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Liposuction of lymphedema

Treatment strategy, pathophysiology and long-term outcome

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Treatment strategy, pathophysiology
and long-term outcome

Mattias Hoffner



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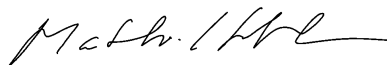
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Liposuction of lymphedema: treatment strategy, pathophysiology and long-term outcome			
<p>Lymphedema is a chronic and complex condition that has major physical, psychological and social implications for the quality of life of patients suffering from it. Any disruption of the lymph flow due to disease or iatrogenic damage (surgery, radiotherapy or trauma) can result in failure to transport lymph back to the blood circulation, and secondary to this, fat deposition will occur in the affected extremity resulting in a lymphedema.</p> <p>Aims: To investigate the incidence of erysipelas in postmastectomy arm lymphedema before and after treatment with liposuction (Paper I), to investigate the quality of life in patients with postmastectomy arm lymphedema before and after treatment with liposuction and in comparison to Swedish norm data (Paper II), to examine the relation of fat and water in the epi- and subfascial compartment of the lymphedema using magnetic resonance imaging (MRI) (Paper III), to investigate the long-term outcome of lymphedema excess volume reduction after liposuction in combination with controlled compression therapy in patients with late stage arm lymphedema (Paper IV).</p> <p>Methods: Paper I. 130 patients with postmastectomy arm lymphedema underwent liposuction between 1993-2012. Pre- and postoperative bouts of erysipelas were analyzed. The mean duration of lymphedema prior to liposuction was 8.8 years (range 1-38, standard deviation (SD) 7.0 years). The mean age at the time of liposuction was 63 years (range 39-89, SD 10 years). The total number of pre-liposuction observation years was 1147, and the total number of post-liposuction observation years was 983. Paper II. Sixty female patients with arm lymphedema were followed for a one-year period after liposuction. The 36-item short-form health survey (SF-36) was used to assess health-related quality of life (HRQoL). Patients completed the SF-36 questionnaire before liposuction, and after one, three, six, and 12 months. The results were compared with Swedish norm data. Paper III. Seven patients with arm lymphedema (median 1239 ml) and six patients with leg lymphedema (mean 4183 ml) were examined with MRI before and after liposuction at four days, and one, three, six and 12 months. Three slices were acquired at eight echo times with voxel size 1.6 x 1.6 x 5 mm³ and fat and water fraction images were reconstructed using a linear least-squares algorithm. Fat and water volumes were calculated within each of the epifascial and subfascial compartments. Paper IV. 105 women with non-pitting edema, a mean age of 64 (range, 41-89) years and a mean duration of arm swelling of 10 (range, 1-38) years underwent liposuction. The mean age at the time of the breast cancer operation, the mean interval between the breast cancer operation and lymphedema start, and the duration of lymphedema were 51 years (range, 34-86), three years (range 0-32), and 10 years (range 1-38) respectively. Aspirate and arm volumes were recorded.</p> <p>Results: Paper I. The incidence of erysipelas decreased from 0.47 attacks/year to 0.06 attacks/year, a reduction of 87%. Paper II. Mental health, physical functioning, bodily pain, vitality, social functioning and composite scores showed higher values after surgery. Compared with SF-36 norm data for the Swedish population, only physical functioning showed lower values than the norm at baseline. Paper III. The excess epifascial fat and water decreased. The excess subfascial fat was unchanged. The excess water in the subfascial compartment was reduced over time, which may have represented a decrease of muscle volume after treatment due to less mechanical load after liposuction. Paper IV. The aspirate mean volume was 1831 ml (range 650-3780) with an adipose tissue concentration of 94 % (range 58-100). The preoperative mean excess volume was 1642 ml (range 570-3520). The postoperative mean reduction was 101 % (range 68-189) at three months and more than 100% during the five years' follow-up when it was 117% (range 25-191), i.e. the lymphedematous arm was somewhat smaller than the healthy arm.</p> <p>Conclusion: We demonstrate that liposuction removes the excess volume completely, without recurrence, and reduces the incidence of erysipelas by 87%. Also, liposuction seems to improve patients' HRQoL, possibly due to the reduced volume of fat and the decreased amount of water/muscle shown by MRI.</p>			
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and long-term outcome

Mattias Hoffner



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List of papers

This thesis is based on the following papers and are referred to in the text by their Roman numerals.

- I. Liposuction of postmastectomy arm lymphedema decreases the incidence of erysipelas.
Lee D, Piller N, **Hoffner M**, Manjer J, Brorson H.
Lymphology 49: 85-92 (2016)
- II. SF-36 shows increased quality of life following complete reduction of postmastectomy lymphedema with liposuction
Hoffner M, Bagheri, Hansson E, Manjer J, Troëng T, Brorson H.
Lymphat Res Biol 15: 87-98 (2017)
- III. Lymphedema leads to fat deposition in muscle and decreased muscle/water volume after liposuction: a Magnetic Resonance Imaging study.
Hoffner M, Peterson P, Månsson S, Brorson H.
Lymphat Res Biol Sep 28. doi: 10.1089/lrb.2017.0042. [Epub ahead of print] (2017)
- IV. Liposuction gives complete reduction of arm lymphedema following breast cancer treatment – a five-year prospective study in 105 patients without recurrence.
Hoffner M, Ohlin K, Svensson B, Manjer J, Hansson E, Troëng T, Brorson H. Submitted for publication (2017)

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Thesis at a glance

I. Liposuction of postmastectomy arm lymphedema decreases the incidence of erysipelas

Aim: To investigate the incidence of erysipelas in postmastectomy arm lymphedema before and after treatment with liposuction.

Method: 130 patients with postmastectomy arm lymphedema underwent liposuction in the period 1993-2012. Pre- and postoperative bouts of erysipelas were analyzed. Mean duration of lymphedema prior to liposuction was 8.8 years (range 1-38, standard deviation (SD) 7.0 years). The mean age at the time of liposuction was 63 years (range 39-89, SD 10 years). The total number of pre-liposuction observation years was 1147, and the total number of post-liposuction observation years was 983.

Results: The incidence of erysipelas decreased from 0.47 attacks/year to 0.06 attacks/year, a reduction of 87%.

II. SF-36 shows increased quality of life following complete reduction of postmastectomy lymphedema with liposuction.

Aim: To investigate the quality of life in patients with postmastectomy arm lymphedema before and after treatment with liposuction and in comparison with Swedish norm data.

Method: Sixty female patients with arm lymphedema were followed for a one-year period after liposuction. The 36-item short-form health survey (SF-36) was used to assess health-related quality of life (HRQoL). Patients completed the SF-36 questionnaire before liposuction, and after one, three, six, and 12 months. The results were compared with Swedish norm data.

Results: Mental health, physical functioning, bodily pain, vitality, social functioning and composite scores showed higher values after surgery. Compared with SF-36 norm data for the Swedish population, only physical functioning showed lower values than the norm at baseline.

III. Lymphedema leads to fat deposition in muscle and decreased muscle/water volume after liposuction: a Magnetic Resonance Imaging study.

Aim: To examine the relation of fat and water in the epi- and subfascial compartment of the lymphedema using magnetic resonance imaging (MRI).

Methods: Seven patients with arm lymphedema (median 1239ml) and six patients with leg lymphedema (mean 4183ml) were examined with MRI before and after liposuction at four days, and at one, three, six, and 12 months. Three slices were acquired at eight echo times with voxel size 1.6 x 1.6 x 5 mm³ and fat and water fraction images were reconstructed using a linear least-squares algorithm. Fat and water volumes were calculated within each of the epifascial and subfascial compartments.

Results: The excess epifascial fat and water decreased. The excess subfascial fat was unchanged. The excess water in the subfascial compartment was reduced over time, which may represent a decrease of muscle volume after treatment due to less mechanical load after liposuction.

IV. Liposuction gives complete reduction of arm lymphedema following breast cancer treatment – a five-year prospective study in 105 patients without recurrence.

Aim: To investigate the long-term outcome of lymphedema volume reduction after liposuction in combination with controlled compression therapy in patients with late stage arm lymphedema.

Methods: 105 women with non-pitting edema, a mean age of 64 (range, 41-89) years and a mean duration of arm swelling of 10 (range, 1-38) years underwent liposuction. The mean age at the time of the breast cancer operation, the mean interval between the breast cancer operation and lymphedema start, and the duration of lymphedema were 51 years (range, 34-86), three years (range, 0-32), and 10 years (range, 1-38) respectively. Aspirate and arm volumes were recorded.

Results: The aspirate mean volume was 1831 ml (range, 650-3780) with an adipose tissue concentration of 94 % (range, 58-100). The preoperative mean excess volume was 1642 ml (range 570-3520). The postoperative mean reduction was 101 % (range, 68-189) at three months and more than 100% during the five years' follow-up when it was 117% (range, 25-191), i.e. the lymphedematous arm was somewhat smaller than the healthy arm.

In summary (Papers I – IV)

In this thesis we demonstrate that liposuction removes the excess volume completely, without recurrence, and reduces the incidence of erysipelas by 87%. Also, liposuction seems to improve patients' HRQoL, possibly due to the reduced volume of fat and the decreased amount of water/muscle shown by MRI.

Introduction

The lymphatic system

The components of the lymphatic system were first reported by Hippocrates (ancient Greek physician), and the anatomy of the lymphatics was characterized almost completely in the 19th century (1).

The lymphatic system is a vital part of the immune system and also of the circulatory system. It is organized as a branched network of lymph capillaries and collecting lymphatic vessels which transport a transparent fluid called lymph. In contrast to blood capillaries, the lymph capillaries are blind-ended and constitute an open system (unlike the circulatory system) where the primary function is to drain the excess interstitial fluid resulting from blood capillary filtration. Approximately three liters per day are drained by this accessory pathway (2).

Anatomy and physiology

Lymph is collected from the interstitial space by lymph capillaries which lack a basement membrane and have discontinuous intercellular junctions. Subsequently, the lymph flows via pre-collecting lymphatic vessels into larger lymphatic collecting vessels (3) (Figure 1).

These vessels are surrounded by smooth muscle cells, have a basement membrane, and contain intraluminal valves (two semilunar leaflets) ensuring a unidirectional lymph flow (Figure 2).

Along the lymphatic pathway the lymph flows through lymph nodes (Figure 3). These are structures of lymphoid tissue and are located at intervals along the lymphatic system. As lymph passes the lymph node, both the lymphocyte count and the concentration of proteins will change. After the node the lymphocyte count increases and the protein concentration decreases (4).

After passing one or more lymph nodes the lymphatic collecting vessels coalesce into larger lymphatic trunks. The right lymphatic duct drains the right arm, the right side of the head, and the right thoracic cavity and empties into the right

subclavian vein. The thoracic duct drains lymph from all other parts of the body, emptying into the left subclavian vein (5) (Figure 4).

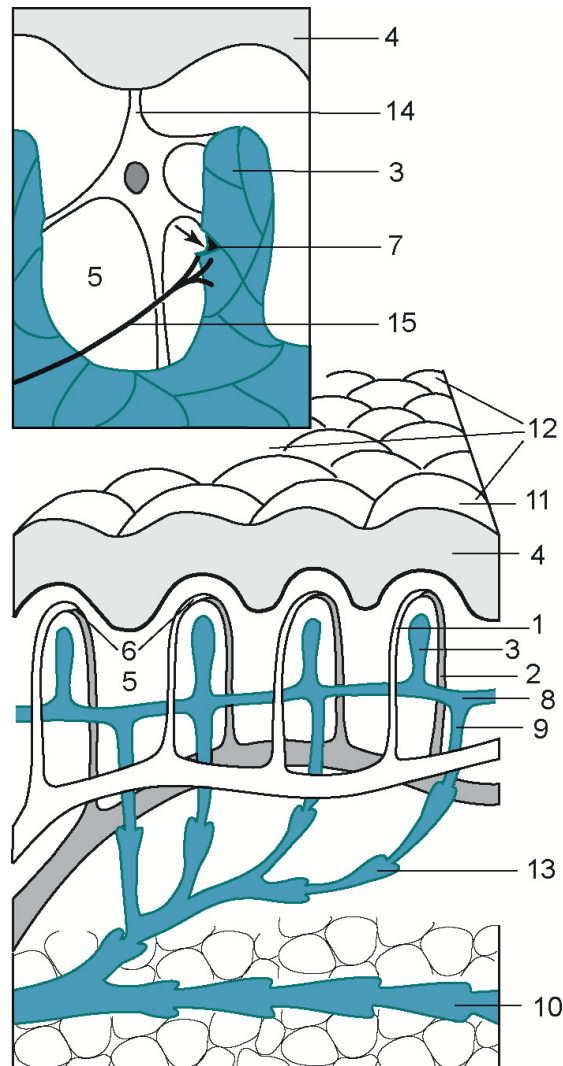


Figure 1. Surrounded by pre-capillary arterioles (1) and post-capillary venules (2) the lymph capillaries (3) penetrate into the dermis (4). Protein, fat molecules and water are filtered to the interstitial space (5) from the blood capillaries (6) and are collected into the lymphatic capillaries, which lack a basement membrane, via discontinuous intercellular junctions (7). Subsequently, the lymph flows via lymphatic capillaries (8) into pre-collecting lymphatic vessels (9) and into larger lymphatic collecting vessels (10). Each pre-collecting lymphatic vessel represents a lymphatic area in the epidermis (11). A larger number of lymphatic areas constitute a lymphatic skin zone (12). In the pre-collecting lymphatic vessels the semilunar valves (13) are found. Connective tissue such as fibroblasts (14) prevents vessels from collapsing and anchors filaments (15), and also contributes to the regulation of the intercellular junctions. Illustration: Lena Lyons

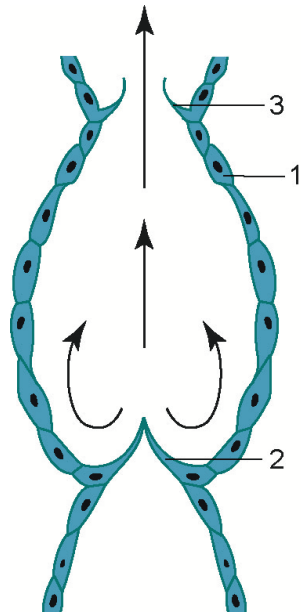


Figure 2. A lymphangion represents a unit of a lymph vessel that lies between two semilunar valves and has smooth muscle cells in the vessel wall (1). Thus the lymphangion is muscular and when the smooth muscles contract the semilunar valves close and prevent lymph from flowing backwards (2). The semilunar valves are directed towards the flow of the lymph and open when the pressure in the first lymphangion is greater than the pressure in the next lymphangion (3). Illustration: Lena Lyons

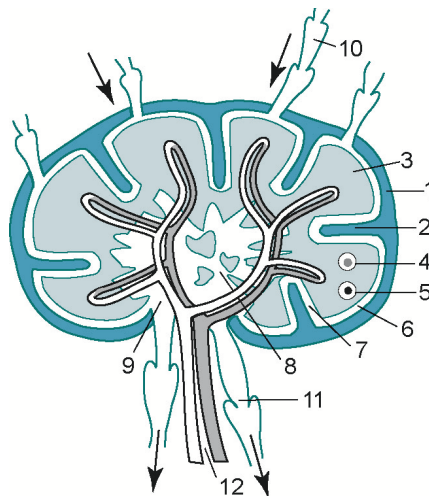


Figure 3. The lymph node consists of a capsule (1) and trabeculae (2). In the medulla (3) the B- and T-lymphocytes are produced (4), (5). The sinusoids consist of a marginal sinus (6), intermediate sinus (7), medullary sinus (8) and terminal sinus (9). In these sinusoids the lymphocytes and macrophages circulate. Afferent (10) and efferent (11) lymph vessels. Artery and vein (12). Illustration: Lena Lyons

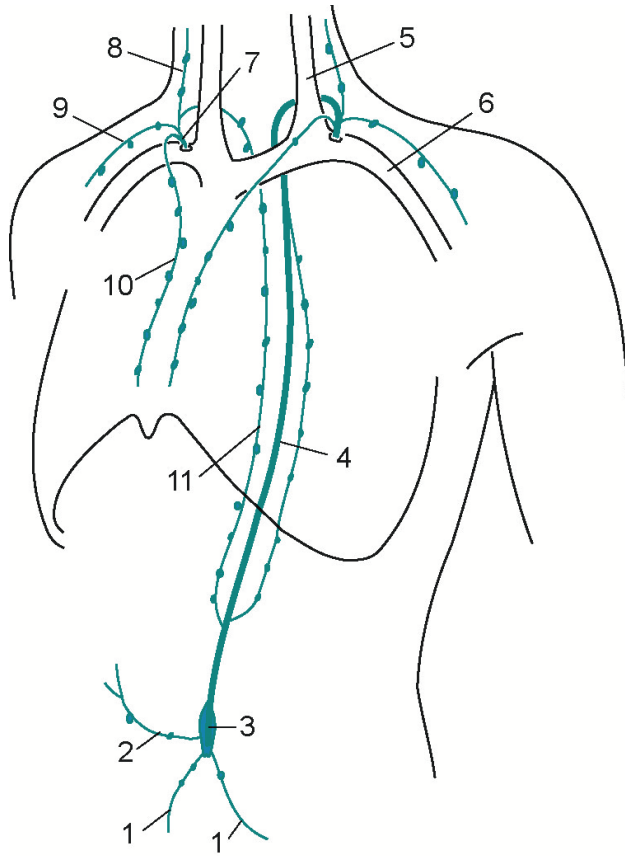


Figure 4. From the inguinal and axillary lymph nodes the lymph is propelled into abdomen and thorax. From lymph nodes in the pelvis and mesentery the lymph flows into the right and left truncus lumbalis (1) and truncus intestinalis (2) and drains into cisterna chyli (3). The cisterna chyli merges into the thoracic duct (4), which drains into the left venous angle between the left internal jugular vein (5) and the left subclavian vein (6). The right lymphatic duct is drained correspondingly (7) after receiving lymph from the right jugular trunk from the head and neck (8), the right subclavian trunk from the right arm and right axilla (9), the right parasternal trunk (10) and the right intercostal trunk from the thorax (11). Illustration: Lena Lyons

Lymph propulsion is regulated by rhythmic compression and expansion of the lymphatic vessels and intrinsic forces generated by the spontaneous phasic contractility of smooth muscle cells (6). Structural defects in lymphatic vessels will impair the ability of the pump mechanism to drain lymph, and a lymphedema will occur (7).

Lymphedema

Handley described breast cancer-related lymphedema more than hundred years ago (8) but the lymphatic system and its related pathological disorders have been the subject of passive neglect over centuries of medical development. Since the lymphatic system plays a key role, both in the human circulation and the immune system, this appears paradoxical. Fortunately, we are experiencing a renaissance in the field of lymphatic research, and awareness of the importance of the lymphatic system and its pathology is growing.

Lymphedema is a progressive and still incurable condition of variably painful swelling that can affect any part of the body. The swelling results from an insufficient lymphatic system and disarranged lymphatic transport and will subsequently lead to swelling of the tissues and eventually thickening of the skin and soft tissue. At a cellular level this inadequate drainage of lymph will lead to accumulation of interstitial fluid, which causes cellular proliferation and inflammation (9). As a result, chronic inflammation leads to dilatation and fibrosis of lymph vessels, which become incompetent with concomitant deposition of subcutaneous fat, and later fibrosis. The excess adipose tissue deposition begins either when the lymphedema becomes clinically significant or can occur within 1-2 years (10, 11).

Lymphedema and pathophysiology

Historically it is believed that lymphedema is an abnormal accumulation of protein-rich fluid in the interstitial matrix (12). The traditional view of the lymphatic capillaries is that the arteriolar end of the capillary filters, while the venular end reabsorbs fluid. However new research points out that if all Starling forces are considered, including interstitial colloid osmotic and hydraulic pressures, there is a net but decreasing filtration along the entire length of the capillary, with no venous reabsorption (13, 14). Due to the complex physiological system, involving different local pressure gradients and mechanical forces, the lymph will either be absorbed by the lymph vessels or accumulate in the interstitial space (15, 16). In addition, any disruption of the lymph flow (i.e., lymph node dissection) can result in failure to transport lymph back to the blood circulation, resulting in a lymphedema in any part of the drainage basin (17).

Chronic lymphedema (Figure 5) contains large amounts of adipose tissue (10, 11) (9). A slow lymph flow accelerates lipogenesis and fat deposition (18). This process is enhanced by the transformation of monocytes to adipocytes (19, 20). Subsequently, subcutaneous lymphedema becomes firm due to activation of fibroblasts, which increase the connective tissue component of the lymphedema

(21, 22). However, recent research has focused on inflammation and upregulation of fat differentiation markers as well as adipogenic differentiation of adipose-derived stem cells leading to adipose tissue deposition (23-25).

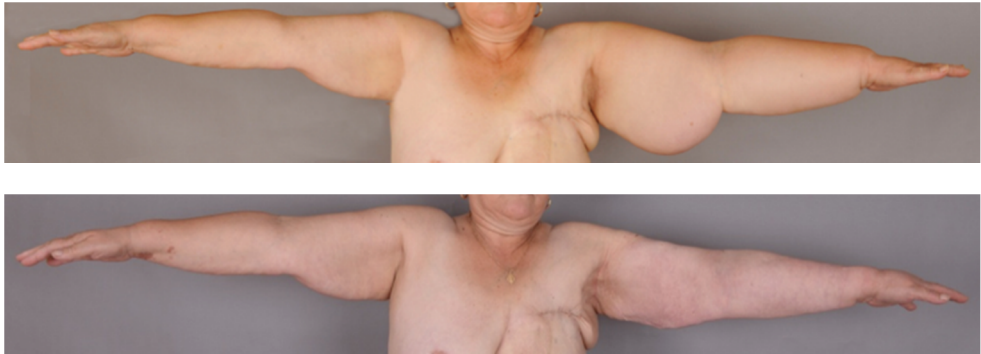


Figure 5. A 57 year-old woman with lymphedema of 4325 ml that had lasted for five years (upper figure). Complete reduction at 1 year after liposuction (lower figure).

Classification

Lymphedema is classified by the etiology and is divided into primary and secondary causes (17). Traditionally, the term ‘primary lymphedema’ is used to describe a genetic or developmental abnormality or dysfunction in the lymphatics, which can be present at birth (congenital) or that can appear later in life around the time of puberty (lymphedema praecox), or presenting in adults older than 35 years (lymphedema tarda). Secondary lymphedema results from disruption or obstruction of normal lymphatics due to disease or iatrogenic processes, for example surgery, infection, radiotherapy or trauma.

Epidemiology

Lymphedema affects millions of people worldwide. Primary lymphedema is rare, afflicting 1/100 000 individuals. Secondary lymphedema, due to damage to a normally developed lymphatic system, affects approximately 1/1000 Americans (26). In developed countries malignant neoplasms and their therapies are the most common cause of lymphedema. In a meta-analysis, DiSipio et al. suggest that more than one in five women who survive breast cancer will develop arm lymphedema (27).

Filiariasis refers to infection by the parasitic nematode *Wuchereria Bancrofti*. Following transmission by a mosquito vector, the adult filarial worms lodge in the lymphatic vessels and initiate an immune response which promotes lymph vessel

hyperplasia and inflammation as a result of the immune response. It is estimated that around 120 million people in the tropics are infected (28).

Diagnostic criteria

There is currently no gold standard for the definition of lymphedema, but a 10% difference in limb volume is a common definition (29).

The diagnosis of lymphedema is based on clinical history, visual inspection and skin palpation, and the determination of volume differences between both limbs. Sequential circumference measurements along designated measure points are widely used. Based on a truncated cone formula the limb volume can then be calculated. Volume measurement by means of the water displacement technique is considered the gold standard and there is a good correlation between that and using circumference measurements (30).

Clinical examination of a pitting is mandatory and is performed by the “pitting test” (Figure 6).



Figure 6. Marked lymphedema of the arm after breast cancer treatment, showing pitting several centimeters in depth (stage I-II edema). The arm swelling is dominated by the presence of fluid, i.e., the accumulation of lymph (**left**).

Pronounced arm lymphedema after breast cancer treatment (stage II-III edema). There is no pitting in spite of hard pressure by the thumb for 1 minute. The “edema” is dominated by adipose tissue (**right**). The term “edema” is unsuitable to use at this stage, since the swelling is dominated by hypertrophied adipose tissue and not by lymph. At this stage, the aspirate contains either no lymph or a minimal amount.

Imaging

There are several imaging techniques that provide support when the diagnosis is unclear. Unfortunately, none of them are standardized in the clinical setting (31).

Lymphoscintigraphy (LS) use radiotracers to detect specific lymphatic pathology. LS provides images of both lymphatic vessels and lymph nodes as well as lymph transport. There is no uniform standardization of LS since radio tracers, different injection sites, injected volumes, and protocols vary.

Other examples of investigational tools to elucidate lymphatic abnormalities are magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography (US) and Dual Energy X-Ray Absorptiometry (DXA) (11, 31).

Newer methods to assess lymphedema are continuously developing. Measurement of local tissue water can be performed by tissue dielectric constant (TDC) or by bioimpedance spectroscopy (BIS) (32, 33). In TDC an instrument transmits an electromagnetic wave into a probe in contact with the skin. The portion of reflected wave depends on the amount of water in the tissue immediately under the probe.

BIS measures the impedance along or transverse to the axis of the limb in parallel to the current flow.

Indocyanine green (ICG) lymphography is also being used to evaluate the function of the lymphatics. ICG binds to albumin, which is taken up into the lymphatics. ICG fluoresces in the near infrared range. Using a special camera, the green colored fluorescence will be detected and lymph flow assessed (34).

Differential diagnoses

There are other reasons than lymphedema for a swollen limb and therefore a thorough medical assessment is done to exclude other causes of swelling (35). It is crucial to explore the correct etiology since it will require different treatment regimens. In bilateral swelling, the edema might be associated with congestive heart failure, chronic venous insufficiency, renal or hepatic dysfunction, medication, hypothyroidism, hypoproteinemia or lipedema. In unilateral swelling, the edema might be associated with acute deep venous thrombosis, post-thrombotic syndrome, arthritis, Baker's cyst, or malignant disease (36, 37).

Lipedema

Lipedema is due to a metabolic disorder and presents with excessive accumulations of fat in the subcutaneous tissue, most commonly in the legs, with sparing of the feet. The skin is soft and elastic and bruises easily. The patients complain of pain on pressure. Lymphoscintigraphy is normally negative when the Body Mass Index is less than around 50. There is no pitting, but when associated with morbid obesity, pitting can be found due to an overload of normal lymphatics (38, 39).

Staging

Staging of lymphedema only refers to the physical condition of the extremities. Pathogenetic mechanisms of lymphedema such as degree of lymph flow, impairment, and degree of lymphatic vessel abnormality are not included.

There are arguments among lymphologists about using a three- or four-stage protocol. A consensus document from the International Society of Lymphology stated an increasing recognition of a four-stage protocol (40). Within each stage severity can be assessed based on volume difference between the healthy and lymphedematous extremity. Minimal (>5 - $<20\%$ increase in limb volume), moderate (20 - 40% increase) or severe ($>40\%$ increase).

Stage 0. Refers to a subclinical condition where swelling of the extremity is not evident despite impaired lymph flow. It may exist for months or years before overt edema (swelling) occurs.

Stage I. The edema subsides with elevation of the extremity representing an early accumulation of lymph fluid. Pitting may occur.

Stage II. The edema will rarely disappear by elevation of the extremity alone. Pitting may or may not be diagnosed depending on the degree of fibrotic tissue changes and fat deposits.

Stage III. Severe edema (lymphostatic elephantiasis) where pitting can be absent, and tissue changes with warty overgrowths, fibrosis and increased fat deposits are manifest.

Treatment

The therapy of lymphedema is divided into conservative (non-surgical) treatment (41, 42) and non-conservative treatment (surgical treatment) (43-46). In combination, skin care with lotions and hygiene is vital to succeed with the treatment and to avoid further damage to the lymphatic system secondary to skin infections. Also, exercise in combination with external limb compression is helpful in managing the lymphedematous limb (47).

Conservative treatment

Combined physical therapy (CPT)

CPT is also known as complex decongestive therapy. It involves a two-stage treatment protocol. The first stage consists of skin care, manual lymph drainage,

exercises and compression with multi-layered bandages. The second stage aims to optimize and conserve the volume reduction obtained in stage one. This is achieved by using a low-stretch elastic garment in combination with skin care and exercises (41). Manual lymph drainage, performed as an isolated technique, has limited benefit (48).

In order to achieve and maintain a successful treatment there are other aspects of CPT that need to be mentioned, such as the importance of availability of highly trained and well educated health care professionals. Also, it is necessary to have the agreement of governments and/or insurance companies to underwrite the costs of treatments and custom-made low-stretch elastic garments, which are a prerequisite to maintain lymphedema reduction (49).

Controlled compression therapy (CCT)

In contrast to CPT, manual lymph drainage is not used. The custom-made compression garment is renewed when needed to compensate for the decrease in excess volume, that is the difference between the affected and normal extremities. In addition, to compensate for loss of elasticity, the garment might be taken in using a sewing machine. The advantage, as compared to CPT, is that the patient can continue to work (50).

Surgical treatment

Surgical treatment is indicated in patients who do not achieve complete reduction with conservative treatment and when the excess volume is still cumbersome. The reason is that bandaging and compression with garments cannot further remove the excess limb volume if the lymphedematous limb has changed from a pitting state to a non-pitting state. This means a change from a state dominated by lymph to a state of hypertrophy of the subcutaneous adipose tissue (10, 11, 23-25).

Liposuction

From a historical point of view, techniques for the removal of subcutaneous fat have undergone gradual development. In the early 19th century a curette was used which caused serious complications such as massive bleeding which sometimes led to limb amputation (51). Later on, the dry (without tumescence) liposuction technique was invented, but this technique was complicated by seromas and hematomas (52). In 1987, Klein introduced a technique that dramatically reduced complications such as bleeding. By using small, blunt cannulas and adding local anesthesia and epinephrine into large volumes of saline the wet technique (tumescence technique) was invented and is still today considered to be the gold standard (53-55).

Microsurgical procedures

Microsurgical reconstruction of the lymphatic system is advancing and there are several techniques that all have the same aims, that is to increase the lymph transport, reduce the lymph load, and to avoid the need for using continuous compression garment after treatment. There are different techniques that try to achieve this: lymphatico-venous anastomoses (44, 56-59), transplantation of lymphatic vessels (60, 61) and transplantation of lymph nodes (46, 62).

Lymphatico-venous anastomosis (LVA). In this technique, collecting lymphatics are identified and anastomosed to adjacent veins to improve the drainage of the limb. This requires microsurgical techniques, as these vessels are often less than 1mm in diameter. Multiple anastomoses are usually performed throughout the length of the limb, commonly under local anesthetic. Modest improvements in limb volume have been reported, but the long-term effectiveness is still to be confirmed (44, 56, 58, 59).

Lymphatic grafting. Functioning lymphatic vessels are harvested from the thigh and either tunneled to the contralateral lymphedematous leg and anastomosed to collecting lymphatics, or removed as a graft and placed between the lymphedematous arm and lymphatics in the neck (60, 61).

Lymph node transfer. A free vascularized lymph node flap is removed from a donor site (the groin, axilla, neck, or omentum) and transferred to the lymphedematous limb where the artery and vein are anastomosed to revascularize the tissue. No lymphatic repair is undertaken. The expectation is that lymphangiogenesis will take place with new lymphatic channels growing from this tissue and anastomosing with lymphatics in the limb, creating new drainage pathways (46, 62).

Although attractive as a concept these microsurgical techniques are not able to remove hypertrophied adipose tissue, and microsurgical techniques have still not achieved complete reduction or long standing results in patients suffering from lymphedema. In addition, many patients need to continue wearing compression garments (63-66).

Lymphedema and infection

The lymphatic system is essential for immunological function and the maintenance of the interstitial fluid balance. Impairment of the lymphatic system leads to a dysfunctioning immunological response (67).

Erysipelas is an infection, most often caused by beta-hemolytic group A streptococci, which involves the superficial layer of the skin with significant

inflammation of the lymphatic vessels (lymphangitis) (68). Classical symptoms are erythema, usually sharply demarcated from intact skin, fever, edema, nausea and pain. It usually affects the legs, and less frequently the arms (69).

Local risk factors for erysipelas are venous insufficiency, previous or current local injury, fungal skin infections and lymphedema. Systemic risk factors include diabetes mellitus, obesity, immunosuppression and alcoholism (70).

Erysipelas in the upper limb mostly occurs in women after surgical treatment for breast cancer following damage to the lymphatics (71). In this group, erysipelas affects up to 24% of women (72).

Cellulitis is a soft tissue infection that involves the deep subcutaneous layer of the skin (73). Distinguishing erysipelas from cellulitis in daily clinical practice is challenging. Difficulties arise from a significant overlap between these two clinical patterns with regard to infective agents, risk factors, the areas of the body that are involved, and the depth of skin involvement (68). Lack of strict criteria or an optimal test for the diagnosis of cellulitis and erysipelas can result in diagnostic errors (74). Some physicians use the terms 'erysipelas' and 'cellulitis' interchangeably, rendering this distinction even more problematic (75).

Despite being a common medical problem, few studies provide good data on the incidence of erysipelas. Epidemiological surveys report a yearly incidence of erysipelas ranging from 1.71 to 2.55 per 1000 patients in 160,000 different patients over 740,000 patient years between 1994-2004 (76). Ellis et al. reported 24.6/1000 person-years in different populations (77).

Erysipelas research is under-represented in publicly funded medical research compared with the global burden it inflicts (78, 79).

Lymphedema and quality of life

Lymphedema following breast cancer surgery remains a common and feared treatment complication to surgery. Affected patients develop a chronic accumulation of interstitial fluid, resulting in fibroadipose deposition and swelling. This swelling has a significant impact on the physical, psychological, and social health of patients (80-82).

Assessments of patient symptoms and health-related quality of life (HRQoL) outcomes are made using patient-reported outcome (PRO) instruments that quantify significant outcome variables from the patient's perspective. When developed and validated according to international guidelines, PRO instruments can facilitate reliable and valid patient assessment. While generic PRO instruments are designed to measure outcomes across diverse patient populations, condition- or

disease-specific measures may provide more sensitive assessment for specific populations, such as patients with lymphedema (83).

The earlier lack of recognition of the effect of edema on patients' HRQoL has contributed to the low priority given to the development of services for the treatment of edema. Therefore research and investigations targeting disease-specific HRQoL are needed.

Evaluating tissue changes in lymphedema

An early stage lymphedema is soft and pitting but will later, due to stagnation of the lymph fluid, change the skin and subcutaneous layer, causing them to become stiff due to fibrosis and fat deposition.

Volumetric or circumference measurements are widely used to diagnose and evaluate progression or treatment outcomes of lymphedema, but these measurements provide no information about the stage of lymphedema. In addition these measurement techniques are influenced by compositional changes in the limb such as bone, muscle and fat mass, which make it difficult to detect subclinical lymphedema.

Detection of lymphedema at an early stage will favor an early start of compression treatment by CPT, which is known to reduce edema and prevent the accumulation of lymph fluid (42).

There is a need for reliable diagnostic imaging techniques. As mentioned before, examples of such investigational tools are MRI, CT, US, and DXA, but no consensus on their use exists (31).

Lymph turns to fat

Lymphatic dysfunction can produce metabolic disarrangements, loss of normal immune responses, or the development of lymphatic vascular insufficiency leading to a lymphedema (9). Understanding the pathogenesis of lymphedema is necessary to facilitate the identification of future therapeutic targets.

The lymphatic vascular system is increasingly recognized to play an important role in a number of pathological conditions, such as tumor metastasis (84), chronic inflammation (85), metabolic diseases (86), and cardiovascular diseases, such as atherosclerosis and myocardial infarction (87).

Interstitial fluid accumulation often occurs early during lymphedema development. Accumulated fluid significantly impacts cellular behavior within the affected region and induces subsequent pathological changes, such as immune cell infiltration and activation of the inflammatory cascade, adipose accumulation, and tissue fibrosis (10, 11, 23-25).

Adipose tissue deposition

The mechanisms through which adipose tissue deposition occurs in lymphedema are poorly understood. It has been shown that lymphatic injury and lymph stasis rapidly and significantly activate adipocytes and upregulate fat differentiation genes, including CCAAT/enhancer-binding protein α and peroxisome proliferator-activated receptor γ in both mouse tail and axillary lymphadenectomy models (23, 24). The degree of adipose deposition is associated with the severity of lymphatic dysfunction and inflammation, as depletion of CD4⁺ T cells or inhibition of Th2 differentiation have a decreasing effect (88). Furthermore lymphedema-associated stem cells have a high adipogenic gene expression and greater ability to undergo adipogenic differentiation (25). These studies suggest that edema and inflammation are the likely initiating factors for excessive adipose tissue deposition. Intriguingly, whereas the proinflammatory cytokine IL-6 is elevated in mouse tail lymphedema and is involved in tissue inflammation, inhibition of this cytokine increases adipose deposition, revealing a unique role of IL-6 in limiting adipose tissue deposition during lymphedema progression (89).

Fibrotic remodeling in lymphedema.

Proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6) seem to play an important role in promoting human filariatic lymphedema (90). However, immune responses in filarial and postsurgical lymphedema appear to be different. A comparison of skin tissue from filarial and postsurgical lymphedema reveals much less infiltration of inflammatory cells such as the CD68⁺ macrophage, CD4⁺, and CD8⁺ T cells in the latter, suggesting a much increased inflammatory response in the filarial lymphedema lesion (91)

In mouse tail and axillary lymphedema models, affected skin tissues display increased CD4⁺ T cells, macrophages, neutrophils, and dendritic cell (DC) infiltration. CD4 cells (helper T cells) can be further divided into Th1 and Th2 cells, which produce cytokines. The response to Th2-type cytokines has been shown to be involved in the development of lymph stasis-induced fibrosis through promotion of transforming growth factor (TGF)- β signaling (92). Blocking Th2 differentiation by IL-4 or IL-13 antibody could prevent as well as reverse lymphatic fibrosis and improve lymphatic function (88).

In an axillary lymph node dissection model of lymphedema, both Th1 and Th17 cells were shown to be associated with edema development and tissue fibrosis (93). Taken together, Th1, Th2, and Th17 cells all appear to play influential roles in promoting postsurgical lymphedema.

Macrophages are known to be associated with a number of pathologies, including tissue repair, chronic inflammation, cancer, and infection (94, 95). Macrophages were found to be present in human skin lesions of postsurgical lymphedema (96).

In mouse models of lymphedema, macrophages were also shown to be present during disease development (97) and to preferentially differentiate into M2-type macrophages (96). Although macrophages promote lymphedema development during acute phases of edema, depletion of macrophages in chronic lymphedema was not able to diminish swelling, adipose tissue deposition, and overall inflammation, but they actually promoted tissue fibrosis (93). The enhanced tissue fibrosis response following macrophage depletion may result from increased CD4⁺ cell accumulation and skewed Th2 differentiation (96).

Lymph stasis-induced inflammation is the principal factor that promotes postsurgical lymphedema progression (98). Jiang et al. (99) have reviewed the role of leukotriene B4 (LTB4) during the evolution of postsurgical lymphedema. LTB4 acts as an important wound healing molecule during the initial stages of postsurgical tissue repair, yet when the concentration rises into an elevated pathological range, LTB4 has the capacity to diminish lymphatic endothelial cells' function, exacerbate lymphatic vascular dysfunction, and promote disease progression. Serum LTB4 levels are significantly elevated in human lymphedema patients, indicating that LTB4 is clinically relevant in postsurgical lymphedema pathophysiology (100).

Fibroblast activation and enhanced production of collagen are major steps leading to excessive extra cellular matrix accumulation and tissue fibrotic remodeling. A Th1/Th2 paradigm in tissue fibrosis has been established (101). It is widely accepted that Th2 cells are involved in wound healing, but they also simultaneously promote tissue fibrotic remodeling and therefore display both beneficial and potentially deleterious effects. They can promote fibrosis by producing profibrotic cytokines such as IL-13 or by indirectly promoting monocyte differentiation toward alternatively activated macrophages.

Studies suggest that Th2 cells are essential in promoting tissue fibrosis in postsurgical lymphedema (92, 102).

Aims

The main objective of the studies was to illustrate the impact of lymphedema treatment with liposuction, in combination with CCT, on the incidence of erysipelas, patients' quality of life, tissue changes (i.e. lymph and fat) in the lymphedematous limb before and after treatment, and finally to conduct a long-term follow-up of patients with chronic non-pitting arm lymphedema.

The specific aims were:

Study I:

To study possible effects of treatment with liposuction, in combination with CCT, on reduction of bouts of erysipelas in previously mastectomized patients.

Study II:

To study patients' quality of life using SF-36 before and after treatment with liposuction, in combination with CCT, and compare these results with Swedish normative data.

Study III:

To investigate epifascial and subfascial fat and water contents using water-fat magnetic resonance imaging (MRI) in patients with chronic arm or leg lymphedema before and after treatment with liposuction, in combination with CCT.

Study

IV: To evaluate the five-year results after liposuction, in combination with CCT, in 105 patients with secondary non-pitting arm lymphedema.

Material and methods

Patients

Study I

130 patients with postmastectomy arm lymphedema following breast cancer were analyzed. All patients were treated with liposuction in combination with CCT at the Lymphedema Center, Department of Plastic and Reconstructive Surgery, Skåne University Hospital in Malmö, Sweden between 1993-2012.

All patients had been treated conservatively before surgery without successful reduction of the excess volume. Thus the preoperative excess volume was still large.

Study II

From 1999-2013, a consecutive cohort of 90 patients with breast cancer-related lymphedema who attended the Lymphedema Center agreed to complete the SF-36 before and after treatment with liposuction in combination with CCT. When responses to the surveys were analyzed, 30 patients had failed to answer one or more of the questionnaires at the different time points. This left 60 patients in the study cohort.

Study III

Seven patients with arm lymphedema and six patients with leg lymphedema participated in this study and were operated on with liposuction of the edematous limb. All arm lymphedema occurred following breast cancer treatment. Of the six leg lymphedema patients, three had been treated for cancer (two for uterus cancer and one for synovial sarcoma in the groin) and three had primary lymphedema, one male and two females).

Study IV

Between 1993 and 2012, 105 patients with arm lymphedema were consecutively operated on and were identified from the lymphedema registry of our department. All patients with lymphedema eligible for liposuction and CCT were entered into the registry at the first consultation and data were collected at each follow-up. Standardized forms were used to collect pre-, peri- and postoperative data.

Patients who met the following inclusion criteria were operated on: (I) diagnosis of secondary arm lymphedema following breast cancer treatment, (II) a significant excess volume, that is the volume of the affected arm was at least 10% larger than that of the unaffected arm with concomitant subjective discomfort, (III) failure of previous conservative treatment to reduce the excess volume completely, (IV) no or minimal pitting (less than 5 mm) as a sign of adipose tissue hypertrophy, and (V) accustomed to the use of compression garments preoperatively. Patients with active cancer, wounds, or infections, and patients unwilling to undergo continuous postoperative CCT were excluded and thus not treated.

Methods

Study I

In order to estimate the incidence of erysipelas the number of bouts and their timing prior to and following the liposuction were obtained from the patients' case histories and hospital charts, which were both scrutinized in detail. Patient characteristics such as age at mastectomy, year of mastectomy, irradiation, onset of lymphedema, year of liposuction, and pre- and post-liposuction erysipelas incidence were recorded.

From these data the following was calculated: 1) time interval from mastectomy to lymphedema onset 2) time interval from lymphedema onset to liposuction (duration of lymphedema) also measured as pre-liposuction total observation years 3) ongoing follow-up after liposuction also measured as post-liposuction total observation years 4) The number of bouts of erysipelas before and after liposuction. In order to get an overall measurement of the risk of erysipelas it is relevant to count for the number of episodes, not just the existence of 'ever/never'. Erysipelas incidence was, hence, calculated as number of attacks divided by observation years. Arm volumes were recorded for each patient using the water displacement technique.

Study II

To assess HRQoL the patients completed a questionnaire with 36 questions, SF-36, before and at one, three, six and 12 months following treatment with liposuction in combination with CCT. All questionnaires were self-administered and sent back to the clinic. The results from the SF-36 in the study group was age-matched and compared to Swedish reference population (103).

Study III

All MRI examinations were conducted with a 1.5 T MRI scanner (MAGNETOM Sonata, Siemens Healthcare). The healthy and edematous limbs of patients were examined with water-fat MRI before liposuction and at five time points (four days, and one, three, six and 12 months) after liposuction. Arms were imaged separately whereas both legs were imaged together. Imaging was centered 10 cm distally of the humeral epicondyle for arms, or 16 cm distally of the femoral condyle for legs. A multi-echo gradient echo sequence was used to image three 5-mm slices. The images were then reconstructed and separated into fat and water images, and from these separated images the fat and water fractions were calculated.

Study IV

Measurement of excess volume and reduction

Plethysmography, a water displacement technique, was used to record arm volumes before and after surgery. Both arms were always measured at each visit, and the difference was defined as the excess volume. The excess volume reduction was also measured as the percentage of the preoperative excess volume.

Liposuction

Power-assisted liposuction (Lipomatic®, Nutational Infrasonic Liposculpture®, Euromi, Andrimont, Belgium) was performed to facilitate liposuction. During 1993-1997 the 'dry technique' was used. During 1997-2012 a tourniquet was utilized in combination with the tumescence technique, to minimize blood loss (Figure 7).

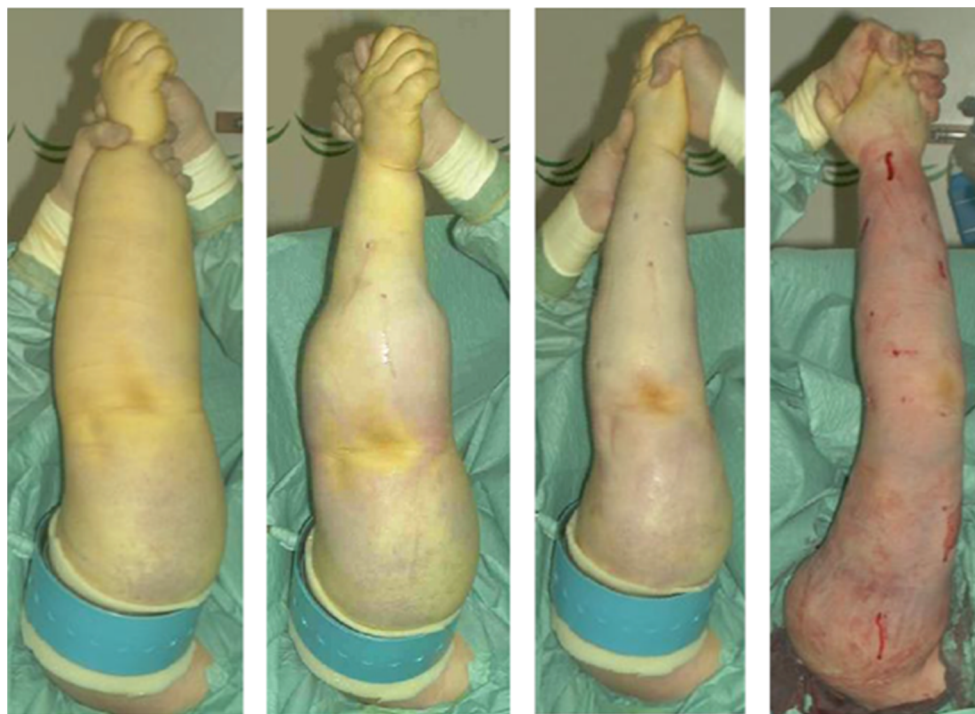


Figure 7. Liposuction of arm lymphedema. The procedure takes about two hours. From preoperative to postoperative state (left to right).

Around 10, 3-mm-long incisions, were made and liposuction was performed using 15- and 25-cm long cannulas with diameters of 3 and 4 mm. Circumferential liposuction was performed from wrist to shoulder, and the excess fat was removed as much as possible using previously measured circumferences of the healthy arm as a control. When the arm distal to the tourniquet had been treated, a sterilized custom-made compression sleeve was applied (Jobst® Elvarex - BSN medical, compression class 2, exerting a pressure of 32 to 40 mmHg) to the arm to minimize bleeding and reduce postoperative edema. A sterilized, standard interim glove (Cicatrex interim, Thuasne Béga, France) was put on the hand. The tourniquet was then removed and the most proximal part of the upper arm was treated using the tumescence technique, where 1000 ml saline mixed with 1 mg adrenaline and 40 ml lidocaine 2% (Xylocaine®, AstraZeneca PLC, London, UK) was infused. Finally, the proximal part of the compression sleeve was pulled up to compress the proximal part of the upper arm (Figure 8) and the position was secured with the strap that came with the sleeve.



Figure 8. The compression garment and interim glove at the end of surgery.

The incisions were left open to drain through the sleeve. The arm was wrapped with a large absorbent compress covering it (60x60 cm, Cover-Dri, www.attends.co.uk) and changed when needed. The following day, the gauntlet (Jobst® Elvarex - BSN medical, compression class 2) was put over the interim glove. In severe hand swelling a glove was used instead. An isoxazolyl penicillin, was given intravenously for the first 24 hours and then orally until the incisions were healed, approximately during 10 days after surgery. In the case of penicillin allergy, clindamycin was used instead.

Volume of removed fat

Aspirate volumes were collected in graded 2 000 ml canisters and the total volume was calculated with an accuracy of 10 ml. When a tourniquet and tumescence was used, the proportion of free fat, the supernatant, was calculated.

Controlled compression therapy and follow-up

Patients were followed up regularly at 0.5, one, three, six, nine and 12 months after surgery, and then every year. Two weeks before the liposuction, measurements for garments were taken using the healthy arm as a template. Following surgery, CCT was started with custom-made compression garments: a sleeve and a glove or gauntlet, i.e., a glove without fingers, but with a thumb (Jobst® Elvarex - BSN medical) with compression class 2. At the three-month visit, the arm was measured for two new sets of custom-made garments. The custom-made sleeve was sometimes taken in to make up for reduced elasticity and reduced arm volume. When the excess volume had decreased as much as possible and a steady state was achieved, new garments were prescribed using the latest measurements. The garments were renewed three or four times during the first year.

Statistical analysis

All data were entered in Microsoft Excel version 14.5.3 and in studies I, II, and IV statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS), version 22.0, for Mac OSX. In study III, all statistical analysis was carried out in Matlab (R2013a, MathWorks, Natick, MA).

Study I: The incidence of erysipelas was calculated as the number of bouts divided by the number of observation years. The preoperative period was defined as the time between the first bout of erysipelas and the time of liposuction. The postoperative period was defined as the period between the liposuction and the end of the follow-up. Since the sample was normally distributed, the parametric t-test was used to test any differences before and after surgery. The number of patients experiencing an episode of erysipelas pre- versus postoperatively was calculated, and the difference was tested using the non-parametric McNemar test.

Study II: The Shapiro-Wilk test was used to test the sample distribution, which showed that only physical functioning before liposuction, general health and vitality at 1 month were normally distributed. Therefore, it would be logical to use a non-parametric test. Torrance et al. stated in 2009 that although scores in each of the eight domains of SF-36 rarely conform to a normal distribution, SF-36 is most widely analyzed using simple parametric statistical techniques (104). Thus a parametric test, the Student's t-test was used to analyze the outcome. One sample t-test was used for statistical comparison of normative data. Our hypothesis was that liposuction would improve HRQoL over time postoperatively, and given this a priori assumption, we chose to use uncorrected p-values. One sample t-test was used for statistical comparison between the study group and the Swedish reference norm. SF-36 scores and excess volume values are presented as mean and standard error of the mean (SEM). A p-value less than 0.05 was considered statistically significant.

Study III: The excess volume was defined as the difference between the lymphedematous limb and the healthy limb in the patient group, and the difference between the dominant and the non-dominant limb in the control group. At each time point, the relative excess volume (percent) was estimated as (volume edematous limb - volume healthy limb)/volume healthy limb for patients and as (volume dominant - volume non-dominant)/volume non-dominant arm for healthy controls. These values were compared between baseline and each postoperative time point using a Wilcoxon signed-rank test. Wilcoxon signed-rank test was also used to compare the edematous and healthy side (patients) at each time point. For volunteers, the dominant and non-dominant arm was measured once. Medians (1st and 3rd quartiles (1q-3q)) were calculated for outcomes. For all tests, $P < 0.05$ was considered a significant result.

Study IV: Data is presented as mean values and standard deviations (SD). The normality of all data points was tested and confirmed using the Shapiro-Wilks' test. The parametric Student's paired t-test was used to analyze the difference in volume before and after surgery. Linear regression was used to determine the relationships between outcomes. The cumulative sum control chart (CUSUM) was used to show any possible learning curve. A p-value less than 0.05 was considered statistically significant.

Ethics

All participants provided their written informed consent to participate. The procedures were in accordance with the 1964 and 2013 Declaration of Helsinki.

Study I, II and IV: The studies were approved by the Ethics of Human Investigation Committee at Lund University (LU 2006/503).

Study III: The study was approved by the Ethics of Human Investigation Committee at Lund University (LU 2006/503 and 2011/45).

Results

Study I

Erysipelas incidence dropped significantly from 0.47 attacks/year (range 0-5.0, SD 0.8 attacks/year) to 0.06 attacks/year (range 0-3.0, SD 0.3 attacks/year) after liposuction, a reduction of 87%. Also, compared to 76 patients who experienced at least one erysipelas episode preoperatively, only 13 patients experienced erysipelas postoperatively. Of the 54 patients who did not have erysipelas preoperatively, six patients had erysipelas postoperatively. The total number of erysipelas attacks observed decreased from 534 to 60 bouts after liposuction. The excess arm volume of 1607 ml (range 570-3950, SD 707) was already reduced to -43 ml (range -945 to 1390, SD 379) after six months and lasted during the postoperative follow-up period of, at most, 18 years.

Study II

The mean \pm SEM preoperative excess arm volume was 1365 \pm 73 ml. Complete reduction was achieved after three months when it was -(minus)26 \pm 40mL at three months and was sustained during follow-up. The adipose tissue volume removed at surgery was 1373 \pm 56ml.

Physical functioning showed impaired scores before surgery as compared to the Swedish norm, and at three months values were better as compared to baseline, which continued during the follow-up. Better scores were found in mental health after one month of liposuction and were better than the Swedish norm at one year. After three months better scores were seen in bodily pain and vitality both compared to baseline and to the Swedish norm. These findings continued through the study. The mental health score was already improved after one month and this improvement continued through the study and showed better values as compared to the Swedish norm at one year. Regarding social functioning, an increase was also seen after one year as compared to the Swedish norm.

Study III

Complete reduction of the excess limb volumes was achieved. The excess epifascial fat was evident in the edematous limbs preoperatively, and a drop – even an overcorrection – was seen following surgery, as well as compared to baseline. There were differences between arms in subfascial excess water at all time points, and at one year there was a decrease in excess water as compared to baseline. Excess subfascial fat was seen in the edematous limbs at all time points. Subfascial excess water/muscle did not show any differences between limbs after surgery. However, starting from three months there was less subfascial water/muscle compared to baseline.

Study IV

The onset, i.e. the mean interval between breast cancer operation and lymphedema start was 2.9 ± 5 years, and the mean duration of lymphedema was 10 ± 7.4 years. The total aspirate mean volume was 1831 ± 599 ml in all patients. The mean volume of aspirate removed when the tourniquet was applied ($n=76$) was 951 ± 405 ml and contained $94 \pm 11\%$ fat. When the fluid in the tumescence fraction was excluded, an aspirate fat content of $96 \pm 7.0\%$ was found. The preoperative mean excess volume (\pm SD) was 1573 ± 645 ml, and a complete reduction was seen already at six months when the reduction was $107 \pm 22\%$ with an excess volume of -51 ± 273 ml. At five years the excess volume was – (minus) 188 ± 300 ml corresponding to a reduction of $117 \pm 26\%$, i.e. the lymphedematous arm was somewhat smaller than the healthy one. The CUSUM-chart showed the accumulated percentage of patients who did not get 90% reduction, that is 9 out of 105 patients (8.6%).

General discussion

Considerations regarding patients and results

Study I

Although this study suggests erysipelas in postmastectomy lymphedema patients, it is important to acknowledge the indistinctness among the terms erysipelas, cellulitis, and dermato-lymphangio-adenitis (DLA) (105). Due to definitional inaccuracies and the conflicting and scarce data currently available, there is much controversy as to which type of skin infection the patient is suffering from in view of the fact that the diagnosis is likely to be made as a clinical diagnosis (75).

The reduction of erysipelas incidence in breast cancer-related lymphedema patients following liposuction leads to decreased antibiotic usage and hospital visits, and decreased risk of worsening of the lymphedema and therefore arm volume increase (71). Lymphedema duration for an average of 8.8 years before liposuction suggests that patients have suffered from erysipelas for years, which imposes physical, social, psychological, and financial burdens on the patients (106).

Study II

One year after liposuction the scores were significantly improved in five out of eight subscales (physical functioning, bodily pain, vitality, social functioning, and mental health). Each of these subscales concerns specific items related to physical and psychological health. The physical functioning subscale concerns items to do with everyday life activities, for example things that we normally do, such as feeding ourselves and dressing. The bodily pain subscale includes items concerned with the extent to which pain has interfered with normal activities and work. The vitality subscale assesses patients' fatigue, which is known to affect patients with chronic diseases. The social functioning and mental health subscales include items such as interference with normal social life due to physical and emotional problems and also feelings of nervousness and depression.

In our study we found a significant improvement after liposuction, suggesting that liposuction (i.e. complete reduction of the excess volume of the arm) has an early impact on patients' physical restraints and seems to improve patient's quality of life.

Only physical functioning showed impaired scores before surgery as compared to the Swedish norm. This was most likely due to the heaviness and of the arm. At three months better values were seen that continued during the follow-up. At three months the study group presented better scores in vitality as compared to baseline and also showed better values than the Swedish norm. This continued during the follow-up.

The decrease in role physical, bodily pain and role emotional at one month was probably an effect of the surgical procedure and concomitant postoperative pain, discomfort and convalescence.

The findings differed from an earlier study of 35 patients that showed only marginal effects of treatment on psychologically oriented domains (107). The reason for this is unclear but different PRO instruments were used in these studies and this might have influenced the outcome.

Study III

This study shows how excess fat and water/muscle volumes in lymphedema change over time in two different compartments after liposuction. Water-fat MRI cannot differentiate between muscle tissue and water, thus, the measured excess subfascial water volume may represent both lymph and muscle. We noticed, starting from three months, a significantly smaller subfascial water volume compared to baseline. The reason for this is unclear, but is most likely due to a switch from a hypertrophied muscle cell state to a normal muscle cell state caused by less mechanical load from the heavy lymphedematous extremity (11, 108).

Our finding of an increased volume of subfascial fat in arm and leg lymphedema has to our knowledge not been reported in the literature. In the future, this finding might help us acquire additional information about the evolution and symptoms connected to lymphedema.

Study IV

We have previously reported stable results over time with a one-year overall edema reduction of 106 percent in 29 patients (109). In a study when liposuction combined with CCT in 30 patients was compared with the use of CCT alone in 14 patients, a reduction of 104 percent was achieved in the liposuction and CCT group while the CCT group only had a reduction of 47 percent of the excess volume (50).

In the present study, the overall edema reduction was increased additionally to 117 percent at five-year follow-up, further strengthening the beneficial long-term effects of the treatment protocol. In addition, several teams have adopted our techniques and reported no signs of recurrence of time (49, 110-112). In a previous scintigraphic study regarding the effect of liposuction on the lymph transport we found no further decrease of the already decreased lymph transport (113). A recent

study has also shown increased lymph transport following liposuction of lymphedema (112).

In brief, our treatment protocol (Datainspektionen, 1996) gives a permanent reduction of lymphedema and seems not to harm remaining lymph transport.

Considerations regarding methods

Lymphedema Center

The Lymphedema Center maintains a registry of all patients who have been diagnosed with limb lymphedema and treated with liposuction and CCT. All data on patients eligible for surgery are entered into the registry at the first consultation and then at each follow-up. Data collected include, for example, type of breast cancer surgery, lymph node removal, postoperative chemotherapy and irradiation, previous conservative treatment, pre- and postoperative bouts of erysipelas, type of compression garments, age at cancer surgery, age at lymphedema start, and at liposuction, onset (time from cancer surgery to lymphedema debut), duration (time from lymphedema start to liposuction).

Teamwork is a prerequisite to achieve optimal treatment results. The staff at our Lymphedema Center consist of a plastic surgeon, a physiotherapist and an occupational therapist. The lymphedema team measure pre- and postoperative volumes, adjust garments when needed, order new garments at regular intervals, distribute and collect questionnaires, as well as encouraging patients when needed. The patients can contact the team at any time during office hours when a problem appears so that it can be remedied at once.

In this thesis all patients were operated on by associate professor Håkan Brorson. Due to his vast experience this would probably favor the results in this study of complete reduction of excess volume.

Medical outcome study – 36 item short-form (SF-36)

SF-36(114) is useful in assessment of general health aspects, but may not be as accurate as disease-specific tools (83). Because of the lack of reliable and validated disease-specific instruments, most HRQoL studies on breast cancer treatment-related arm lymphedema have been performed using generic instruments, and the most commonly used tool is SF-36 (115).

The SF-36 consists of 36 items constituting eight domains: physical functioning (PF), role limitations as a result of physical problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The first three domains (PF, RP, and BP) measure physical well-being, and the last three

domains (SF, RE, and MH) relate to emotional well-being. The two remaining domains (GH and VT) are associated with both physical and emotional dimensions.

These eight domains can be aggregated into two summary measures: the Physical (PCS) and Mental (MCS) Component Summary scores. GH and VT are domains shared by PCS and MCS. In addition, PCS encompasses PF, RF, and BP, whereas MCS includes SF, RE, and MH. A high score on the subscales signifies a higher level of function and HRQoL.

The Swedish version of SF-36 has been validated, and normative data for Swedish women are available. The Swedish normative sample comprised 8930 subjects (15-93 years, mean 43) and an almost equal gender distribution (48% men). The age and sex distributions, geographical area, and the proportions with mandatory versus higher education, married or cohabiting versus all others, and employed versus all others matched the Swedish population levels. Sixty percent had more than mandatory education, 69% were married or cohabiting, 64% were gainfully employed, and 13% were aged 65 or over (103).

Magnetic resonance imaging (MRI)

Fat quantification using fat-water-fat MRI is a well-established technique that has been used to gain insights into the pathophysiology of metabolic diseases including obesity, metabolic syndrome, or type 2 diabetes (116).

Using water-fat MRI, the fat and water contents may be both quantified and localized in the various compartments in the lymphedematous limb. A water-fat MRI cannot differentiate between muscle tissue and water. The measured excess subfascial water volume can represent both edematous fluid and muscle tissue.

Considerations regarding ethics

Liposuction of lymphedema is a routine treatment at our Lymphedema Center. The studies were approved by the Ethics of Human Investigation Committee at Lund University (LU 2006/503 and 2011/45). In this thesis we study how treatment of lymphedema with liposuction in combination with CCT affects patients. All parts of this thesis are subject to ethical permission (3§, 4§, Etikprövningslagen 2003:460) since surgery (physical intervention) is performed on our study patients. Our treatment method affects the study patients both physically and mentally, and there are risks of causing injury to the study patients. Also, we manage sensitive personal data (§13 Personuppgiftslagen 1998:208). All patients were well informed about the surgical procedure and the need for life-long treatment with CCT. The risks of the surgical procedure in relation to the new

knowledge achieved were judged to be low and assessed to be of value for future patients.

Considerations regarding study limitations

Study I

No reports regarding the reduction of erysipelas after CPT have been published. Since all patients, on average, already had complete reduction after six months we found no correlation between the excess volume reduction and the reduction in incidence of erysipelas. Therefore, it is not possible to determine whether the reduction in incidence of erysipelas was due to liposuction per se or due to a reduction in lymphedema excess volume. A more plausible factor that may influence the reduction of the incidence of erysipelas is the improved skin blood flow seen after liposuction that may possibly remove bacteria that have entered through a minor wound of the skin (117). Also a reduction in the accumulation of proteinaceous fluid and adipose tissue, which can act as a substrate for bacteria, may contribute, and the wearing of protective compression garments and lubricating the arm daily may also play a role (117). There is much controversy as to which type of skin infection condition the patient may suffer from and a confounding factor has to do with definitional inaccuracies (erysipelas, cellulitis and DLA) and conflicting and limited data currently available (74). Liposuction seems to be effective not only in terms of arm volume reduction but also in reducing the number of patients suffering from bouts of erysipelas.

Study II

During 1999 to 2013 a consecutive cohort of 90 patients who attended our Lymphedema Center agreed to complete the SF-36 prior to and following liposuction at different time points. When responses to the surveys were analyzed, 30 patients had failed to answer one or more of the questionnaires at the different time points. The failure of patients to answer/respond must be considered when using questionnaires such as SF-36. We found no differences in the characteristics (age at the time of breast cancer treatment, age at liposuction, onset, duration of lymphedema and time from breast cancer treatment to liposuction) of the studied patients and non-responding patients.

The number of patients was relatively small (n=60), and using a generic questionnaire like SF-36 causes a potential bias since it has been found that disease-specific questionnaires have an advantage over more global assessments of HRQoL. In spite of this, we have shown that the treatment has beneficial effects as regards most of the outcome parameters.

Study III

The study population was relatively small, including seven patients with arm lymphedema and six with leg lymphedema, thus statistical analysis was performed without differentiating between arm and leg lymphedema. Consequently, we cannot exclude the possibility that outcomes might be different for arms and legs. Also, only three cross-sections of 5 mm each (in total 15mm) were investigated in each limb, which may not be representative for the whole limb.

Water-fat MRI cannot differentiate fluid from muscle, which makes it difficult to evaluate subfascial tissue changes. Regarding the controls, these were not age-matched, but since each control individual is its own control (right and left arm) this may not have had a significant impact on the outcome. Both forearms of the healthy volunteers were examined with MRI at one time point, and their right forearm was imaged a second time with repositioning to evaluate the method's repeatability. This investigation has previously been described (118) and resulted in a high repeatability where the 95 % confidence interval of repeated measures of the percentage fat content within the subfascial compartment was within ± 0.4 %. At six months, three patients could not be measured due to technical problems. At one year, 12 patients were measured and one could not be measured because of recurrence of the breast cancer.

Study IV

Between 1993 and 2012, a total of 127 consecutive women were operated on. Twenty-two could not be followed for five years: 18 died before the last follow-up (10 because of breast cancer and eight of other causes), one with recurrence of breast cancer, one stopped using CCT, one moved abroad, and in one case there was missing data from the therapist. Thus 105 women with non-pitting lymphedema remained in the study. The dropout of 22 patients might have influenced the outcome, but these patients also had a complete reduction at six months that persisted until dropout; thus we believe that the dropout of patients did not influence the outcome. One surgeon performed all the surgery, which made a favorable outcome more likely due to the surgeon's vast experience, but the technique has been taught to many teams with the same favorable outcome and some have also published their results (49, 110-112).

While our early patients achieved adequate clinical results, there was a significant correlation between the operation serial number and excess volume reduction in percent after five years. It is therefore possible that increased skill with the operative technique will improve outcome, which also can be seen in the cumulative sum control chart (Figure 9).

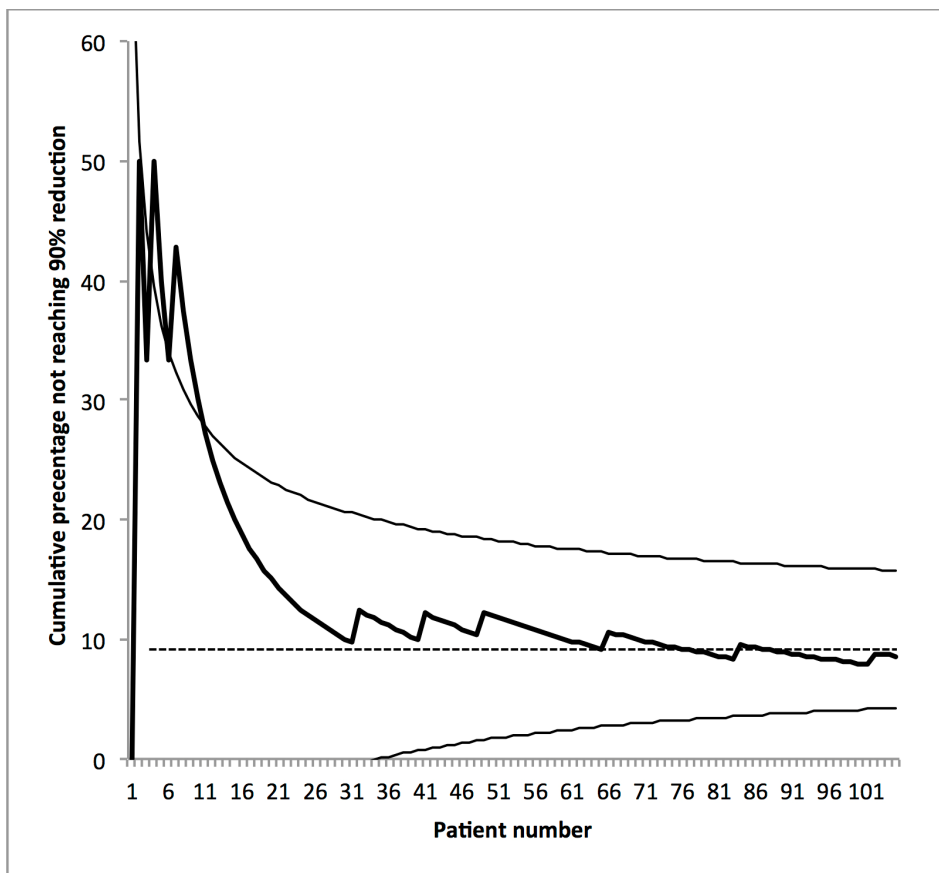


Figure 9. The cumulative sum control chart (CUSUM) of the operation serial number with expected 90% success at five years with a 95% confidence interval. Thus 9 out of 105 patients (8.6%) did not get 90% reduction.

Conclusions

Study I

Liposuction as a surgical intervention for lymphedema patients is not only effective in excess arm volume reduction, but is also beneficial in significantly reducing the incidence of erysipelas.

Study II

Liposuction of arm lymphedema combined with CCT improves patients' HRQoL when measured with SF-36. The treatment seems to target both physical and mental health domains. These findings contrast with a previous study of 35 patients that showed only marginal effects of treatment on psychologically oriented domains (107). Compared to the Swedish reference population, the study group showed the same, or even better HRQoL when analyzing specific subscales.

Study III

The excess volume of epifascial fat and water decreased after liposuction. Also, the excess volume of the lymphedematous limbs was reduced completely. An excess volume of fat in the subfascial compartment in the lymphedematous limbs that did not change over time was found and these findings have not been described previously. In contrast, the excess volume of water in the subfascial compartment was reduced over time, which may represent a decrease of muscle volume after treatment due to reduced mechanical load after liposuction.

Study IV

The results of this prospective long-term study of 105 patients demonstrate that liposuction is an effective and safe method for treatment of chronic, non-pitting arm lymphedema resistant to conservative treatment. So far, it is the only known method that completely reduces excess volume at all stages of arm lymphedema as the removal of hypertrophied adipose tissue is a prerequisite for complete reduction. The complete reduction is maintained through continuous use of compression garments postoperatively.

Future perspectives

Blocking inflammation

In order to improve the treatment of patients with lymphedema there is a need for further research and also education about lymphedema among health care professionals. Better understanding of the pathophysiology and knowledge about different treatment options may prevent further damage to the lymphatic system and thereby improve patients' HRQoL.

Advances in diagnostic imaging techniques will serve as catalysts to develop internationally accepted methods for determining subcategories of staging in patients with lymphedema. An early diagnosis and accurate staging can have beneficial effects on treatment and control of the lymphedema.

Standard treatments of lymphedema involve physical therapies such as CPT and surgery if conservative treatment fails. These treatments cause a physical burden and also an economic burden, both for the patient and the health care system. In relation to this, research on the pharmacological treatment of lymphedema might lead to development of new specific anti-inflammatory drugs that slow progression and even prevent lymphedema.

In a recent animal study using a mouse model Tian et. al. (100) showed that the products of the 5-lipoxygenase enzyme have a great capacity to create inflammation. When using a specific anti-inflammatory drug, bestatin, the lymphedema resolved and the tissue was normalized when analyzed under a microscope.

The enzyme 5-lipoxygenase and the inflammatory mediators it creates, leukotrienes, seem to be the key components of inflammation in lymphedema. It appears that if it is possible to block the production of leukotriene B₄ with a specific drug it will lead to repair of lymphatic system and tissue healing (99).

Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) decreased inflammation and adipogenesis in a study of endocrine ophthalmopathy where excess intraorbital adipose tissue led to exophthalmos. The authors discuss the possibility that NSAID treatment may represent a future treatment for endocrine ophthalmopathy (119). As an extension of these findings, use of NSAIDs could also be a future treatment to decrease adipose tissue deposition in lymphedema.

Genetic research

Studying which genes are upregulated or downregulated in association with adipose tissue deposition and fibrosis formation may provide future genetic therapies that can interrupt these sequelae (7).

Populärvetenskaplig sammanfattning på svenska – Summary in Swedish

Lymfödem innebär en svullnad av arm eller ben och drabbar människor med försämrad lymfcirkulation. Försämrad lymfcirkulation kan antingen vara medfödd eller orsakas av olika typer av behandling som till exempel kirurgisk behandling eller strålbehandling. Om en bröstcancer spridit sig till lymfkörtlar måste man operera bort dessa lymfkörtlar. På detta sätt riskeras lymfbanorna skadas och ett lymfödem uppstår. Varje år insjuknar i Sverige omkring 9000 kvinnor i bröstcancer och av dessa riskerar så många som var femte kvinna drabbas av lymfödem i varierande svårighetsgrad.

Tidigare trodde man att svullnaden vid lymfödem enbart utgjordes av vätska. Man ansåg därför att massage och kompression med hjälp av bandagering skulle kunna ”bota” patienten, vilket inte var fallet. Tidigare forskning i vår forskargrupp har visat att lymfödem på sikt leder till nybildning av fettväv, vilket tidigare var okänt.

Lymfödem kan behandlas med kompression (bandagering) om svullnaden består av vätska men om lymfödemet framför allt består av nybildad fettväv är fettsugning en väl dokumenterad metod. Detta förklarar också varför enbart bandagering inte kan minska svullnaden helt utan fettet måste avlägsnas med hjälp av fettsugning för svullnaden ska försvinna helt.

I samtliga delarbeten görs analys före och efter fettsugning av lymfödem.

I delarbete I analyseras och jämförs skillnaden i antalet insjuknanden i rosfeber, före och efter behandling med fettsugning, hos patienter med armlymfödem efter bröstcancerbehandling. I studien ingår 130 patienter som samtliga blev opererade under en tidsperiod av 20 år. Sammanfattningsvis minskade antalet insjuknanden i rosfeber från 0.47 insjuknanden/år före operation till 0.06 insjuknanden/år efter fettsugning. Detta innebär att risken att insjukna i rosfeber minskas med 87% hos de patienter som genomgår behandling med fettsugning.

Delarbete II utvärderar hur livskvaliteten hos lymfödempatienter påverkas av behandling med fettsugning. Från 60 patienter med armlymfödem efter bröstcancerbehandling har data insamlats och analyserats med livskvalitéformuläret SF-36 före och under 12 månaders uppföljning efter operation. SF-36 mäter både den fysiska och psykiska hälsan. Resultatet visar

förbättring avseende fysisk funktion, fysisk rollfunktion, vitalitet, social funktion. Totalvärden för skattningsskalorna visade förbättrade resultat beträffande både fysisk och psykisk hälsa ett år efter operation. Studien visar att fettsugning av armlymfödem ökar patienternas livskvalitet.

I delarbete III utvärderas vävnadsförändringar efter behandling av lymfödem hos 7 patienter med arm- och 6 med benlymfödem med magnetresonanstomografi (MR). Kroniskt lymfödem består framförallt av ökad mängd fettväv i skiktet mellan hud och muskel. Det har därför framgångsrikt kunnat behandlas med fettsugning. Det skulle även kunna föreligga en ökad mängd fettväv i musklerna, men detta har aldrig tidigare undersökts. Med MR-undersökning har mängd och lokalisation av fett, muskel och vatten (ödem) utförts. En ökad mängd fett inne i musklerna sågs i lymfödemet och mängden förändrades inte under uppföljningstiden. Fettet i skiktet mellan hud och muskel minskade som väntat efter operation. Å andra sidan reducerades vattnet inne i muskeln efter operation, vilket kan representera en minskning av muskelvolymen (MR visar samma signal för muskel som för vatten) efter behandling. Sannolikt beror detta på att armen eller benet blir lättare efter fettsugning vilket gör att muskelcellerna återgår till normal storlek. Efter ett år hade också vattnet i skiktet mellan hud och muskel minskat. En fullständig minskning av svullnaden sågs redan 6 månader efter operation.

Delarbete IV visar resultaten av en uppföljning av 105 patienter med armlymfödem med avseende på volymminskning av svullnaden av lymfödemet. En medelvolymminskning på 117% sågs vid 5-årskontrollen, vilket innebär att den opererade armen har en något mindre volym jämfört med den friska armen. Inga återfall av svullnaden noterades.

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Prizes

Paper II

SF-36 shows increased quality of life following complete reduction of postmastectomy lymphedema with liposuction

Best paper presented at the Swedish Association of Plastic Surgeons, Kirurgveckan. Malmö, Sweden 2016.

Paper III

Magnetic Resonance Imaging shows increased content of epi- and subfascial fat and subfascial muscle tissue/water in arm and leg lymphedema

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References

1. Crivellato E, Travan L, Ribatti D. The Hippocratic treatise 'On glands': the first document on lymphoid tissue and lymph nodes. *Leukemia*. 2007;21(4):591-2.
2. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. *J Am Acad Dermatol*. 2017;77(6):1009-20.
3. Natale G, Bocci G, Ribatti D. Scholars and scientists in the history of the lymphatic system. *J Anat*. 2017;231(3):417-29.
4. Meens MJ, Sabine A, Petrova TV, Kwak BR. Connexins in lymphatic vessel physiology and disease. *FEBS Lett*. 2014;588(8):1271-7.
5. Schmid-Schonbein GW. Microlymphatics and lymph flow. *Physiol Rev*. 1990;70(4):987-1028.
6. Scallan JP, Wolpers JH, Davis MJ. Constriction of isolated collecting lymphatic vessels in response to acute increases in downstream pressure. *J Physiol*. 2013;591(2):443-59.
7. Kriederman BM, Myloyde TL, Witte MH, Dagenais SL, Witte CL, Rennels M, et al. FOXC2 haploinsufficient mice are a model for human autosomal dominant lymphedema-distichiasis syndrome. *Hum Mol Genet*. 2003;12(10):1179-85.
8. Handley WS. Two Cases of Lymphangioplasty for the Brawny Arm of Breast Cancer. *Proc R Soc Med*. 1908;1(Clin Sect):186-90.
9. Rockson SG. The unique biology of lymphatic edema. *Lymphat Res Biol*. 2009;7(2):97-100.
10. Brorson H, Ohlin K, Olsson G, Nilsson M. Adipose tissue dominates chronic arm lymphedema following breast cancer: an analysis using volume rendered CT images. *Lymphat Res Biol*. 2006;4(4):199-210.
11. Brorson H, Ohlin K, Olsson G, Karlsson MK. Breast cancer-related chronic arm lymphedema is associated with excess adipose and muscle tissue. *Lymphat Res Biol*. 2009;7(1):3-10.
12. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema: a comprehensive review. *Ann Plast Surg*. 2007;59(4):464-72.
13. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovascular research*. 2010;87(2):198-210.
14. Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *The Journal of clinical investigation*. 2014;124(3):915-21.
15. Planas-Paz L, Lammert E. Mechanical forces in lymphatic vascular development and disease. *Cellular and molecular life sciences : CMLS*. 2013;70(22):4341-54.

16. Breslin JW. Mechanical forces and lymphatic transport. *Microvascular research*. 2014.
17. Browse NL, Stewart G. Lymphoedema: pathophysiology and classification. *J Cardiovasc Surg (Torino)*. 1985;26(2):91-106.
18. Larsen OA, Lassen NA, Quaade F. Blood flow through human adipose tissue determined with radioactive xenon. *Acta Physiol Scand*. 1966;66(3):337-45.
19. Smahel J. Adipose tissue in plastic surgery. *Ann Plast Surg*. 1986;16(5):444-53.
20. Ryan TJ. Lymphatics and adipose tissue. *Clin Dermatol*. 1995;13(5):493-8.
21. Casley-Smith JR, Gaffney RM. Excess plasma proteins as a cause of chronic inflammation and lymphodema: quantitative electron microscopy. *J Pathol*. 1981;133(3):243-72.
22. Gaffney RM, Casley-Smith JR. Excess plasma proteins as a cause of chronic inflammation and lymphoedema: biochemical estimations. *J Pathol*. 1981;133(3):229-42.
23. Zampell JC, Aschen S, Weitman ES, Yan A, Elhadad S, De Brot M, et al. Regulation of adipogenesis by lymphatic fluid stasis: part I. Adipogenesis, fibrosis, and inflammation. *Plast Reconstr Surg*. 2012;129(4):825-34.
24. Aschen S, Zampell JC, Elhadad S, Weitman E, De Brot M, Mehrara BJ. Regulation of adipogenesis by lymphatic fluid stasis: part II. Expression of adipose differentiation genes. *Plast Reconstr Surg*. 2012;129(4):838-47.
25. Levi B, Glotzbach JP, Sorkin M, Hyun J, Januszyk M, Wan DC, et al. Molecular analysis and differentiation capacity of adipose-derived stem cells from lymphedema tissue. *Plast Reconstr Surg*. 2013;132(3):580-9.
26. Greene AK. Epidemiology and Morbidity of Lymphedema. In: Greene A, Slavin S, Brorson H (eds) *Lymphedema* Springer, Cham. 2015; 33-44.
27. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *The Lancet Oncology*. 2013;14(6):500-15.
28. Organization WH. Lymphatic filariasis - epidemiology. 2017.
29. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat Res Biol*. 2005;3(4):208-17.
30. Brorson H, Hoijer P. Standardised measurements used to order compression garments can be used to calculate arm volumes to evaluate lymphoedema treatment. *J Plast Surg Hand Surg*. 2012;46(6):410-5.
31. Tassenoy A, De Strijcker D, Adriaenssens N, Lievens P. The Use of Noninvasive Imaging Techniques in the Assessment of Secondary Lymphedema Tissue Changes as Part of Staging Lymphedema. *Lymphat Res Biol*. 2016;14(3):127-33.
32. Cornish BH, Ward LC, Thomas BJ, Bunce IH. Quantification of lymphoedema using multi-frequency bioimpedance. *Appl Radiat Isot*. 1998;49(5-6):651-2.
33. Nuutinen J, Ikaheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. *Physiol Meas*. 2004;25(2):447-54.

34. Burnier P, Niddam J, Bosc R, Hersant B, Meningaud JP. Indocyanine green applications in plastic surgery: A review of the literature. *J Plast Reconstr Aesthet Surg*. 2017;70(6):814-27.
35. Andrade M. Clinical Diagnosis: General Overview. In: Lee B, Bergan J, Rockson S (eds) *Lymphedema* Springer, Cham. 2011:83-8.
36. Bull RH, Gane JN, Evans JE, Joseph AE, Mortimer PS. Abnormal lymph drainage in patients with chronic venous leg ulcers. *J Am Acad Dermatol*. 1993;28(4):585-90.
37. Guex JJ. [Physiopathology of post-thrombotic syndrome. Update 1994]. *J Mal Vasc*. 1994;19(1):12-6.
38. Peled AW, Slavin SA, Brorson H. Long-term Outcome After Surgical Treatment of Lipedema. *Ann Plast Surg*. 2012;68(3):303-7.
39. Maclellan RA, Zurakowski D, Grant FD, Greene AK. Massive Localized Lymphedema: A Case-Control Study. *J Am Coll Surg*. 2017;224(2):212-6.
40. International Society of L. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. *Lymphology*. 2003;36(2):84-91.
41. Foldi E, Foldi M, Weissleder H. Conservative treatment of lymphoedema of the limbs. *Angiology*. 1985;36(3):171-80.
42. Casley-Smith JR, Boris M, Weindorf S, Lasinski B. Treatment for lymphedema of the arm--the Casley-Smith method: a noninvasive method produces continued reduction. *Cancer*. 1998;83(12 Suppl American):2843-60.
43. Baumeister RG, editor *Treatment of lymphoedemas by microsurgical autogenous lymph vessel transplantation*. 6th Congress of the European Association of Plastic Surgeons; 1995; Strasbourg, France.
44. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg*. 2000;16(6):437-42.
45. Brorson H. Liposuction in arm lymphedema treatment. *Scand J Surg*. 2003;92(4):287-95.
46. Becker C, Assouad J, Riquet M, Hidden G. Postmastectomy lymphedema: long-term results following microsurgical lymph node transplantation. *Ann Surg*. 2006;243(3):313-5.
47. Johansson K, Klernas P, Weibull A, Mattsson S. A home-based weight lifting program for patients with arm lymphedema following breast cancer treatment: a pilot and feasibility study. *Lymphology*. 2014;47(2):51-64.
48. Huang TW, Tseng SH, Lin CC, Bai CH, Chen CS, Hung CS, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *World J Surg Oncol*. 2013;11:15.
49. Boyages J, Kastanias K, Koelmeyer LA, Winch CJ, Lam TC, Sherman KA, et al. Liposuction for Advanced Lymphedema: A Multidisciplinary Approach for Complete Reduction of Arm and Leg Swelling. *Ann Surg Oncol*. 2015;22 Suppl 3:S1263-70.

50. Brorson H, Svensson H. Liposuction combined with controlled compression therapy reduces arm lymphedema more effectively than controlled compression therapy alone. *Plast Reconstr Surg*. 1998;102(4):1058-67; discussion 68.
51. Flynn TC, Coleman WP, 2nd, Field LM, Klein JA, Hanke CW. History of liposuction. *Dermatol Surg*. 2000;26(6):515-20.
52. Fischer G. Liposculpture: the "correct" history of liposuction. Part I. *J Dermatol Surg Oncol*. 1990;16(12):1087-9.
53. Klein JA. Anesthesia for liposuction in dermatologic surgery. *J Dermatol Surg Oncol*. 1988;14(10):1124-32.
54. Wojnikow S, Malm J, Brorson H. Use of a tourniquet with and without adrenaline reduces blood loss during liposuction for lymphoedema of the arm. *Scand J Plast Reconstr Surg Hand Surg*. 2007;41(5):243-9.
55. Ahern RW. The history of liposuction. *Semin Cutan Med Surg*. 2009;28(4):208-11.
56. O'Brien BM, Sykes P, Threlfall GN, Browning FS. Microlymphaticovenous anastomoses for obstructive lymphedema. *Plast Reconstr Surg*. 1977;60(2):197-211.
57. O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg*. 1990;85(4):562-72.
58. Yamamoto Y, Sugihara T. Microsurgical lymphaticovenous implantation for the treatment of chronic lymphedema. *Plast Reconstr Surg*. 1998;101(1):157-61.
59. Campisi C, Davini D, Bellini C, Taddei G, Villa G, Fulcheri E, et al. Lymphatic microsurgery for the treatment of lymphedema. *Microsurgery*. 2006;26(1):65-9.
60. Baumeister RG, Siuda S. Treatment of lymphedemas by microsurgical lymphatic grafting: what is proved? *Plast Reconstr Surg*. 1990;85(1):64-74; discussion 5-6.
61. Baumeister RG, Frick A. [The microsurgical lymph vessel transplantation]. *Handchir Mikrochir Plast Chir*. 2003;35(4):202-9.
62. Lin CH, Ali R, Chen SC, Wallace C, Chang YC, Chen HC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. *Plast Reconstr Surg*. 2009;123(4):1265-75.
63. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. *Breast Cancer Res Treat*. 2009;113(2):199-206.
64. Vignes S, Blanchard M, Yannoutsos A, Arrault M. Complications of autologous lymph-node transplantation for limb lymphoedema. *Eur J Vasc Endovasc Surg*. 2013;45(5):516-20.
65. Raju A, Chang DW. Vascularized lymph node transfer for treatment of lymphedema: a comprehensive literature review. *Ann Surg*. 2015;261(5):1013-23.
66. Tourani SS, Taylor GI, Ashton MW. Vascularized Lymph Node Transfer: A Review of the Current Evidence. *Plast Reconstr Surg*. 2016;137(3):985-93.
67. Damstra RJ, van Steensel MA, Boomsma JH, Nelemans P, Veraart JC. Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic

- study of 40 patients with unilateral erysipelas of the leg. *Br J Dermatol*. 2008;158(6):1210-5.
68. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med*. 1996;334(4):240-5.
 69. Keast DH, Despatis M, Allen JO, Brassard A. Chronic oedema/lymphoedema: under-recognised and under-treated. *Int Wound J*. 2015;12(3):328-33.
 70. Jorup-Ronstrom C. Epidemiological, bacteriological and complicating features of erysipelas. *Scand J Infect Dis*. 1986;18(6):519-24.
 71. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. *Am J Med*. 1992;93(5):543-8.
 72. Harris SR, Hugi MR, Olivetto IA, Levine M, Steering Committee for Clinical Practice Guidelines for the C, Treatment of Breast C. Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. *CMAJ*. 2001;164(2):191-9.
 73. Swartz MN. Clinical practice. Cellulitis. *N Engl J Med*. 2004;350(9):904-12.
 74. Arakaki RY, Strazzula L, Woo E, Kroshinsky D. The impact of dermatology consultation on diagnostic accuracy and antibiotic use among patients with suspected cellulitis seen at outpatient internal medicine offices: a randomized clinical trial. *JAMA Dermatol*. 2014;150(10):1056-61.
 75. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41(10):1373-406.
 76. Bartholomeeusen S, Vandenbroucke J, Truyers C, Buntinx F. Epidemiology and comorbidity of erysipelas in primary care. *Dermatology*. 2007;215(2):118-22.
 77. Ellis Simonsen SM, van Orman ER, Hatch BE, Jones SS, Gren LH, Hegmann KT, et al. Cellulitis incidence in a defined population. *Epidemiol Infect*. 2006;134(2):293-9.
 78. Karimkhani C, Boyers LN, Prescott L, Welch V, Delamere FM, Nasser M, et al. Global burden of skin disease as reflected in Cochrane Database of Systematic Reviews. *JAMA Dermatol*. 2014;150(9):945-51.
 79. Karimkhani C, Boyers LN, Margolis DJ, Naghavi M, Hay RJ, Williams HC, et al. Comparing cutaneous research funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases with 2010 Global Burden of Disease results. *PLoS One*. 2014;9(7):e102122.
 80. Rockson SG. Lymphedema. *Am J Med*. 2001;110(4):288-95.
 81. Moffatt CJ, Franks PJ, Doherty DC, Williams AF, Badger C, Jeffs E, et al. Lymphoedema: an underestimated health problem. *QJM : monthly journal of the Association of Physicians*. 2003;96(10):731-8.
 82. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. *J Clin Oncol*. 2008;26(35):5689-96.
 83. Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. *Int Wound J*. 2005;2(1):47-62.

84. Swartz MA, Lund AW. Lymphatic and interstitial flow in the tumour microenvironment: linking mechanobiology with immunity. *Nat Rev Cancer*. 2012;12(3):210-9.
85. Kim H, Kataru RP, Koh GY. Inflammation-associated lymphangiogenesis: a double-edged sword? *The Journal of clinical investigation*. 2014;124(3):936-42.
86. Karaman S, Hollmen M, Robciuc MR, Alitalo A, Nurmi H, Morf B, et al. Blockade of VEGF-C and VEGF-D modulates adipose tissue inflammation and improves metabolic parameters under high-fat diet. *Mol Metab*. 2015;4(2):93-105.
87. Aspelund A, Robciuc MR, Karaman S, Makinen T, Alitalo K. Lymphatic System in Cardiovascular Medicine. *Circ Res*. 2016;118(3):515-30.
88. Avraham T, Zampell JC, Yan A, Elhadad S, Weitman ES, Rockson SG, et al. Th2 differentiation is necessary for soft tissue fibrosis and lymphatic dysfunction resulting from lymphedema. *FASEB J*. 2013;27(3):1114-26.
89. Cuzzzone DA, Weitman ES, Albano NJ, Ghanta S, Savetsky IL, Gardenier JC, et al. IL-6 regulates adipose deposition and homeostasis in lymphedema. *American journal of physiology Heart and circulatory physiology*. 2014;306(10):H1426-34.
90. Babu S, Nutman TB. Immunology of lymphatic filariasis. *Parasite Immunol*. 2014;36(8):338-46.
91. Olszewski WL, Jamal S, Manokaran G, Lukomska B, Kubicka U. Skin changes in filarial and non-filarial lymphoedema of the lower extremities. *Trop Med Parasitol*. 1993;44(1):40-4.
92. Avraham T, Daluvoy S, Zampell J, Yan A, Haviv YS, Rockson SG, et al. Blockade of transforming growth factor-beta1 accelerates lymphatic regeneration during wound repair. *Am J Pathol*. 2010;177(6):3202-14.
93. Ogata F, Fujiu K, Matsumoto S, Nakayama Y, Shibata M, Oike Y, et al. Excess Lymphangiogenesis Cooperatively Induced by Macrophages and CD4(+) T Cells Drives the Pathogenesis of Lymphedema. *J Invest Dermatol*. 2016;136(3):706-14.
94. Sica A, Erreni M, Allavena P, Porta C. Macrophage polarization in pathology. *Cellular and molecular life sciences : CMLS*. 2015;72(21):4111-26.
95. Vannella KM, Wynn TA. Mechanisms of Organ Injury and Repair by Macrophages. *Annu Rev Physiol*. 2017;79:593-617.
96. Ghanta S, Cuzzzone DA, Torrisi JS, Albano NJ, Joseph WJ, Savetsky IL, et al. Regulation of inflammation and fibrosis by macrophages in lymphedema. *American journal of physiology Heart and circulatory physiology*. 2015;308(9):H1065-77.
97. Rutkowski JM, Moya M, Johannes J, Goldman J, Swartz MA. Secondary lymphedema in the mouse tail: Lymphatic hyperplasia, VEGF-C upregulation, and the protective role of MMP-9. *Microvascular research*. 2006;72(3):161-71.
98. Tabibiazar R, Cheung L, Han J, Swanson J, Beilhack A, An A, et al. Inflammatory manifestations of experimental lymphatic insufficiency. *PLoS Med*. 2006;3(7):e254.
99. Jiang X, Nicolls MR, Tian W, Rockson SG. Lymphatic Dysfunction, Leukotrienes, and Lymphedema. *Annu Rev Physiol*. 2017.
100. Tian W, Rockson SG, Jiang X, Kim J, Begaye A, Shuffle EM, et al. Leukotriene B4 antagonism ameliorates experimental lymphedema. *Sci Transl Med*. 2017;9(389).

101. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. *Nat Rev Immunol*. 2004;4(8):583-94.
102. Cho S, Roh K, Park J, Park YS, Lee M, Cho S, et al. Hydrolysis of Hyaluronic Acid in Lymphedematous Tissue Alleviates Fibrogenesis via TH1 Cell-Mediated Cytokine Expression. *Sci Rep*. 2017;7(1):35.
103. Sullivan M, Karlsson J. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. *J Clin Epidemiol*. 1998;51(11):1105-13.
104. Torrance N, Smith BH, Lee AJ, Aucott L, Cardy A, Bennett MI. Analysing the SF-36 in population-based research. A comparison of methods of statistical approaches using chronic pain as an example. *J Eval Clin Pract*. 2009;15(2):328-34.
105. Olszewski WL. Episodic dermatolymphangioadenitis (DLA) in patients with lymphedema of the lower extremities before and after administration of benzathine penicillin: a preliminary study. *Lymphology*. 1996;29(3):126-31.
106. Brorson H. Liposuction gives complete reduction of chronic large arm lymphedema after breast cancer. *Acta Oncol*. 2000;39(3):407-20.
107. Brorson H, Ohlin K, Olsson G, Langstrom G, Wiklund I, Svensson H. Quality of life following liposuction and conservative treatment of arm lymphedema. *Lymphology*. 2006;39(1):8-25.
108. Case TC, Witte CL, Witte MH, Unger EC, Williams WH. Magnetic resonance imaging in human lymphedema: comparison with lymphangioscintigraphy. *Magn Reson Imaging*. 1992;10(4):549-58.
109. Brorson H, Svensson H. Complete reduction of lymphoedema of the arm by liposuction after breast cancer. *Scand J Plast Reconstr Surg Hand Surg*. 1997;31(2):137-43.
110. Damstra RJ, Voesten HG, Klinkert P, Brorson H. Circumferential suction-assisted lipectomy for lymphoedema after surgery for breast cancer. *Br J Surg*. 2009;96(8):859-64.
111. Schaverien MV, Munro KJ, Baker PA, Munnoch DA. Liposuction for chronic lymphoedema of the upper limb: 5 years of experience. *J Plast Reconstr Aesthet Surg*. 2012;65(7):935-42.
112. Greene AK, Voss SD, Maclellan RA. Liposuction for Swelling in Patients with Lymphedema. *N Engl J Med*. 2017;377(18):1788-9.
113. Brorson H, Svensson H, Norrgren K, Thorsson O. Liposuction reduces arm lymphedema without significantly altering the already impaired lymph transport. *Lymphology*. 1998;31(4):156-72.
114. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-83.
115. Keeley V. Quality of life assessment tools in chronic oedema. *British journal of community nursing*. 2008;13(10):S22-7.
116. Baum T, Cordes C, Dieckmeyer M, Ruschke S, Franz D, Hauner H, et al. MR-based assessment of body fat distribution and characteristics. *Eur J Radiol*. 2016.

117. Brorson H, Svensson H. Skin blood flow of the lymphedematous arm before and after liposuction. *Lymphology*. 1997;30(4):165-72.
118. Peterson P, Romu T, Brorson H, Dahlqvist Leinhard O, Mansson S. Fat quantification in skeletal muscle using multigradient-echo imaging: Comparison of fat and water references. *J Magn Reson Imaging*. 2016;43(1):203-12.
119. Vondrichova T, de Capretz A, Parikh H, Frenander C, Asman P, Aberg M, et al. COX-2 and SCD, markers of inflammation and adipogenesis, are related to disease activity in Graves' ophthalmopathy. *Thyroid*. 2007;17(6):511-7.

Liposuction of lymphedema



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