Liposuction is one of the most frequently performed procedures by plastic surgeons. The increased safety associated with the surgical settings, technical refinements, and level of patient satisfaction have contributed to the popularity gained by this intervention since it was first introduced by Ilouz in 1979 (4). Moreover, among medical communities and the media, concerns have risen regarding not only the drastic changes in patients’ appearance but also the safety of the procedure. Fat tissue is known to act as a legitimate endocrine organ (5), being the primary depository for triglycerides, which classically relate to atherosclerosis and insulin resistance (6, 7). Recent work has linked lipid metabolism in adipocytes to the maintenance of low levels of systemic inflammation through a series of mediators (8-10). Scientific evidence (11) revealed an increase in the percentage of obese people in our country, as well as a considerable proportion of overweight people. This study also investigates the relationship between the prevalence of diabetes and hypertension. The classic association between body mass index and common metabolic diseases has led to investigations focused on several factors involved in this relationship, along with research work directed at the treatments available. The discovery of leptin in the 1990s (12) highlights the regulatory properties of the adipose tissue, whereas recent studies (5, 13) have established a link with the synthesis of other factors. In this study, we aimed to perform a review of literatures that discuss the current state-of-the-art of scientific research, in which we organized published works in a didactic manner in order to facilitate better understanding, and promote the safety and efficacy of liposuction.

**Keywords:** Lipectomy; Cholesterol; Tumor Necrosis Factor Alpha; Triglycerides; Interleukins.
INTRODUCTION

Liposuction is the surgical procedure used for the removal of fat deposits in areas perceived as unaesthetic. It was initially designed to treat specific regions, but the technical advances have expanded its application to include large areas, which requires consideration of hematological and metabolic changes and procedural adaptations. Because of these changes, the application of liposuction has become versatile, ranging from minor surgical interventions performed in private practices to more elaborate surgeries performed in hospitals, accompanied by all the required support measures.

Liposuction has evolved over time and remains as one of the most frequently performed procedures by plastic surgeons. The increased safety in surgical settings, technical refinement, and levels of patient satisfaction have contributed to its gain in popularity since it was first introduced by Ilouz in 1979. Furthermore, among medical communities and the media, concerns have arisen regarding not only the drastic changes in patients’ appearance but also the safety of the procedure, which includes hematological and metabolic alterations, as well as its associated potential complications.

Currently, adipose tissue is known to act as a legitimate endocrine organ, in addition to being the main storage of triglycerides, molecules classically related to atherosclerosis and insulin resistance. Recent work has linked lipid metabolism in adipocytes to the maintenance of low levels of systemic inflammation, mediated by a series of factors. Scientific evidence showed that the percentage of obese people among the total population of Brazil has increased, from 11.4% in 2006 to 15.8% in 2011, and that the proportion of overweight people is high at 48.5%. This study also links the prevalence of diabetes (6% of the general population) and hypertension (22.7% of the general population) to obesity. The classic close relationship between the amount of body fat and metabolic diseases has led to research focused on the elements involved in this process and on treatment options.

The discovery of leptin in the 1990s highlighted the regulatory properties of the adipose tissue through the production and secretion of proteins. Meanwhile, more studies have been performed, establishing further connections to the synthesis of other factors such as interleukin 6, angiotensinogen, tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), adiponectin, apolipoproteins, and resistin.

In light of the considerable amount of recently published evidence on the hematological and metabolic changes associated with liposuction, published sporadically and often not integrated in a wider context, we decided to review the literature...
to determine the actual state-of-the-art of the research and to organize and present published works in a more informative manner to facilitate better understanding, in the hope that it will lead to a safer and more efficient management of patients undergoing liposuction.

**SERUM LIPID LEVELS**

The identification of cholesterol as a constituent of atheroma plaques has raised questions regarding the contribution of lipid metabolism in the development of coronary disease. Cholesterol is present in several tissues as part of cell membranes and as a precursor for bile acids and steroid hormones. It is transported in the bloodstream as part of lipoproteins, particles formed by lipid and protein moieties, which can be divided into three main classes, namely low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and very-low-density lipoproteins (VLDLs).

LDL, which carries approximately 70% of the total cholesterol in the serum, is the lipoprotein that mostly contributes to atheromas, as observed in the population affected by genetic conditions leading to hypercholesterolemia and precocious atherosclerosis. It is formed by only one apolipoprotein (apo B) and is currently the main target of risk reduction therapies. HDL associates with 20–30% of the serum cholesterol and is formed by the apolipoproteins A-I e A-II. It is considered an independent risk factor, and several studies have associated its low levels with an increase in morbidity and mortality.

Concerning triglycerides, some reports have established an association with coronary disease. However, other studies that conducted multivariate analyses did not recognize triglycerides as an isolated risk factor. Triglycerides are believed to indirectly contribute to atherosclerosis. The main therapies currently used to improve lipid levels are the use of fibrates and nutrition re-education combined with physical activity.

Samdal was the first to test the response of serum lipids after liposuction. In a study with nine obese female patients, a significant increase in HDL and apolipoprotein A-I was observed 1 year after surgery. Baxter later detected a decrease in total cholesterol levels without changes in the HDL/HDL ratio. Vanderwey determined the lipid profile during and immediately after liposuction in 10 patients, thus establishing the metabolic safety of the procedure. Robles-Cervantes detected in a patient with 3 weeks of postsurgical follow-up a significant decrease in total cholesterol level. Other authors have also reported positive results. Conversely, some reports showed a lack of correlation between surgical fat removal and the improvement of lipid profiles, which emphasizes the importance of maintaining a negative energetic balance to maintain the benefits of the procedure.

The complex metabolism of adipocytes warrants new investigations that can improve understanding of the exact role of liposuction in controlling risk variables.

**GLUCOSE METABOLISM**

Since the development of surgeries and other procedures that lead to significant weight loss, many patients have been able to lower their insulin resistance and even to totally control type 2 diabetes. Taking these data into account and considering the positive effect of traditional weight loss plans, several authors have suggested that the surgical removal of body fat can lead to improved glucose metabolism.

According to Perez, the observed results can have two possible explanations as follows: either the removal of hypertrophic adipocytes, with increased leptin levels, or the reduction of ghrelin levels, which has been shown to occur after liposuction. The new hormonal configuration would lead to decreased energy intake and, consequently, an increase in insulin sensitivity. Based on studies concerning women who had undergone dermolipectomy, Rizzo linked lower levels of free fatty acids detected with improved glucose metabolism to the procedure. The author refers to the well-known inhibitory role of these markers in insulin activity and oxidative metabolism.

Positive results were described in several publications. Giese, in a pilot study including 14 patients, observed a significant reduction in serum insulin level after 4 months of postsurgical follow-up. In a study with 15 nonobese women, Robles-Cervantes observed a reduction in blood sugar levels and insulin secretion (determined by the homeostasis model assessment test) at 3 postoperative weeks. Giugliano also described improved insulin resistance in 30 obese patients. By contrast, Klein did not detect any changes in the glycemic profiles and insulin stimulation test results in both diabetic and nondiabetic patients in two studies performed. Critics have argued that perhaps the short follow-up was the reason for the negative results. Ybarra also showed no significant results at 4 postoperative months, despite a reduction in the levels of other metabolic markers.

Insulin resistance is well known to link type 2 diabetes and obesity, as well as cardiovascular pathological conditions associated with these conditions. Recent studies have established a direct relationship between increased serum insulin levels and adverse events such as endothelial malfunctions, atherosclerotic processes, and thrombogenic processes, even in patients with similar glycemic profiles. This information suggests the importance of new research to address the possible beneficial effects of liposuction.
LEPTIN

Leptin is a helicoidal hormone secreted by the adipose tissue and mostly detected in the plasma and cerebrospinal fluid. Its discovery originated from the study of recessive mutations in the genes ob and db in rats with morbid obesity phenotype. Its name was later coined from the Greek root "leptos," meaning "thin, fine." Leptin has a central activity over certain hypothalamus areas, which control energy ingestion. Leptin stimulates the production of anorexigenic peptides and also increases energy consumption.

A direct link between leptin level and body mass index BMI has been demonstrated, and increased leptin level is also associated with alcohol ingestion. Nevertheless, leptin levels are lower in thin people and during fasting. These observations highlight the role of leptin in regulating body energy consumption, through the control of energy stored in the form of fat. Leptin injections have been shown to reduce body weight in guinea pigs. This hormone is also known to regulate immune response in patients with malnutrition, whereas immune system suppression could be reverted by leptin injections. Despite being a well-studied mediator that has a known function, leptin was not considered a viable treatment option for obesity. This is because several possible parameters compromise its activity and food intake can be controlled by numerous variables.

Our conclusion, from the point of view of plastic surgery, is that the benefits of this molecule have not been fully exploited. Schreiber observed a tendency for leptin levels to increase after liposuction in 35 rats with an obesity phenotype. On the contrary, Rizzo reported a reduction in serum leptin levels on the 40th postoperative day in 20 obese patients who had undergone dermolipectomy and liposuction.

ADIPONECTIN AND RESISTIN

Adiponectin is a protein that has a gene expression exclusive to the adipose tissue and structural homology to collagen types 8 and 10, as well as to the complement C1q factor. Its activity has anti-inflammatory effects and improves insulin resistance via its direct and indirect effect on glucose absorption. Some studies showed that plasma adiponectin levels are reduced in patients with obesity, diabetes, and coronary disease; eventually, serum levels can normalize after significant weight loss.

The possibility of modulating this system led to the inclusion of this cytokine in studies that evaluate the surgical removal of fat tissue. In a study with 30 obese and 30 normal-weight women, Giugliano observed reduced presurgical levels of the hormone in the obese group. Approximately 6 postoperative months, a significant increase in adiponectin level was observed in both groups, which was directly proportional to the recovered volume and inversely proportional to TNF-α levels. Rizzo also showed an inverse relationship between serum adiponectin level and BMI (BMI = weight/height²), as well as an increase in adiponectin levels after dermolipectomy. Klein and Schreiber—the latter study used guinea pigs—did not report any alterations in the adiponectin levels before and after liposuction.

Resistin is another hormone of the adipose tissue that was recently described, being secreted mostly by adipocytes, monocytes, and other adjacent cells. Its exact role is still a matter of debate, but some studies have shown an increase in insulin resistance after its administration to guinea pigs, as well as an improvement in glycemic profiles after injection of anti-resistin antibodies. This can be further evidence of a relationship between obesity and diabetes, but so far, no reports have correlated serum levels with the liposuction procedure.

INTERLEUKIN 10

Interleukin 10 (IL-10) is a main mediator of immunity, acting on various immune cell types. Its central role is to inhibit and stop inflammatory response by regulating tolerance to external agents and contributing, for example, to tissue damage control during infection. Genes that are homologous to human IL-10 can be found in viruses such as the Epstein-Barr virus and cytomegalovirus, which stresses the repressive role of this interleukin. The purpose would be to facilitate viral infection by suppressing immunological response.

Work in guinea pigs showed that exogenous administration of IL-10 controlled bronchial reactivity, delayed beta-cell destruction in type 1 diabetes, and contributed to the management of other conditions such as Crohn disease and rheumatoid arthritis. Another experimental work also stressed the role of IL-10 in endothelial protection in diabetic rats, which also seems to occur in patients with acute myocardial infarction (AMI), where reduced IL-10 production is associated with poorer prognosis and plaque instability.

This cytokine seems to also participate in glycemic control, perhaps by increasing insulin sensitivity, thus countering the effects of IL-6 and TNF-α. Moreover, low IL-10 levels have been linked to the development of metabolic syndrome and type 2 diabetes. In a study with 20 obese patients who had undergone dermolipectomy, Rizzo reported a significant increase in serum IL-10 level approximately 40 postoperative days. These increased levels, together with the low levels of other markers, are suggested to reflect a decrease in systemic inflammation as a consequence of adipose tissue removal.

INTERLEUKIN 6

Interleukin 6 (IL-6) is a cytokine with an important role in the physiopathological mechanisms of several diseases. It has been implicated in the development...
of autoimmunity, hypothyroidism, atherosclerosis, osteopenia, and other metabolic disorders. IL-6 still controls the hypothalamic-pituitary-adrenal axis by stimulating the release of the adrenocorticotropic hormone and acting as a regulator of metabolic responses in trauma. Its mechanism of action is mostly unknown, but IL-6 is known to have a series of tissue receptors, which can antagonize the activities of other markers, thus being known for both its anti-inflammatory and pro-inflammatory potentials. Some studies used IL-6 quantification of prognosis in patients with unstable angina and AMI.

Its involvement in controlling energy balance and lipid metabolism is another role of IL-6 that is particularly of interest to plastic surgeons. Among the several cell types that secrete II-6, adipocytes are responsible for approximately one third of the production, and its high plasma levels correlate with increased insulin resistance, the levels of circulating fatty acids, and the risk of type 2 diabetes. Moleculally, the inhibitory action of IL-6 compromises the signal transduction of insulin receptors in hepatocytes.

In a study with 60 patients (30 obese and 30 nonobese), Giugliano compared IL-6 levels before surgery between the two groups and detected IL-6 release of molecules that facilitate cell adhesion. Other studies have also showed a positive correlation between higher levels of body fat and circulating CRP, also in association with higher risk of diabetes. Giugliano quantified CRP before liposuction and found higher levels in obese patients than in nonobese patients. After liposuction, a considerable reduction of this marker was observed in both groups. Klein did not detect any changes in CRP level 3 months after liposuction in 15 obese patients.

**C-REACTIVE PROTEIN**

C-reactive protein (CRP) is produced in the liver, and small amounts can usually be found in the plasma. Its structure has been preserved throughout evolution, with homologs in several vertebrate and invertebrate species. The mechanism of action of CRP is complex and seems to act both as an anti- and pro-inflammatory factor. In guinea pigs, this protein has a protective role in that it recognizes pathogens and triggers the complement cascade, thus regulating the host response to infection and delaying the development of autoimmune diseases in preconditioned models. Other in vitro studies that used human recombinant CRP identified proatherosclerotic properties that were possibly caused by inhibition of basal nitric oxide synthesis and the release of molecules that facilitate cell adhesion.

With inflammation, CRP levels increase up to a thousand times, which led to the choice of CRP as the central marker of inflammatory status, being routinely assayed in laboratory tests. Recently, a series of studies showed an important association between small increases in serum levels and the development of cardiovascular diseases, metabolic syndrome, and some types of cancer. These results support the hypothesis that subclinical chronic inflammation can affect the development of such conditions.

Other studies have also showed a positive correlation between higher levels of body fat and circulating CRP, also in association with higher risk of diabetes. Giugliano quantified CRP before liposuction and found higher levels in obese patients than in nonobese patients. After liposuction, a considerable reduction of this marker was observed in both groups. Klein did not detect any changes in CRP level 3 months after liposuction in 15 obese patients.

**TUMOR NECROSIS FACTOR ALPHA**

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine secreted by activated macrophages, extensively studied throughout the literature, and already used in established therapies for autoimmune diseases and cancer. TNF was first hinted at in the 19th century, when spontaneous tumor regressions in cancer patients were reported, mostly in cases of concomitant bacterial infections. However, it was only in the 1970s that Old described TNF based on tumor necrosis that developed after infusion with plasma from rats infected with Bacillus Calmette-Guérin. The purification of this plasma led to the isolation of a protein with apoptotic capacities over various neoplastic tissues.

TNF-α is produced as a 25-kD protein, posteriorly cleaved to 17 kD, when it enters circulation. It acts on two receptors (types 1 and 2), which can be found in most tissues, as well as in soluble forms, which is believed to modulate TNF-α effects. This cytokine has, generally, a regulatory function in immune cells, inducing cachexia, fever, sepsis, apoptosis, inhibition of viral replication, among others. Due to its potent role as inducer of inflammatory responses, TNF-α is responsible for a part of the clinical manifestations that associate with autoimmune conditions such as rheumatoid arthritis, asthma, and psoriasis. Recently, these manifestations have been counteracted with the use of monoclonal antibodies (infliximab) or fusion proteins (etanercept) that neutralize TNF-α activity.

Besides its roles in the immune system, TNF-α also regulates energy balance, acting mostly at the level of the metabolism of adipocytes. The activity of TNF-α has been implicated in the development of diseases such as obesity, dyslipidemia, diabetes, and atherosclerosis. Concerning lipid metabolism, TNF-α seems to stimulate lipolysis and inhibit...
the recovery of free fatty acids\textsuperscript{102}, which may be a possible explanation for the hyperlipidemia observed in patients with infections and obesity. High TNF-α levels are also responsible for the development of insulin resistance in cancer, sepsis, trauma and, as recently reported, in obese patients\textsuperscript{93}. The reasons behind these observations are believed to be, among others, the disruption of signal transduction that facilitates glucose uptake by cells. A direct relationship between TNF-α and leptin levels was also observed, which could intensify the anorexigenic and adipostatic effects of leptin\textsuperscript{103,105}.

Giugliano\textsuperscript{77,58} observed a reduction in the levels of this marker in obese patients who underwent liposuction. Rizzo\textsuperscript{41} established a positive correlation between BMI and TNF-α levels before surgery, as well as a reduction of this factor after dermolipectomy surgery. It should be stressed that both authors have also reported a considerable improvement in insulin resistance after surgery, which emphasizes the role of TNF-α in this context. In sharp contrast, Klein\textsuperscript{31} observed neither any reduction in the levels of this factor nor any improvement in insulin resistance in a study that included 15 obese patients.

**LEUCOCYTE COUNT**

The link between leukocytosis and cardiovascular diseases was proposed in the final years of the 1920s\textsuperscript{106}. Since the 1940s, some studies have reported that patients that had AMI and presented with leukocyte counts higher than 15,000 had a significantly worse prognosis than those with counts below 11,000\textsuperscript{107,108}. Further studies have corroborated these results\textsuperscript{109-111}, and a meta-analysis that included more than 7,000 patients with 8 years of medical follow-up showed a relative risk of 1.5 for coronary disease in patients with leukocyte counts in the upper third of the reference range\textsuperscript{41}.

Leukocytosis is not only a sign of systemic inflammation, as well as its associated metabolic consequences, but also in itself a cause of damage. An increase in the number of leukocytes would lead to a prothrombotic state through platelet recruitment and adhesion, the production of oxygen free radicals, interleukins, metaloperoxidase, and growth factors\textsuperscript{112-114}. Concerning white cells, neutrophils and monocytes are closely related to new ischemic events\textsuperscript{115-117}, which lead to the production of inflammatory mediators known for their roles in arteriogenesis. Another study tested approximately 6,000 patients in order verify that higher leukocyte levels lead to the development of cancer and an increase in mortality associated with AMI or other factors. The same report also showed a 14% decrease in mortality for each thousand points of reduction in leukocyte count.

Obesity has been associated with the maintenance of subclinical inflammatory status, and some reports have shown a positive relationship between BMI and leukocyte counts\textsuperscript{119-121}. The mechanisms behind these findings are complex and unknown; however, the release of proinflammatory cytokines by the adipose tissue, such as IL-6 and TNF-α, should be taken into consideration. A reduction in body weight, either due to diet or exercise, led to reduced counts of neutrophil, among other markers\textsuperscript{122}. Swanson\textsuperscript{29} reported reduced levels of leukocytes in the third postoperative month in patients who underwent liposuction, suggesting that surgical removal of body fat can have metabolic benefits.

**DISCUSSION**

The importance of assaying hematological alterations relates with the fact that blood loss usually accompany any surgical procedure, including liposuction. When blood loss volume is large (>5000 mL in total), support measures may be required, as well as prolonged hospitalization, readmission, and even blood transfusion.

Metabolic alterations have recently gained attention with the discovery of the endocrine function of adipose tissue. The clinical implications are particularly important for obese patients who undergo removal of large fat tissue volumes via liposuction. Moreover, new risk markers of atherosclerosis and degenerative conditions are being developed. Hence, body fat can be considered as an agent that promotes chronic inflammatory status. Some of the studies discussed here have shown a significant reduction in inflammation after liposuction. Conversely, a randomized study by Benatti\textsuperscript{123} showed an increase in visceral fat deposition after liposuction, without any changes in adipocyte size or gene expression of the factors associated with lipid metabolism.

Safety protocols are difficult to establish owing to the many variables that should be considered. The Federal Council of Medicine, in its resolution number 1711, from December 2003, established the following maximum values for fat removal: 7% of body weight for any infiltrative procedure and 5% for dry procedures. However, it is not specified if the values refer to the total volume aspirated or just the removed fat. In addition, the area to be treated was restricted to 40% of the total body area.

For each patient, the choice of treatment depends on the clinical status of the patient, including BMI, number of regions to be subjected to surgery, previous diseases, and volume to be removed, as well as on the preferences of the plastic surgeon concerning the technical aspects of the surgery, the infiltration procedure, whether anesthetics should be used, the type of anesthesia, and the volume to be removed. With this many variables to be taken into consideration, a meta-analysis type of review, which was our intention from the beginning, became impossible owing to the lack of standardized procedures reported in the literature.

Future studies that guide evaluations of specific liposuction procedures, always accounting for blood
and/or metabolic changes, will be required for the establishment of increasingly reliable security criteria, which will minimize the adverse effects of liposuction.

CONCLUSION

From its beginning, liposuction procedures were accompanied by concerns regarding blood loss. Currently, parameters for consideration have been established and legislation has been specifically enforced. However, as the frequency of use of liposuction procedures has increased worldwide, metabolic alterations and their effect on patient recovery and final outcome have become a current concern. This has led to a new era in liposuction research. Taking into consideration variables such as the techniques used, infiltration type, and anesthesia, the need to investigate specific metabolic changes for each different procedure has become more imperative to ensure safety and quality. Current reports have been published but are discrepant and have not been extensively corroborated. Therefore, new research that specifically focuses on each technique is warranted to guide the standardization of the discussed parameters.

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Liposuction: metabolic risks factors actualization and clinical-surgical value


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