

INCLUSION OF TARGETED SKIN PRODUCTS IN THE PRE-SURGICAL TREATMENT REGIMEN OF PERIPHERAL LYMPHEDEMA & LIPEDEMA

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ABSTRACT

Advanced lymphedema is associated with a number of adverse skin changes including color, thickening of the epidermis, dryness, and hyperkeratosis. These changes are related to prolonged lymph stasis and contribute to an increased risk of infection. Similarly, lipedema is associated with skin thickening and appearance of nodular adipose deposition. Skin care is essential in both conditions. We examined whether inclusion of targeted skin products for 2 weeks to an established pre-surgical conservative treatment program was associated with beneficial effects on the skin condition in 150 patients with lymphedema and lipedema. Patients were randomly assigned to control or one of two treatment groups. All three groups (and for both lymphedema and lipedema) demonstrated a significant reduction in softness. Dimpling/redness was significantly reduced in the targeted skin product groups for both patients with lymphedema or lipedema. Only patients with lipedema demonstrated a significant reduction in dryness/hyperkeratosis following targeted skin product treatment. This study demonstrates that short-term use of targeted skin products in both patients with lymphedema and lipedema can be of benefit and further

studies are needed to replicate these results and explore possible mechanisms.

Keywords: lymphedema, lipedema, skin care, dermatological sequelae, pre-operative conservative treatments, CLyFT Genoa protocol

Peripheral lymphedema remains an often poorly recognized disease, can cause significant morbidity, and in advanced cases, physical limitations and increased risk of infection risk (1,2). Chronic lymphedema is associated with fibrotic tissue changes and adipose formation ('non-pitting' edema) that is irreversible when untreated (3-6). Conservative treatments are time-consuming and expensive and can be ineffective in halting the progression of the disease (2,7). Lymphatic microsurgery is able to obtain stable long-term volume reduction in treated limbs. At the Genoa Lymphatic Surgery Center, lymphatic-venous anastomoses are performed at a single-site using larger lymphatic vessels attached to collateral branches of the main veins close to vein valves to avoid backflow of blood and the closure of the anastomosis (8,9). This treatment for peripheral lymphedema is conducted according to a prescribed protocol ("Complete Lymphedema Functional Therapy" – CLyFT),

including conservative treatments like manual and mechanical lymphatic drainage (9). This study explores the effects of adding specific phytotherapeutic natural products to the pre-operative treatment regimen in order to soften the limb as much as possible before surgery.

Skin Changes Associated with Lymphatic Disorders

Disruption in the transport capacity of lymphatic vessels and nodes will cause a buildup of fluid in that area. In the early stages of lymphedema, accumulation of fluid in the interstitium gives rise to a soft 'pitting' edema. In later stages, prolonged lymphatic stasis and subsequent changes in albumin transport and accumulation of hyaluronic acid (10,11) triggers a progressive, chronic inflammation with the accumulation of fibroblasts, adipocytes, and keratinocytes (12,13). This translates clinically into a thickened, hard, fibrotic limb, with changes occurring within months in some cases or years in others, and primarily in the epidermis. Lymphedema predisposes the skin to dryness as a result of the skin being stretched and reduction of oil secretion by sebaceous glands. In severe cases, there is a thickening of the outer layer of the skin (hyperkeratosis), which predisposes the skin creases to cracking and can be an entry point for bacteria and fungi and the development of infection (12,13). This factor has been noted to be key to the skin changes that occur with podoconiosis, a non-filarial lymphedema (14,15).

In lipedema, the skin changes are different, including (in advanced stages) lobular deformation of the skin surface with increased adipose tissue. These fatty nodules vary in size and also known as 'peau d'orange' skin, which can be identified by pressing the skin (16). Skin thickening can also occur, and patients often report that the fatty nodules are painful and bruise easily (16). This tendency to fatty cellulitic deposition in lipedema patients is associated with an eventual development of lymphatic flow injuries, leading to super-im-

posed lymphedema and more associated skin changes (17). For this reason, good clinical practice in both lymphedema and lipedema should include skin hygiene practices to avoid infection and creams/emollients to retain moisture levels to help with maintenance of the water barrier of the skin (12-16).

The use of pharmacological and phytotherapeutic natural therapies for lymphedema has mainly been studied with regard to coumarins. Meta-analyses of 20 trials of oral benzopyrones (omitting non-double-blind or non-peer-reviewed trials) showed robust reductions in edema volume, and in incidence of secondary acute inflammation, including infections (18). Casley-Smith, Morgan, and Piller (18) found that benzopyrone significantly reduced arm and leg circumference, softened the tissue, and improved subjective feelings of tension, heaviness, and pain compared to the placebo period where arm volume increased (19). With regards to skin creams, Brookes et al found that glycerine in water helped to restore the skin barrier in patients with podoconiosis (20). Further investigation of the efficacy of these substances in patients with other forms of lymphedema is warranted.

Combined Treatment of Lymphedema

Microsurgical interventions are part of an integrated treatment protocol called 'Complete Lymphedema Functional Therapy' (CLyFT) (8,9). The other elements of the protocol consist of manual and mechanical lymphatic drainage and intermittent negative pressure therapy, in conjunction with appropriate compressive garments. Mechanical lymphatic drainage refers to the use of uniform and sequential pneumatic devices. In Genoa, CLyFT is applied in three phases: an intensive pre-operative phase to reduce the size of the affected limb as much as possible prior to the microsurgical intervention; a gentle post-operative phase in which the pressure of the lymphatic drainage is gradually increased as healing continues; and finally a long-term maintenance phase of daily mechanical lymphatic drainage

and physical remedial exercise (particularly swimming) to strengthen the anastomotic connections over time. The timing of the treatment protocol depends on the pre-operative stage of the disease but, in general, there is one-to-two weeks of pre-operative CLyFT, the microsurgical intervention, and then one-to-two weeks of post-operative CLyFT before patients initiate the maintenance phase.

The current study investigates the addition of targeted phytotherapeutic natural treatments to the CLyFT pre-surgical treatment program. As mentioned above, the aim of pre-surgical treatment is to reduce the excess volume as much as possible and to soften the limb in order to obtain the best outcome from the surgery. To this end, phytotherapeutic natural substances that help improve drainage and soften tissue may be useful to add to the CLyFT protocol. We examine the possible benefit of these substances in both cream and tablet form. A control group that only completed the CLyFT protocol is included to ensure that any improvements in the skin can be attributed to these phytotherapeutic natural substances.

MATERIAL AND METHODS

Patients

150 patients treated in the Genoa Lymphedema Surgery Center gave written and verbal consent to be involved in this study. The study was approved by the International Review Board (IRB) of the University of Genoa and University of Pavia, Italy. They were randomly (all names were placed into two containers and the first 30 lymphedema patients were assigned to the control group, the next 30 to the first treatment group and so on, also for the lipedema patients) divided into three groups; 2 treatment groups and one control group of 50 patients each. Within each group, there were 30 patients with unilateral or bilateral leg lymphedema and 20 patients with lipedema. The two treatment groups differed in terms of the composition of the phytotherapeutic natural substances given throughout the pre-surgical treatment program; Lipolipase Cream® or Linfolipase Tablets® (AMNOL Chimica Biologica – <http://www.amnol.net>). A control

TABLE 1
Demographic Information for Enrolled Study Subjects

Variable	Number (% or range)
Age Range of All Subjects	
20-29 years	37 (24.7%)
30-39 years	45 (30.0%)
40-49 years	29 (19.3%)
50-59 years	27 (18.0%)
60+ years	12 (8.0%)
Lymphedema (LY) in Treatment Groups	
Primary	27 (31.7%)
Secondary	33 (68.3%)
Lipedema (LI) in Treatment Groups	40
Males in Treatment Groups	
LY	27
LI	0
Females in Treatment Groups	
LY	33
LI	40
Control Group	
<i>Lymphedema</i>	
Primary	9 (34.6%)
Secondary	15 (65.4%)
<i>Lipedema</i>	20
<i>Male</i>	13 (lymphedema)
<i>Female</i>	37 (13 with lymphedema)

group was included to be certain that any beneficial effects were due to these phytotherapeutic natural substances and not due to the CLyFT pre-surgical treatment program. These three groups were matched for gender with one third male and two thirds female in each group and also for lymphedema type (approximately one third with primary lymphedema and two thirds with secondary lymphedema in each group). With regards to age, there were no pre-study statistical differences between the three groups ($F(2,149)=0.031$, $p=ns$). The demographic details of the patients are provided in *Table 1*.

Dermatological Ratings

Ratings of the softness of the limb, redness (lymphedema)/dimpling (lipedema), and dryness (lipedema)/hyperkeratosis (lymphedema) were made at the beginning and end of the treatment sessions by a Dermatologist (CS Campisi) on the following 4-point scales (specific to lipedema in parenthesis): REDNESS (DIMPLING): 0 = none, 1 = mild, 2 = moderate, 3 = severe; SOFTNESS: 0 = soft, 1 = thickened, 2 = thickened/fibrotic, 3 = fibrotic/hard; HYPERKERATOSIS (DRYNESS): 0 = none, 1 = mild, 2 = moderate, 3 = severe. The average ratings, pre- and post-treatment were compared for the two treatment groups and the control group.

Phytotherapeutic Natural Products

1) Linfolipase Tablets® – are food supplements with components that are useful for the elimination of excess bodily fluids and improvement of microcirculation, including green tea, sweet clover (*Melilotus Officinalis*), birch extract, bromelain (pineapple extract), and co-enzyme Q10. Full details of the components can be found at: <http://en.amnol.net/specialization/lymphology/linfolipase>

2) Lipolipase Cream® – a light cream that includes ingredients that improve the microcirculation and stimulates lipolytic enzymes. This cream includes sweet clover (*Melilotus*

Officinalis), faselip, carnitine, caffeine, and theophylline. The cream bottle has three metal balls in the lid area that can be used to gently massage the skin when applying the cream to stimulate circulation and help with absorption. The cream was applied to the length of the lower limbs to the inguinal region, including the dorsum of the foot, in light circles, distally to proximally, until the cream was completely absorbed. Full details of the components of the cream can be found at: <http://en.amnol.net/specialization/lymphology/lipolipase-cremagel>

Study Protocol

All patients from both the control and treatment groups were in the pre-surgical phase and were attending the Genoa Center to complete pre-surgical intensive treatment under the CLyFT protocol. This entailed coming to the clinic for 10 sessions of 4-5 hours in a two-week period. Prior to starting the treatment period, each patient was evaluated by the Dermatologist to note the skin condition and the pre-treatment ratings of softness etc. were made for each patient. The same evaluation was made for each patient at the end of the two week treatment period.

Patients in the control group completed only the 10 CLyFT treatment sessions. Patients in the Linfolipase Tablet® group took one tablet each day before lunch for the two-week period and completed the CLyFT program. Patients in the Lipolipase Cream® group applied approximately 15 ml. of cream to their legs morning and night, massaging lightly until absorbed, for the two week period and completed the CLyFT program.

Data Analysis

Data are presented as mean ratings on each skin condition scale. Data were analyzed using Microsoft Excel 2011 using the Real Statistics Resource Pack software (Release 4.3). Copyright (2013-2015) Charles Zaiontz. www.real-statistics.com.

TABLE 2
Dermatological Pre- and Post-Treatment Results for
Dimpling/Redness, Dryness/Hyperkeratosis, and Softness for the Control Group

		Average Pre-Treatment Score (0-3)	Average Post-Treatment Score (0-3)	Significance
DIMPLING	LIPE.	0.8	0.6	t(19)=1.52, p=ns
REDNESS	LYMP.	1.733	1.6	t(29)=1.44, p=ns
DRYNESS/ HYPERKERATOSIS	LIPE.	0.55	0.5	t(19)=0.57, p=ns
	LYMP.	1.633	1.6	t(29)=0.44, p=ns
SOFTNESS	LIPE.	1.25	0.95	t(19)=2.35, p=0.029
	LYMP.	2.233	1.433	t(29)=7.18, p=<0.0001

t(n) = t value (degrees of freedom); LIPE. = lipedema patients; and LYMP. = lymphedema patients.

TABLE 3
Dermatological Pre- and Post-Treatment Results for
Dimpling/Redness, Dryness/Hyperkeratosis, and Softness for the
Lipolipase Cream® Treatment Group

		Average Pre-Treatment Score (0-3)	Average Post-Treatment Score (0-3)	Significance
DIMPLING	LIPE.	0.8	0.3	t(19)=3.68, p=0.006
REDNESS	LYMP.	1.733	0.567	t(29)=9.14, p=<0.0001
DRYNESS/ HYPERKERATOSIS	LIPE.	0.6	0.45	t(19)=1.17, p=ns
	LYMP.	1.667	1.00	t(29)=6.02, p=<0.0001
SOFTNESS	LIPE.	1.25	0.75	t(19)=4.36, p=0.0003
	LYMP.	2.1	1.51	t(29)=5.46, p=<0.0001

t(n) = t value (degrees of freedom); LIPE. = lipedema patients; and LYMP. = lymphedema patients.

TABLE 4
Dermatological Pre- and Post-Treatment Results for
Dimpling/Redness, Dryness/Hyperkeratosis, and Softness for the
Linfolipase Tablets® Treatment Group

		Treatment Score (0-3)	Treatment Score (0-3)	Significance
DIMPLING	LIPE.	0.75	0.35	t(19)=2.99, p=0.004
REDNESS	LYMP.	1.667	0.433	t(29)=1.7, p=0.04
DRYNESS/ HYPERKERATOSIS	LIPE.	0.75	0.55	t(19)=1.71, p=ns
	LYMP.	1.663	1.133	t(29)=2.38, p=0.01
SOFTNESS	LIPE.	1.15	0.65	t(19)=4.36, p=0.0003
	LYMP.	2.133	1.3	t(29)=9.96, p=<0.0001

t(n) = t value (degrees of freedom); LIPE. = lipedema patients; and LYMP. = lymphedema patients.

RESULTS

The first analysis demonstrated that there were no pre-existing differences between the treatment groups and the control groups in terms of the ratings of skin condition of the patients with the following results [(t value (degrees of freedom)]: Redness - t(98)=0.11, p=ns; Dimpling - t(98)=0.31, p=ns; Dryness - t(98) = 0.82, p =ns; Hyperkeratosis - t(98) = 0.21, p =ns; Softness (lymphedema) - t(98) = -0.34, p =ns; Softness (lipedema) - t(98) = 1.00,

p =ns. Therefore, for each group, the ratings of the Dermatologist pre-treatment were compared to the post-treatment ratings.

Control Group

There was a significant improvement in the Dermatologist's ratings for softness of the skin in both control patients with lipedema (t(19)= 2.35, p= 0.029) and lymphedema (t(29) = 7.18, p= <0.0001), indicating that the CLy-FT pre-surgical treatment protocol is able to

soften the treated limb. There were no significant effects in terms of reduction in redness, dimpling, or hyperkeratosis for the control group patients, compared to their pre-treatment status (*Table 2*).

Treatment Group – Lipolipase Cream®

There were significant effects of the Lipolipase Cream® for the patients with lymphedema in terms of a reduction in redness ($t(29) = 9.14$, $p < 0.0001$) and hyperkeratosis ($t(29) = 6.02$, $p < 0.0001$). Patients with lipedema showed a significant reduction in dimpling of the skin ($t(19) = 3.68$, $p = 0.0016$). There was no significant effect of the addition of the Lipolipase Cream® in reducing dryness in patients with lipedema ($t(19) = 1.17$, $p = \text{ns.}$). For both groups there was a significant improvement in the ratings of limb softness ($t(29) = 5.46$, $p < 0.0001$ and $t(19) = 4.36$, $p = 0.0003$ for lymphedema and lipedema patients, respectively) (*Table 3*).

Treatment Group – Linfolipase Tablet®

There were significant effects in the reduction of hyperkeratosis for patients with lymphedema ($t(29) = 2.38$, $p = 0.01$ and a tendency towards a reduction in redness ($t(29) = 1.76$, $p = 0.04$). Lipedema patients experienced a reduction in skin dimpling ($t(19) = 2.99$, $p = 0.004$) but not dryness ($t(19) = 1.71$, $p = \text{ns.}$). For both groups there was a significant improvement in the ratings of limb softness ($t(29) = 9.96$, $p < 0.0001$ and $t(19) = 4.36$, $p = 0.0003$ for lymphedema and lipedema patients, respectively) (*Table 4*).

No patient reported any adverse effects with either of targeted skin products. Anecdotally, patients in the Lipolipase Cream® group noted that the applicator with the rolling balls was easy to use and the massage sensation was pleasant. The cream left a sensation of freshness/coolness to the skin and was lightly perfumed. The Linfolipase Tablet® group had no difficulty with swallowing the tablets and noted a slight 'herbal' taste that was not unpleasant.

DISCUSSION

This brief study examined the effects of introducing targeted skin products to an established pre-surgical treatment protocol for lymphedema and lipedema patients. Both products are reputed to contain properties that may be helpful in ameliorating skin conditions associated with lymphedema and lipedema. For example, *Melilotus Officinalis* (sweet clover) has been shown to be effective in reducing edema in some studies (18,19), although evidence is variable (21). Given the redness and hyperkeratosis that develops with advanced stages of lymphedema, we hypothesized that the Lipolipase Cream® in particular may be helpful to ameliorate these symptoms. Alternatively, the bromelain and co-enzyme Q10 components of the Linfolipase Tablets® are reported to stimulate protein breakdown to reduce inflammation (22). With the inclusion of *Melilotus Officinalis* as well to increase microcirculation and drainage, the Linfolipase Tablets® may also be useful to improve the skin condition in lymphedema patients. In patients with lipedema, skin changes are associated with skin dimpling and thickening due to excess adipose tissue deposition. In these cases, we hypothesized that the cream applicator with the massaging balls might help to soften and breakdown the fatty deposits.

We included a control group so that we were able to elucidate the effects of the CLyFT pre-surgical treatment program in isolation. We found that 10 treatment sessions was enough to produce an evident improvement in skin softness in both patients with lymphedema and lipedema. As expected, patients with lymphedema had higher scores of skin thickening and fibrosis at the initial measurement compared to patients with lipedema. Nevertheless, both types of control patients (those with lymphedema and those with lipedema) benefitted in terms of improvement in skin softness from the CLyFT treatment sessions. It is probable that the CLyFT program also reduces the excess volume in the affected limb(s) by improving the lymphatic drainage,

but volume reduction was not the focus of this study so it was not directly measured. The CLyFT program alone was not sufficient to improve the redness, skin dimpling, or dryness/hyperkeratosis from baseline conditions for all patients in the control group.

Lipolipase Cream®, containing products that act on microcirculation and lymphatic drainage, improves the skin condition in patients with lymphedema by reducing redness, relieving dryness, and improving hyperkeratosis. In patients with lipedema, there was an improvement in skin dimpling. The cream was reported to be easy to use and absorbed readily. No adverse effects were noted. We must, however, acknowledge that we did not have a control group of a neutral cream base in order to determine if similar hydrating effects may have been achieved by this cream alone or were due to the Lipolipase Cream® additional ingredients. It is possible that the reduction in skin dryness may have been related only to the base emollient. Lipolipase Cream® has a glycerine base. Glycerine washes have been very successful in reducing skin barrier damage in patients with podocniosis (non-filarial lower limb elephantiasis) and the associated skin wounds and lymphangitic attacks (20). The glycerine solution can help to reduce transepidermal water loss and therefore reduced the skin cracking that allowed bacteria to penetrate. Therefore, Lipolipase Cream® with its glycerine-base should also have a role in infection reduction by helping to maintain the integrity of the skin barrier in patients with lymphedema.

Likewise, improvement in microcirculation promoted by the Linfolipase Tablets® contributes to an overall improvement in redness and hyperkeratosis that is a result of prolonged lymph stasis in lymphedema patients. A similar improvement is achieved in the leg dimpling in patients with lipedema, possibly due to a reduction in adipose tissue. These results are comparable to those achieved with the Lipolipase Cream®. Additionally, just as with the cream, no patient reported any adverse events or side effects from the Linfoli-

pase Tablets®.

It must be noted that this study is a relatively short study with only two weeks duration, as it maps onto the usual pre-surgical treatment phase of patients from the Genoa Lymphatic Surgery Center. It was our intention to examine the possible benefits of adding these targeted skin products to our treatment program and therefore these results may not be generalizable to all patients with lymphedema and lipedema. While the results are promising, in terms of a significant improvement in skin condition for both lymphedema and lipedema patients, they need to be replicated in larger studies in order to confirm the results. We also acknowledge the limits of our study that investigated the skin changes with relation to those visible to the naked eye or palpable by touch. For example, any extent of epidermal thickening must be confirmed by histology or imaging, such as MRI. Future studies should include these modalities in order to truly understand the effects on lymphoedematous skin that could be possible with such targeted skin products.

In summary, Lipolipase Cream® and Linfolipase Tablets®, when added to the CLyFT pre-surgical treatment program were beneficial for patients with lymphedema in terms of a perceived reduction in skin reddening and dryness/ hyperkeratosis compared to pre-treatment conditions. Patients with lymphedema benefitted from these targeted skin products in terms of a reduction in skin dimpling from excess adipose tissue deposits. In addition, the two substances were well-tolerated by all patients.

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CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no competing financial interests exist.

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