Cosmetic Liposuction Causes Only Transient Elevation of Acute Inflammatory Response and Does Not Advance to Oxidative and Nitrosative Stress

Pi-Yueh Chang,¹ Tsu-Lan Wu,¹ Kuo-Chien Tsao,¹ Chien-Feng Sun,¹ Lily L. Wu,² and James T. Wu^{2*}

¹Departments of Pathology, Chang Gung Memorial Hospital, Taipei, Taiwan

²ARUP Laboratories, Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, Utah

Cosmetic liposuction is a surgical procedure performed on normal nonobese subjects to remove unwanted fat. We are interested to know whether the impact of acute inflammatory response induced by liposuction differs from that of chronic inflammation and whether acute inflammatory response will also advance further and cause oxidative and nitrosative stress leading to various clinical complications. In our investigation we monitored 15 nonobese women prior to liposuction, and one day and one month after the surgery with multiple markers associated with chronic inflammation and oxidative stress. Our results indicate that liposuction causes only a transient elevation of acute inflammatory markers such as interleukin-6 (IL-6), high sensitive C-reactive protein (hCRP), and

serum amyloid A (SAA), and a transient decrease of nitric oxide (NO). Apparently the impact of liposuction for normal subjects did not advance beyond acute inflammatory response; there was little change in the levels of markers corresponding to downstream events of chronic systemic inflammation such as adhesion molecules, urinary microalbumin (uMA), homocysteine (Hcy), uric acid (UA), and markers of oxidative stress, including urinary 8-hydroxydeoxyguanosine (8-OHdG) and 3-nitrotyrosine (3NT). It appears that the acute inflammatory response of cosmetic liposuction does not lead to impaired renal function and oxidative and nitrosative damage, which are frequently associated with chronic inflammation. *J. Clin. Lab. Anal.* 21:418–425, 2007. © 2007 Wiley-Liss, Inc.

Key words: liposuction; acute inflammation; hCRP; IL-6; SAA; oxidative and nitrosative stress

INTRODUCTION

It is well-known that chronic inflammation is the major causative factor for several severe clinical disorders including macro- and microvascular disease (1–4), type 2 diabetes (T2DM) (5), nephropathy (6), asthma (7), chronic obstructive pulmonary disease (COPD) (8,9), and cancer (10,11). Chronic inflammation can be viewed as repeated episodes of acute inflammation (if the risk factor(s) is not removed) that eventually spread systemically, and progress to oxidative and nitrosative stress (12,13). A sequence of events have been identified in atherogenesis in association with chronic inflammation. In the coronary artery, it starts with endothelium dysfunction, then followed by expression of adhesion molecules, recruitment of leukocyte,

Abbreviations: CVD, cardiovascular diseases; ICAM-1, intercellular adhesion molecule; IL-6, interleukin-6; ELISA, enzyme linked immunosorbent assay; Hcy, homocysteine; MCP-1, monocyte chemoattractant protein; NO, nitric oxide; 3NT, 3-nitrotyrosine; 8-OHdG, 8-hydroxydeoxyguanosine; SAA, serum amyloid A; T2DM, type 2 diabetes; TNF- α , tumor necrosis factor-alpha; uMA, urinary microalbumin; UA, uric acid; VCAM-1, vascular cell adhesion molecule.

*Correspondence to: James T. Wu, ARUP Laboratories, Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, UT 84108. E-mail: wuj@aruplab.com

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migration of monocytes to the arterial intima, and transformation of macrophage into foam cells, in this order, and finally the onset of atherosclerosis (14).

On the other hand, as pointed out by Gabay et al. (15), conditions associated with a single episode of acute inflammation, which commonly lead to substantial changes in the plasma concentrations of acute-phase proteins in high sensitive C-reactive protein (hCRP), serum amyloid A (SAA), and fibrinogen, can be derived from infection, trauma, surgery, burns, tissue infarction, and various immunologically-mediated and crystal-induced inflammations. In fact, elevation of acute inflammation markers can also be detected after strenuous exercise, postprandial hyperglycemia, heat-stroke, and childbirth. However, it is not clear whether these acute inflammatory responses will also continue to advance, following the same sequence of events found in chronic inflammation as have been found in the coronary artery (14). In other words, the exact impact of a single episode of acute inflammation is not known (when the risk factor is no longer present). It is not known whether a single episode of acute inflammation will also lead to systemic oxidative and nitrosative stress and eventually to various fatal diseases.

Liposuction is a surgical procedure performed on normal nonobese subjects to remove unwanted fat from various parts of the body; it involves a tiny surgical incision and an ultrasound procedure to liquefy the fat tissue to be removed. It is conceivable that this surgical procedure will induce an acute inflammatory response. Because most recipients of this operation are normal, nonobese women, they are therefore the ideal candidates for the evaluation of the impact of acute inflammatory response. Any acute inflammatory response caused by liposuction should return to normal if acute inflammation does not progress further to oxidative and nitrosative stress.

Soluble markers corresponding to the individual events of chronic inflammation have been identified (12–14); therefore, measuring these multiple soluble markers allows for the assessment of how extensive the acute inflammatory response will advance.

In the present investigation, in all women who underwent liposuction, we monitored this panel of multiple markers, at three different times: prior to the procedure, and one day and one month after liposuction. Our results indicate that only interleukin 6 (IL-6), (a proinflammatory cytokine), hCRP, and SAA (both acute-phase reactants) responded acutely to the insult and became elevated one day following liposuction. However, both proinflammatory cytokine and acute-phase reactants returned to the baseline one month following the surgery. In other words, acute inflammatory response does not progress to oxidative and

nitrosative stress as commonly found in chronic inflammation. In most cases, we did not find elevation of adhesion molecules, urinary microalbumin (uMA), 8-hydroxydeoxyguanosine (8-OHdG), or 3 nitrotyrosine (3NT), markers of the downstream events associated with chronic inflammation.

MATERIALS AND METHODS

Commercial Assay Kit

Adiponectin enzyme-linked immunosorbent assay (ELISA) kit, total nitric oxide (NO) assay kit, and high-sensitive tumor necrosis factor- α (TNF- α) enzyme immunoassay (EIA) kit were from R&D Systems (Minneapolis, MN). Human leptin ELISA kit was from DSL (Webster, TX). The 3-nitrotyrosin ELISA kit was purchased from Northwest Life Science Specialties (Vancouver, WA).

Subjects

A total of 15 nonobese females with normal body mass index (BMI), as also indicated in most of their normal levels of lipocytokine (leptin and adiponectin in Table 1) preoperatively, aged from 21 to 39 years old, paid the plastic surgeon to perform cosmetic liposuction in Chang Gung Hospital.

Specimens

Serum, plasma, and random urine samples were sent to the clinical laboratories in the Chang Gung Hospital by the plastic surgeon as part of routine patient management. We took advantage of the leftover specimens, including specimens prior to liposuction, and one day and one month after liposuction from all individuals subjected to the procedure. All subjects had normal

TABLE 1. Changes of circulating level of markers of chronic inflammation, and also adipocytokines in the first day following cosmetic liposuction

Marker	Preliposuction	First day postliposuction	P value
hCRP (mg/L)	1.0 $\pm$ 1.4	34.3 $\pm$ 22.8	<0.001
IL-6 (pg/mL)	5.0 $\pm$ 8.8	47.8 $\pm$ 49.0	0.003
SAA (g/mL)	1.4 $\pm$ 1.1	190.3 $\pm$ 100.8	<0.001
Leptin (ng/mL)	29.9 $\pm$ 14.8	39.8 $\pm$ 23.4	0.010
Adiponectin (g/mL)	11.2 $\pm$ 9.9	7.1 $\pm$ 4.4	0.029
NO (M)	44.9 $\pm$ 32.4	27.5 $\pm$ 16.1	0.094
Nitrotyrosine (nmol/L)	68.6 $\pm$ 129.8	58.6 $\pm$ 94.5	0.331
Microalbumin/creatinine (mg/mg)	13.8 $\pm$ 21.0	14.2 $\pm$ 23.7	0.969
8-OHdG/creatinine (ng/mg)	35.7 $\pm$ 17.5	47.8 $\pm$ 17.2	0.029

chemistry profile and normal renal and liver function testing.

All samples were frozen for less than a month at -70°C and thawed at the same time immediately before assay.

Other Assays

Most markers were measured with ELISA, developed in-house by us, including hCRP (16), adhesion molecules (17,18), uMA (19), homocysteine (Hcy) (20), 8-OHdG (21), IL-6 (22), and 3NT (23). All of the in-house kits have been compared with the corresponding commercial kits with good to excellent correlation. Uric acid (UA) was determined by a Hitachi 7600-210 autoanalyzer (Hitachi, Tokyo, Japan). Serum adiponectin was determined by an R&D Adiponectin ELISA kit (R&D Systems). Serum TNF- α was determined with an R&D high-sensitive TNF- α EIA kit (R&D Systems). Serum NO was determined using an R&D total NO

assay kit (R&D Systems). Serum 3-nitrotyrosin was determined with a Northwest Nitrotyrosine ELISA kit (Northwest Life Science Specialties).

RESULTS

Transient Elevation on the First Day Postliposuction

As shown in Table 1 that on average all acute inflammation markers such as hCRP, IL-6, and SAA showed a significant increase in their circulating concentrations on the first day following the liposuction procedure. Most elevations of all these three markers were above their respective upper cutoffs (Fig. 1). However, all elevated levels were found to return to normal baseline one month after the surgery.

We have found that leptin and adiponectin, known as adipocytokines (14), also became transiently elevated and reduced, respectively, in some individuals one day following liposuction. However, only 40% (6/15) of

Fig. 1. Transient alteration of levels of IL-6, hCRP, SAA, and NO on day 1 following liposuction. IL-6, a proinflammatory cytokine, and both acute inflammatory markers, hCRP and SAA, became elevated on day 1 after liposuction. All three markers returned to baseline (compared with levels before surgery) one month after surgery. On the other hand, NO decreased on day 1 before returning to baseline one month after surgery. Upper cutoffs used: IL-6, 6.4 pg/mL; CRP, 3 mg/L; SAA, 6.7 $\mu\text{g/mL}$; and NO, 15.5 $\mu\text{mol/L}$. Normalized level is the determined value divided by its upper cutoff. It allows the direct comparison of various markers with different units. Therefore, any normalized value above 1 (represented by a horizontal dotted line) means elevated and below 1 means normal.

all leptin values rose above the upper cutoff (Table 1; Fig. 2). Moreover, all changes in leptin and adiponectin were found to return to the baseline one month after liposuction.

Slight elevations were also found on the first day after liposuction in both TNF- α and monocyte chemoattractant protein (MCP-1). As a proinflammatory cytokine, the elevation of TNF- α was much less sensitive compared to IL-6 in their response to liposuction (data not shown). Elevation in MCP-1, a chemokine, was also not significant. Again, both markers returned to the baseline one month after the liposuction.

Transient Endothelial Dysfunction

NO is a well-known marker of endothelial dysfunction (24). Reduced (not elevated) concentration of NO is usually associated with endothelial dysfunction. As shown in Table 1, in most cases the decline of NO did not appear to be significant. However, significant decline of NO was found in some women who have underwent

liposuction. As shown in Fig. 1, about 53% (8/15) of women showed a transient decrease of NO one day following liposuction. Only two of the eight women did not have their reduced level of NO return to the baseline. It is not clear whether it was because a longer time, i.e., longer than one day, was required for endothelial dysfunction to be fully recovered.

Assessing Oxidative Damage and Impaired Renal Function

We monitored uMA to find out whether there was damage to renal function caused by liposuction (25). We also monitored both markers of oxidative stress, including plasma 3NT (22) and urinary 8-OHdG (26), in this investigation, to find out whether there might be some oxidative damage caused by this procedure. As shown in Table 1, cosmetic liposuction apparently did not cause any oxidative and nitrosative damage since both 3NT and 8-OHdG did not show significant elevation, and the small increase in 8-OHdG was mostly

Fig. 2. Transient alteration of nitrotyrosine (NT), urinary 8-OHdG, and uMA on day 1 following liposuction. Majority of recipients for liposuction had normal 3NT and 8-OHdG, indicating no oxidative stress to begin with and were back to the baseline one month later. Few exceptions did exist but no increased oxidative stress was found to be generated by liposuction. Similar situation was found in uMA, a marker of renal function. See legend of Fig. 1 for its normalized value. The cutoffs are as follows: 3NT, 25 nmol/L; 8-OHdG, 58 ng/mg creatinine; and uMA, 17 μ g/mg creatinine.

Fig. 3. Impact of liposuction on the level of adipocytokines. It appears that the acute inflammatory response of liposuction would transiently decrease the level of adiponectin and increase that of leptin. They all returned to baseline one month later. See legend of Fig. 1 for normalized value. The cutoffs are as follows: leptin, 37.8 ng/mL; and adiponectin, 4.6 μ g/mL.

confined within the normal range. The few rises of these two markers above their respective upper cutoffs were back to the baseline one month after liposuction. We also did not find any renal impairment as reflected in the level of uMA (a marker of renal function) resulting from this surgical procedure. Like other markers measured in this study, any rises of uMA found on day 1 were back to the baseline one month after liposuction (data not shown).

Change of Adipocytokines

It is well known that both leptin and adiponectin are adipocytokines secreted from fat cells (25). Since liposuction is a process of removing unwanted fat, we decided to find out how this procedure impacts the level of adipocytokines. It is interesting to find that liposuction did transiently affect levels of both adiponectin and leptin. Even though most changes in these two markers eventually returned to the baseline, it was apparent that acute inflammation induced by liposuction impacted both markers' level only transiently. In other words, liposuction transiently raises and reduces the level of leptin and adiponectin, respectively. We also found two of the reduced levels of adiponectin failing to return to the original level at one month after surgery. The reason was not clear (Fig. 3).

Adhesion Molecules

Usually the appearance of elevated levels of soluble adhesion molecules follows that of proinflammatory cytokines (14). In this study we detected the elevation of IL-6 but not adhesion molecules. In fact, a slight decrease in levels of vascular cell adhesion molecule-1

(VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin were found on day 1 in the majority of the cases; and all elevations returned to the baseline in one month (data not shown). Since all changes remained within the normal range, it was not likely that any severe endothelial dysfunction occurred in association with these changes.

Hcy and UA

Recently, it has been recognized that both Hcy and UA will become elevated in response to inflammation (26,27). Because elevation of Hcy and UA responding to inflammation is based on different mechanisms, we decided to measure both markers and find out how they respond to liposuction. As shown in Fig. 4, both markers were not increased on day 1. There was only one woman (1/15) whose Hcy became slightly elevated but returned eventually to the baseline one month after liposuction. In other words, acute inflammatory response of liposuction did not progress further to raise Hcy or UA as is often observed in diseases associated with chronic inflammation. It should be noted that acute inflammatory response transiently affects levels of UA and Hcy.

DISCUSSION

A more recent article (28) appearing in the literature arrived at almost the same results as we have reported here but was dealing with patients with severe periodontitis. These investigators found that patients with severe periodontitis had elevated C-reactive protein (CRP) and IL-6 at day 1 as the result of acute inflammatory response to this inflammatory disease

Fig. 4. Transient alteration of UA and Hcy one day after liposuction. In most cases there were very small changes in both levels of UA and Hcy. Most alterations were confined to the normal range. Changes all returned to baseline one month afterward. See legend of Fig. 1 for normalized value. The cutoffs are as follows: UA, 8 mg/dL; and Hcy, 12 μ mol/L, for both men and women.

(periodontitis is a common potential source of chronic inflammation). However, after intensive, successful periodontal treatment (back to normal after the removal of the inflammatory risk factor) acute inflammatory markers such as CRP and IL-6 returned to baseline at day 7. Their levels remained normal even at six months following intensive treatment. These investigators concluded that with intensive periodontal treatment (similar to normal women after liposuction in our investigation) there was only a short-term systemic inflammation and endothelial dysfunction (in our study the NO was transiently decreased). This report did not find serious adverse effects in patients with severe periodontitis with acute inflammatory response and no cardiovascular events occurred. Even though periodontitis has been shown to be associated with atherosclerosis and an increased risk of myocardial infarction and stroke (29) because of its association with chronic inflammation (2), with intensive treatment (remove the risk factor, consequently, disrupt the chronic inflammation) the acute inflammatory response apparently will not lead to oxidative and nitrosative stress and adverse effects.

The result of our study indicates that a single episode of acute inflammation (as in the case of surgery) causes only a transient elevation of acute inflammatory markers. Much like the well-known transient elevation of circulating tumor markers following surgery. In other words, our results suggest that liposuction does not lead to the elevation of markers corresponding to oxidative and nitrosative stress. Liposuction does not result in clinical complications such as renal dysfunction, myocardial infarction, or cancer. It appears that only chronic inflammation or repeated acute inflammations (such as in asthma), with repeated bombardment of various target cells, will advance downstream from the onset of acute inflammatory response to the subsequent

events, such as recruitment of leukocytes and oxidative and nitrosative stress.

In this investigation we have measured multiple markers associated with sequential events derived from chronic systemic inflammation in the coronary artery, which include acute phase reactants, markers signaling endothelial dysfunction (represented by adhesion molecules), markers signaling the onset of impaired renal function (represented by uMA), and molecules representing the presence of oxidative and nitrosative stress (represented by 8-OHdG and 3NT). Liposuction is a surgical procedure, which is known to induce acute inflammatory response. As expected, we were able to detect elevation of acute inflammatory markers at day 1 following liposuction. However, all elevated acute inflammatory markers were found to return to the baseline one month after the surgery. Most importantly, all markers, including markers corresponding to the subsequent inflammatory events, were normal (back to baseline) and remained normal after one month.

Both NO and adhesion molecules have been considered as marker of endothelial dysfunction (22). Our results from this investigation indicate that NO apparently is a more sensitive indicator for endothelial cell injury than that of adhesion molecules. The small changes seen in NO also support the fact that acute inflammation does not cause severe damage to endothelial cells.

It is important to point out that there were individual variations in responses to this surgical procedure. Individuals' response may be slightly deviated from the average response due to genetic polymorphism. Therefore, we recommend that individuals subjected to liposuction should be monitored with multiple markers, especially uMA, 8-OHdG, and 3NT, one month later to make certain that no harm was done.

Since liposuction is a procedure of removing unwanted fat, we were curious to know what the effect of liposuction was on adipocytokines even though levels of adipocytokines were normal in most women prior to the surgery (Fig. 3). We found that levels of both adipocytokines are impacted by acute inflammatory response to liposuction, but only transiently. Apparently, liposuction will transiently raise the level of leptin and decrease the level of adiponectin. Based on the results of this study we believe that the level of many markers such as NO, leptin, adiponectin, UA, and Hcy will all be altered transiently by acute inflammatory response. Therefore, it is important not to perform measurements immediately following exposure to strenuous exercise, postprandial hyperglycemia, injury, surgery, and infection that are known to induce acute inflammatory response.

It should be cautioned that the impact of acute inflammation on patients with preexisting cardiovascular disease is different from that of normal individuals. The transient elevation of acute inflammatory markers caused by surgery may trigger clinical complications such as myocardial infarction, as reported by Podgoreanu et al. (30). The inflammatory response triggered by cardiac surgery with cardiopulmonary bypass is a primary mechanism in the pathogenesis of postoperative myocardial infarction.

There were few individuals who were apparently slightly obese based on their preoperative leptin concentration (even though the average mean was normal, as shown in Table 1). We found that most of their leptin levels declined to levels lower than that prior to surgery. It appears, in contrary to the report by Klein et al. (31), liposuction may have a slight benefit to people with obesity.

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