduction methods." A specific classification is required to guide readers as to what each method entails, since in addition to the differences mentioned above, they may act on adipose hyperplasia or hypertrophy, at systemic or at local level, directly or indirectly, and in an invasive or non-invasive way.

Any attempt to classify procedures should take into account such differences, although some are essential while others are secondary. However, using differences as the criteria for grouping treatments would make any classification quite complex and therefore a useless tool. Thus, the classification below that is proposed only for

localized fat reduction treatments is based solely on 3 simple criteria which are easy to assess and which value the process underlying the procedures, rather than their specific characteristics. The criteria we have selected are: a) reversibility, b) membrane disruption or inflammation, and c) action selectivity.

Category 1. pro-lipolysis

Carbohydrates, fats and proteins are the fuels that our engines are capable of processing. Except for a few indispensable substances, such as vitamins, these 3 are all we need. Water, electrolytes, and all of the non-metabolizable foods which make up "fiber" complete our diet. However, energy cannot come from the latter. Usually, the quintessential energetic food is glucose. The entire human metabolic machine revolves around glucose, whether it is present or not.

When we limit carbohydrate intake (and at the same time lipid intake, as in a protein diet), our bodies feed from the circulating glucose and from the glycogen reserves in the liver, which start mobilizing. It is acknowledged that the complete depletion of mobilizable carbohydrates in humans takes place less than one day after carbohydrate intake has been interrupted. Although muscle contains far greater reserves, these cannot be released due to the lack of a specific enzyme required for this task: glucose-6-fosfatase. When this happens, most tissues which are capable of using a different fuel do so, since the brain, erythrocytes, and a few others cannot. In order to live, they need the body to produce this glucose which it is not taking in: *de novo* glucose.

Glucose can be synthesized from multiple precursors such as lactic acid, pyruvate, glycerol, and certain amino acids (AAs). AAs capable of providing carbon structures which can be incorporated into glucose molecules are referred to as *glucogenic*, while those which are not capable of that and only provide carbons for the synthesis of acetyl CoA are referred to as *ketogenic*. Two-carbon acetyl CoA enters the Krebs cycle and binds with 4-carbon oxaloacetate to form 6-carbon citrate. However, after several reactions, in what is known as the tricarboxylic acid cycle or Krebs cycle (a full cycle run), 2 carbon molecules are lost as CO2 and, in addition to obtaining a significant amount of energy, oxaloacetate is again obtained. In order to synthesize glucose from an AA, a skeleton of carbon atoms (one molecule of oxaloacetate) must be capable of being extracted from intermediate metabolism. Only a few AAs satisfy this requirement. It is the same reason why glucose cannot be synthesized from fatty acids, which may be considered polymers of the acetyl CoA bicarbonate structure. The opposite does happen, and it happens all the time: excess sugar is converted into fat and stored.

When circulating glucose and the glycogen reserves in the liver have run out, the body covers the energy needs of almost all of its tissues by mobilizing the lipid reserve: lipolysis. Pro-lipolysis treatments enhance lipolysis indirectly, instead of triggering lipolyisis by a real lipolytic stimulus. They drive metabolism toward a catalytic state with lipid consumption.

Reversibility, no membrane disruption, no selectivity and no inflammation are the key characteristics of pro-lipolysis procedures.

Category 2. lipolysis

Unlike pro-lipolytic treatments, where lipolysis is the result of central regulation and an induced catabolic state, in lipolisys treatments the lipolytic response appears due to a direct stimulus. Also, pro-lipolysis treatments represent an equal stimulus to every adipocyte (not selective and systemic) while lipolytic treatments are completely specific and local.[13] The destruction of triglycerides is stimulated by means of the use of drugs which activate the lipolytic cascade, regardless of the body's energy status. The typical example is intradermal injection of active ingredients such as methylxanthines, thyroid hormone analogs, or selective α-2 blockers.

At the cellular level, the effect of lipolysis is expressed as adipocyte hypotrophy. The cell is not destroyed and its contents are not released; it only metabolizes its lipid load. Therefore, lipolysis does not disrupt the adipocyte membrane nor does it trigger any inflammatory reaction. Treatments that seek to stimulate or speed up this pathway are lipolytic, typically topical preparations and intradermal injections. Inflammation may be triggered by the injected substances or by the physical effect of the needle, but not as a direct consequence of lipolysis. There is no correlation between lipolysis and inflammation:

Reversibility, no membrane disruption, high selectivity and no inflammation are the key characteristics of lipolysis.

Category 3a. clastic adipocytolysis

In aesthetic medicine, clastic adipocytolysis is, in general, the result of the mechanism of action of substances such as sodium deoxycholate[14] or phosphatidylcholine.[15,16] though it may also be seen as a minor effect of carboxytherapy and other treatments.

The "clastic" category applies to the procedures whose action mechanisms result in membrane disruption and cell destruction. Consequently, content poured into the extracellular matrix triggers an inflammatory reaction

which is, as in any other case, local, completely unspecific, and governed by its usual signs. The four classic signs of inflammation are referred to as Celsus' signs after Aulus Cornelius Celsus (circa 50 AD), who first described them: heat, pain, redness, and swelling. In the mid-19th century a fifth cardinal sign of inflammation was added: *functio laesa*, or function impairment. It was proposed by Rudolf Virchow (1858), although for a long time it was mistakenly ascribed to Galen of Pergamon or to Thomas Sydenham, allegedly due to a "joke" by Virchow himself.

Clastic adipocytolysis is the simplest process for adipocyte destruction. Most active principles play a direct contact role or inflict mechanical stress on the cell. Irreversibility, membrane disruption, absence of selectivity and inflammation are the key characteristics of clastic adipocytolysis.

Category 3b. phagic adipocytolysis

Phagic adipocytolysis is the result of the mechanism of action of technologies which, although adipocytolytic, do not destroy adipocytes directly: lipocryolysis. By means of various physical principles, these technologies seek to cause structural changes in several elements of adipocytes in order to induce apoptotic responses. Unlike what occurs during clastic adipocytolysis processes, apoptosis does not trigger any inflammatory response. Adipocytes will be finally phagocytized.

Irreversibility, no membrane disruption, high selectivity and no inflammation are the key characteristics of phagic adipocytolysis.

Category 4. lipectomy / liposuction

Aesthetic lipectomies can be tracked as far as Dujarrier's 1926 report.[2] These are surgical fat tissue ablations. When they are performed in combination with skin ablation (almost always), the intervention is called dermolipectomy. Many different lipectomy techniques have been developed and with the years, they have become extremely frequent and effective aesthetic surgical procedures that can be practiced in almost any anatomical location.

Liposuction, on the other hand, is considered to be a minor surgical procedure. Mechanical aspiration of the fat with cannulae is its distinct characteristic. Original liposuction was performed manually, though it evolved into "assisted" procedures. Today, liposuction assisted with a modest aspirator coupled to the tubing coexists with much more sophisticated systems. Liposuction can be assisted with ultrasound,[17] laser,[18] mechanical aids,[19,20] water,[21] or radiofrequency.[22] The term liposuction is too often used indistinctly with lipoaspiration, lipoplasty or liposculpture. This must be avoided, for there are technical aspects that distinguish them. Commenting on these would exceed the scope of this work, though it is important to remark that all of them fit perfectly in this group.

A wide range of procedures can be found in this group. Still, their main characteristics (by which they are classified) remain the same: invasive, irreversible, not selective and not inflammatory methods (inflammation occurs because of injury, which is a disadvantage of the actual invasiveness capability or an unavoidable consequence of the methods we have to use; it is not due to fat removal itself).

Category 5. combined action

Technologies and techniques included in this group are the ones that also fulfill the criteria to be included in any other 2 groups at the same time. Irreversibility, membrane disruption, selectivity and inflammation will be in accordance to each treatment lipolytic/ adipocytolytic balance and/or characteristics.

Final comment

There might be controversy regarding the treatments that should or should not be included in each group. A good example could be lipocryolysis. The crystals it creates inside adipocytes may unleash apoptosis. But also, aside the fact that an immediate massage on the treated area will destroy additional adipocytes, it will also account for a minor direct traumatic effect. With every new study, the elucidation of action mechanisms and tissue-technology-interaction understanding increases. In the future, treatments that were originally included in a certain group may be excluded, since much knowledge that is taken for granted today will be found incorrect or, most probably, incomplete.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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