Chronic lymphedema remains a challenging problem that often lacks curative treatment options. The incidence of lymphedema varies from 9% to 41% in patients who have undergone axillary lymph node dissection and from 4% to 10% in patients who have undergone sentinel node dissection.

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**Background:** Recent reports have shown that microvascular lymph node transfer may improve lymphatic drainage in lymphedema patients. Lymphatic anastomoses are expected to form spontaneously in response to lymphatic growth factor [vascular endothelial growth factor C (VEGF-C)] secreted by the transferred lymph nodes.

**Methods:** We have analyzed the results of 19 lymph node transfer patients operated on 2007–2012. Postoperative lymphatic function of the affected arm was evaluated using semiquantitative lymphoscintigraphy (transport index) and limb circumference measurements. To investigate the postoperative VEGF-C secretion, we examined axillary seroma fluid samples after different surgical operations, including lymph node transfer.

**Results:** The transport index was improved postoperatively in 7 of 19 patients. Ten of the 19 patients were able to reduce or even discontinue using compression garments. Arm circumferences were reduced in 12 of 19 patients. Six of the 7 patients with preoperative erysipelas infections have not had infectious episodes postoperatively during 15–67 months follow-up. Neuropathic pain was relieved in 5 of 5 patients. VEGF-C protein was detected in the axillary seroma fluid both after lymph node transfer and normal breast reconstruction.

**Conclusions:** Reconstructing the lymphatic anatomy of the axilla with a lymph node flap may offer possibilities that other reconstructive options are lacking. However, we will need further reports and comparative studies about the clinical efficacy of this new promising technique. In addition to the transferred lymph nodes, lymphatic growth factor production may also be induced by other factors related to microvascular breast reconstruction.

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biopsy.¹⁻³ Conventional treatment options for chronic lymphedema aim at alleviating symptoms and are mainly based on physiotherapy and compression therapy, whereas reconstructive surgical treatment options have been limited.¹ Late-stage lymphedema, which is accompanied by adipose tissue hypertrophy and fibrosis, can be managed with liposuction as a symptomatic treatment.⁴ However, a prerequisite to maintaining the effect of liposuction is the continuous use of compression garments.⁵

Recent studies have shown that autologous microvascular lymph node transfer from the groin area into the axillas or wrists of the lymphedema patients may improve lymphatic drainage of the affected limb.⁶⁻⁹ The fact that the lymph node transfer is easily combined with breast reconstruction has made this technique attractive also for patients with early stage disease.⁸ To provide more information about the clinical efficacy of the lymph node transfer, we have evaluated the upper limb lymphatic flow pre- and postoperatively using a highly sensitive and specific transport index method.¹⁰,¹¹

In the lymph node transfer technique, the lymphatic vessel anastomoses are expected to form spontaneously. Understanding of the molecular mechanisms of lymphangiogenesis has increased considerably in the recent years. Vascular endothelial growth factor C (VEGF-C) is known to be the most important growth factor for lymphatic vascularization.¹² Human lymph nodes express endogenous VEGF-C, providing a biological basis for the microsurgical lymph node transfer method.⁹ However, the level and the role of endogenous VEGF-C production after lymph node transfer are not known. Therefore, we decided to evaluate the secretion of VEGF-C in the axillary seroma fluid of the lymph node transfer patients and compare the results with seroma VEGF-C concentrations of microvascular breast reconstruction and axillary dissection (lymph node removal) patients.

**PATIENTS AND METHODS**

**Patients**

Clinical efficacy of the lymph node transfer surgery was evaluated in 19 patients operated during May 2007 to March 2012 in Turku University Hospital. For most patients, lymph node transfer was performed simultaneously with free lower abdominal breast reconstruction (n = 13) (LN-BR). Indications for microvascular lymph node transfer alone (n = 6) (LN) were lymphedema with recurrent erysipelas infections or chronic pain in the upper limb. For patients with chronic lymphedema characterized by deposition of fat and fibrotic tissue (nonpitting edema), we performed combined lymph node transfer and liposuction of the affected arm (n = 5) (Fig. 1).

**Operative Technique**

For 13 postmastectomy patients with lymphedema symptoms, we used a modified lower abdominal flap containing lymph nodes and lymphatic vessels surrounding the superficial circumflex vessel pedicle (LN-msTRAM/LN-DIEP) as described in our earlier publication.⁸ In our first patients, we harvested the superficial inferior epigastric vessels as a second pedicle for the lymphatic flap. Because we found minor changes in lymphoscintigraphies of the donor legs in our first patients,¹³ we have avoided using the superficial inferior epigastric vessels and dissection medial to the femoral vessels.

Liposuction of the affected arm was performed simultaneously with lymph node transfer in 5 patients with a long history of nonpitting edema. Liposuction volumes are shown in Table 1.

**Postoperative Care**

The perfusion of the flap was monitored by tissue oxygen sensor Licox for 3–4 days postoperatively. Compression was used in the lower abdominal wall and inguinal area for 4 weeks to prevent seroma formation. Manual drainage of the upper limb (physiotherapy) was started on the second postoperative day (or on day 14 to 21 on liposuction patients) and recommended 2 times a week for 3 months after surgery. For the first 6 months postoperatively, all patients used an elastic compression dressing in their symptomatic arm.

**Evaluation of the Effect of Lymph Node Transfer on Recipient Site (Upper Limb)**

Patients were followed up in our outpatient clinic 1, 3, and 6 months postoperatively and annually thereafter. All complications were noted, and patients were asked about symptoms in their arms (erysipelas, chronic pain). Lymphedema symptoms were assessed pre- and postoperatively by upper limb diameter measurements. The measurements were made at wrist, 10 cm below the elbow, and 10 cm above the elbow. The average difference in circumferences between lymphedema arm and normal arm was calculated. Six months after the operation, patients were encouraged to stop using the compression garment.

**Lymphoscintigraphy**

For lymphoscintigraphy, 40 MBq of technetium-labeled sulfur nanocolloid (99mTc-Nanocoll, GE
Healthcare) in a volume of 0.1–0.2 ml was injected intradermally in the first interdigital space of both hands. Anterior and posterior planar images of upper extremities were scanned in supine position at 5, 15, 30, 45, 60, and 120 minutes with Infinia Hawkeye SPECT/CT (General Electric Medical Systems, Milwaukee, WI). Lymphoscintigraphy images were analyzed as a consensus by 2 experienced nuclear medicine physicians. For semiquantitative evaluation of lymphatic drainage, a numerical transport index (Ti) was used as described previously.\textsuperscript{10,11} This index is based on 5 criteria: lymphatic transport kinetics, distribution pattern of the radiopharmaceutical, time to appearance of lymph nodes, and visualization of lymph nodes and lymph vessels.\textsuperscript{10} The lymphoscintigraphy of the upper limbs was performed 3 months, 6 months, 1 year, 1.5 years, and 2 years after operation with some exceptions (Fig. 2A).

| Table 1. Summary of the Results |
|--------------------------------|
| **Patient** | **Duration of Symptoms (mo)** | **Age at Operation** | **Transport Index** | **VEGF-C (pg/ml)** | **Average Circumference Difference** | **Liposuction (ml)** | **Additional Effect of Treatment** | **Follow-up (mo)** |
|-----------|----------------|----------------|----------------|-----------------|-----------------|----------------|-----------------|-----------------|
| 1         | 84             | 56             | 11.2           | 2               | 2.9             | 900            | E, CR           | 67              |
| 2         | 80             | 40             | 3.6            | 0.3             | 1.3             | 60             | P, CR           | 60              |
| 3         | 49             | 50             | 45             | 2              | 3.7             | 59             | CD             | 59              |
| 4         | 45             | 62             | 11.4           | 2.7             | 7.7             | 41             | E, CD           | 41              |
| 5         | 30             | 55             | 45             | 4.2             | 0.3             | 39             |                |                 |
| 6         | 26             | 51             | 4.2            | 1.7             | 5.5             | 33             |                |                 |
| 7         | 120            | 65             | 26.8           | 6               | 3               | 29             |                |                 |
| 8         | 6              | 43             | ND             | 1.3             | 1               | 27             |                |                 |
| 9         | 62             | 60             | 3.2            | 0.8             | 0.5             | 24             |                |                 |
| 10        | 120            | 38             | 45             | 2.9             | 0.5             |                | P, CD           | 19              |
| 11        | 17             | 74             | 19.2           | 770             | 1.500           |                | E, CR           | 19              |
| 12        | 19             | 56             | 45             | 2.7             | 0               |                |                | 20              |
| 13        | 45             | 61             | 19.8           | 948             | 700             |                | P, E, CR        | 16              |
| 14        | 28             | 53             | 3.6            | 3.6             | 2.5             |                |                 | 15              |
| 15        | 70             | 50             | 12.8           | 2487            | 550             |                | P, E, CR        | 12              |
| 16        | 73             | 56             | 12.8           | 1000            | 11              |                | CR             |                 |
| 17        | 59             | 10.4           | 14.8           | 3572            | 0               |                |                | 11              |
| 18        | 51             | 20.8           | 18.8           | 968             | 0               |                |                | 10              |
| 19        | 69             | 22.8           | 20.4           | 1436            | 0               |                |                | 10              |

CD, compression therapy discontinued; CR, compression therapy reduced; E, no erysipelas infections; P, pain relieve; ND, not done.
Patient Samples for VEGF-C Analysis

Permission for collecting patient seroma samples was approved by the Ethical Committee of the Turku University Hospital. Postoperative axillary seroma fluid samples were collected from all voluntary lymph node transfer patients [LN (n = 5) and LN-BR (n = 9)]. For controls, we collected axillary seroma samples from normal lower abdominal breast reconstruction (BR) patients (n = 10), axillary lymph node dissection (ALND) patients (n = 10), and seroma samples from the flap donor area (abdominal wound, n = 8). BR group consisted of postmastectomy patients without lymphedema symptoms. ALND patients underwent a routine breast cancer operation with removal of axillary lymph nodes. Samples (15 ml) of seroma fluid were collected from axillary drains on the first and the sixth postoperative days and from flap donor site drains on the first postoperative day.

Evaluation of Seroma Fluid VEGF-C

A protease inhibitor (cOmplete EDTA-free; Roche Diagnostics, Mannheim, Germany) was added to the seroma fluid. The samples were centrifuged and frozen at −70°C for later use. VEGF-C protein concentrations were measured using enzyme-linked

![Fig. 2. A, Transport index indicating the pre- and postoperative lymphatic flow. B, Pre- and postoperative lymphoscintigraphy of patient 1. Note the lymph node in the axilla in the 5-min postoperative image. *The patient was able to reduce or discontinue compression treatment.](image-url)
immunosorbent assays (R&D systems, Minneapolis, MN) according to the manufacturer’s instructions. Optical densities were read at 450 nm (using wavelength correction set to 540 nm) with a microplate reader (Infinite 200; Tecan Group Ltd., Männedorf, Switzerland) and converted to pg/ml using a standard curve.

**Statistical Analysis**

All statistical analyses were performed using IBM SPSS Statistics Version 20.0.0 (IBM Corporation, Armonk, NY). The VEGF-C concentrations of the first and sixth postoperative days were logarithmically transformed before analysis due to nonnormal distribution and heterogeneity of variance and assessed separately for each day with one-way analysis of variance. Significant results were followed by Gabriel’s pairwise comparisons test and nonsignificant results with a post hoc power analysis. Effect sizes are reported as $\eta^2$ (eta-squared) for analysis of variances and Cohen’s $d$ for post hoc pairwise comparisons. To analyze differences between the VEGF-C concentrations of flap recipient and donor sites on the first postoperative day, the concentrations from donor site drains were grouped together. Another group was formed using the VEGF-C concentrations from the recipient site drains of the corresponding patients. These 2 groups were compared using paired-samples $t$ test. Effect size is reported as Cohen’s $d$ (using Cohen’s guidelines of $d$ values translated to correlated-scores design, with observed paired-samples correlation of 0.606: 0.23 = small, 0.56 = medium, and 0.90 = large). All data were back-transformed to the original scale for presentation. Results are graphed as geometric means and 95% confidence intervals. $P$ values < 0.05 were considered to be significant.

**RESULTS**

**Patient Characteristics**

We analyzed the results of 19 lymph node transfer patients (6 LN and 13 LN-BR) operated during May 2007 to March 2012 (see patient list in Table 1). Most of the patients (18 of 19) were postmastectomy patients with upper limb lymphedema, with previous axillary dissection and radiotherapy. One of the patients (patient 10) had developed upper limb lymphedema after lymph node biopsy and oncological treatment of Hodgkin’s disease. Seven patients had at least 1 episode of erysipelas infection preoperatively (patients 1, 4, 7, 10, 11, 12, and 14). Five patients had neuropathic pain in the lymphedema arm. One of the patients had diabetes and 4 patients had hypertension. None of the patients were smokers. The mean age of the patients was 54.3 years (range, 38–74). The average body mass index was 28.6 (range, 21–36.7). Five patients underwent an upper extremity liposuction at the time of lymph node transfer (patients 10, 11, 13, 14, and 18). There were 4 cases of postoperative infection on donor sites (patients 1, 8, 15, and 18), 5 seromas on donor sites (patients 1, 4, 11, 12, and 14), and 1 on recipient site (patient 16). Five patients had delayed wound closure on abdominal wound (patients 2, 7, 8, and 17) and 1 on recipient site (patient 12). Patient 18 needed intravenous antibiotics due to an infection. All complications were treated conservatively within 4 months and patients did not need hospitalization.

**Lymphatic Vessel Function Pre- and Postoperatively**

The lymphatic vessel function was assessed pre- and postoperatively by upper limb diameter measurements and isotopic lymphangiography. The necessity of using compression garment was also investigated. The results are summarized in Table 1. A minor reduction in arm circumference was measured in 12 of 14 patients at 6 months to 4.5 years time point (patients with liposuction are excluded). In postoperative lymphoscintigraphy, the lymphatic transport index showed improvement in 7 of 19 patients (Table 1 and Figs. 2A, B). Patient 14 did not give permission for any postoperative lymphoscintigraphy. Five (5 of 19) patients were able to reduce compression garment usage and 5 (5 of 19) were able to discontinue compression treatment at 6–24 months after operation (Fig. 3). Interestingly, 2 (2 of 5) patients with liposuction were also able to reduce compression treatment (dashed lines in Fig. 3). Six (6 of 7) erysipelas patients have not had upper limb infections postoperatively during 8–65 months follow-up. Neuropathic pain was relieved in all 5 patients.

**VEGF-C Concentration in Seroma Fluid**

On the first postoperative day, VEGF-C concentrations were higher in BR, LN, and LN-BR groups compared to ALND group, $F(3, 30) = 12.91, P < 0.001, \eta^2 = 0.563$ (large effect) (Fig. 4). Pairwise comparisons: $P < 0.001, d = 2.83$ (large effect) for BR vs ALND; $P = 0.017, d = 1.66$ (large effect) for LN vs ALND; $P < 0.001, d = 2.80$ (large effect) for LN-BR vs ALND. There were no statistically significant differences between BR, LN, and LN-BR groups ($P > 0.05$ for all comparisons). Furthermore, the level of VEGF-C protein was significantly higher in seroma fluid samples obtained from flap recipient (axillary) wounds compared to flap donor (abdominal) wounds; $t(7) = 4.54, P = 0.003, d = 1.54$ (large effect). On the sixth postoperative day, VEGF-C concentrations were low in all groups and no surgery-related differences were observed;
F(3, 28) = 1.56, \( P = 0.507 \), \( \eta^2 = 0.152 \) (large effect). Due to the observed effect size being considerably smaller than assumed in our a priori power analysis, a post hoc power analysis was conducted (power = 0.80, \( \alpha = 0.05 \)), in which our group size on the sixth postoperative day turned out insufficient. For an effect of this size, a sample of at least 68 patients would be required to obtain an acceptable level of statistical power (0.80). The possible correlation between the VEGF-C concentration and clinical result of lymph node transfer cannot be reliably evaluated with this small patient material (Table 1).

**DISCUSSION**

Lymph node transfer is easily combined with routine microvascular breast reconstruction, and this new method is now gaining popularity. To provide more information about the efficacy of this surgery, we present here the results of our first patients. One third of our lymph node transfer patients showed improvement of the lymphatic flow function in postoperative lymphoscintigraphy. The arm circumference was slightly reduced in majority (12 of 19) of the patients. Half of the patients (10 of 19) were able to discontinue or reduce compression garment usage at 6–24 months after surgery. Most of the erysipelas patients (6 of 7) have not had upper limb infections during 15–67 months follow-up, and all patients with neuropathic pain reported significant relieve of pain postoperatively (5 of 5).

Unlike in our earlier report, we have now been using a more specific and sensitive transport index method in the analysis of the lymphoscintigraphy results. This method takes into account not only the isotopic marker flow velocity but also visualization of vessels, nodes, and distribution pattern of the marker. A longer follow-up demonstrates slight improvement of the lymphatic function in many of our lymph node transfer patients. The clinical benefits of the surgery are also seen with a delay because patients may need to wait for 1 or 2 years before they can reduce the use of compression garments. Results from the experimental animal models have also demonstrated that lymphatic vessel maturation after surgical operation is a rather slow process.

For most of the patients in this study, lymph node transfer operation was performed in combination with routine breast reconstruction, which is typically performed 1–2 years after oncological treatments of breast cancer. Lymphedema is known to develop relatively slowly after surgery or radiation. Therefore, some of our patients had very mild lymphedema symptoms at the time of surgery. For several patients, the indication for axillary lymph node transfer was neuropathic pain of the arm. As described previously, all of these patients also seemed to benefit from the operation. In our material, a fairly low preoperative transport index seems to predict better outcome after operation. We also believe that optimal time for lymph node transfer is during the early stage of the disease, before the secondary changes of lymphedema occur. However, we do not know what would have been the prognosis of these patients without the lymph node transfer surgery.

Over half of our patients showed reduction in arm circumferences. However, the amount of edema...
varies during a day, and it is dependent on temperature, amount of physical work, and the quality of compression garment used on the day of the examination. For more accurate information, the arm volumetry should be performed both with and without the use of compression therapy pre/postoperatively.

In early stages of lymphedema, the swelling is due to an excess amount of fluid in the subcutaneous tissue. As the condition progresses, the amount of fat and fibrotic tissue increases. For patients with severe nonpitting edema, we decided to perform liposuction simultaneously with reconstructive surgery. Liposuction is a symptomatic treatment for lymphedema, and previous reports from Brorson and Svensson have shown that liposuction patients have to continue using compression therapy to maintain the result of surgery. Interestingly, 2 (2 of 5) of our combined lymph node transfer and liposuction patients were able to reduce the use of compression garment and 16 months after the surgery without increasing edema thus far (follow-up 15 and 19 mo). Transport indices were also improved in 2 liposuction patients. These very primary results may provide new hope also for patients with chronic lymphedema.

Interestingly, human lymph nodes are known to produce lymphatic vessel growth factor VEGF-C. Transfer of the lymph nodes and the resulting endogenous VEGF-C expression may thereby enhance the regeneration of the lymphatic network in the axilla. In the present study, we show that, compared to ALND patients, the increased concentration of VEGF-C protein can be found in axillary seroma fluid of LN, LN-BR, and BR patients on the first postoperative day. VEGF-C is known to play a role in normal wound healing, and therefore, it is expected that large wound surface area in BR and LN-BR patients may produce high amounts of growth factors. However, the VEGF-C concentrations in the large abdominal donor wounds were lower than in the recipient site wounds. One reason for the high VEGF-C concentration in BR patients might be the fact that patients, who have not developed lymphedema after axillary clearance, have actually functioning residual axillary lymph nodes, which are producing VEGF-C (Fig. 5). Recruited macrophages have been shown to be the source of VEGF-C after flap transfer in a mouse model, suggesting another potential mechanism for the elevated VEGF-C level in LN, LN-BR, and BR groups.

Evidently, results of the present study raise a question whether lymphedema could be surgically treated with traditional breast reconstruction. There are previous studies suggesting that immediate breast reconstruction reduces lymphedema risk in the breast cancer patients and that delayed breast reconstruction may reduce the lymphedema symptoms of the affected arm. However, reconstructing the lymphatic anatomy of the axilla with a lymph node flap offers possibilities that other reconstructive options are lacking. In the ideal situation, lymphatic, sentinel, and immunological functions of the lymphatic system are retained. In the experimental studies, both sentinel node and immunological functions of the transferred lymph nodes have been regained after

![Graph A](image1)

**Fig. 4.** The lymphatic growth factor (VEGF-C) concentration in seroma fluid in different patient groups. A, First postop day: High concentrations of VEGF-C protein were found in axillary seroma fluid of BR, LN, and LN-BR groups compared to ALND group. No statistically significant differences between BR, LN, and LN-BR groups. Sixth postop day: VEGF-C concentrations were low in all groups, no surgery-related effects were observed. B, The level of VEGF-C protein was significantly higher in seroma fluid samples obtained from flap recipient (axillary) wounds compared to flap donor (abdominal) wounds on the first postoperative day. *P < 0.05; **P < 0.01; ***P < 0.001.
In our data, 7 patients had erysipelas infections preoperatively. Six of them have not had infectious episodes after lymph node transfer. Similarly, Becker et al have reported decreased episodes of erysipelas and lymphangitis after lymph node transfer. Previous studies, together with our own observations, indicate that not all patients benefit from the lymph node transfer surgery. Results from the experimental studies demonstrate that endogenous production of VEGF-C does not always seem to be sufficient to rebuild lymphatic vascular networks. In the animal models, VEGF-C gene transfer therapy has been shown to increase lymphangiogenesis and functionality of the transferred lymph nodes. In the future, it would be feasible to combine VEGF-C therapy with the lymph node transfer to gain more efficacy for the treatment of lymphedema patients.

**CONCLUSIONS**

Lymph node transfer is a promising technique, and it seems to be more beneficial for patients with fairly mild lymphedema. However, it is not possible to know whether the symptoms of these early phase...
patients would have been relieved after traditional breast reconstruction as well. Therefore, a prospective randomized study and long-term follow-up in lymphedema patients comparing the effect of breast reconstruction and lymph node transfer and the effects on donor site are needed. Lymphedema patients are susceptible to recurrent infections of the affected limb, and lymph node transfer seems to be immunologically beneficial for these patients. It would thus be of interest to study the immunological functions of transferred lymph nodes as well.

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