Breast Cancer-Related Chronic Arm Lymphedema Is Associated with Excess Adipose and Muscle Tissue

Article in Lymphatic Research and Biology - March 2009
DOI: 10.1089/lrb.2008.1022 · Source: PubMed

4 authors, including:

Håkan Brorson
Plastic and Reconstructive Surgery, Skane University Hospital, Malmö
88 PUBLICATIONS 2,012 CITATIONS

Magnus K Karlsson
Lund University
535 PUBLICATIONS 13,414 CITATIONS

Some of the authors of this publication are also working on these related projects:

Mechanical Imaging of the breast
Malmö Perimenopausal Project

All content following this page was uploaded by Håkan Brorson on 22 May 2014.

The user has requested enhancement of the downloaded file.
Breast Cancer-Related Chronic Arm Lymphedema Is Associated with Excess Adipose and Muscle Tissue

Håkan Brorson, M.D., Ph.D., 1 Karin Ohlin, O.T.R., 1 Gaby Olsson, R.P.T., L.T., 1 and Magnus K. Karlsson, M.D., Ph.D. 2

Abstract

Background: Arm lymphedema is a common complication after breast cancer treatment. Although conservative treatment can be used to reduce swelling, treatment often fails, possibly due to chronic edema being transformed from lymph fluid to subcutaneous fat, a condition called nonpitting lymphedema. It is currently unknown if the excess volume is solely due to excess in fat. This study evaluated whether dual energy X-ray absorptiometry (DXA) could be used to estimate the excess fat, muscle, and bone tissue in patients with arm lymphedema.

Methods and Results: Eighteen women with arm lymphedema were investigated. Measurements were converted to volume values and compared with values obtained using plethysmography (PG). Linear regression equations and correlation equations were used to compare the DXA and the PG techniques in regard to total volume and excess volume in the lymphedematous arm. DXA was used to estimate excess fat, muscle, and bone volume in the lymphedematous arm. Both DXA and PG provided similar total arm volume and excess volume measurements for the lymphedematous arm. The lymphedematous arm showed 73% more fat, 47% more muscle, and 7% more bone by volume in the lymphedematous arm.

Conclusions: Both excess fat and muscle volume contributed to the total excess volume in nonpitting arm lymphedema; excess soft tissue developed the first few years after breast cancer surgery. DXA can be used to identify patients with excess fat in their arms and thus unsuitable for conservative treatment and may be useful in estimating the amount of fat to remove in patients scheduled for liposuction.

Introduction

Breast cancer is the most common cancer in women. In most cases it is treated with surgery with or without adjuvant irradiation and chemotherapy. One common complication following surgery is arm lymphedema. The incidence of lymphedema after breast cancer treatment varies between 8% and 80%, depending on whether axillary lymph nodes have been removed and whether postoperative irradiation has been given. Lymph node removal and irradiation can lead to tissue scarring and to the destruction of lymphatic vessels; the remaining lymphatic vessels become unable to transport the lymph, with the result that the lymph collectors become dilated and overloaded. The valves become insufficient, preventing them from performing their function. This failure spreads distally until even the most peripheral lymph vessels that drain into the affected system become dilated.

In parallel with lymphatic vessel dilation, mononuclear phagocytic cells in the mesenchymal tissues begin to lose their ability to remove accumulating proteins. The interstitial proteins that accumulate are osmotically active molecules that attract fluid to the area. This accumulation of protein and fluid usually occurs after surgery during a 1- to 3-week transitory phase.

There may be no clinical signs of lymphedema in the latent phase that follows the transitory phase and can occur from 4 months to 10 years after surgery. At the end of the latent phase, pressure in the edematous arm usually leads to ‘pitting’. When the edematous tissue is pushed with a fingertip, a depression is formed as the lymph is squeezed into the surroundings. This condition can involve both excess...
fluid and adipose tissue, and can be objectively measured using a tissue tonometer to detect decreased tissue compressibility.3,4

Traditionally, the swelling of a lymphedematous arm has been thought to be solely due to an accumulation of lymph fluid. Noninvasive conservative regimens such as physiotherapy, involving manual lymph drainage, skin care, remedial exercises, and compression bandaging complemented with compression garments have been the treatments of choice.5 However, noninvasive treatment often fails in patients with chronic edema, as does microsurgery using lympho-venous shunts or lymph vessel transplantation.6,7 In such patients, liposuction has been used with good results.8–10 Aspirate analysis during liposuction has shown that this technique removes excess adipose tissue in the swollen arm; further, swelling of the arm does not recur after liposuction.8–10 However, even though liposuction has been reported to be successful in treating arm lymphedema, currently there is no consensus as to whether the increase in volume is due entirely to excess fat or whether there is also an increase in muscle and bone tissue. Furthermore, there is no consensus about why this condition can develop either right after the operation or up to many years afterwards.

We wished to determine which tissue or tissues comprise the excess tissue or volume in patients with unilateral postmastectomy, nonpitting arm lymphedema. The aim of this study was to evaluate whether measurements using dual energy X-ray absorptiometry (DXA) were similar to those obtained using plethysmography (PG), which is the gold standard for estimating lymphedematous arm volume. We also wanted to determine whether DXA could be used to compare unaffected and lymphedematous arm volumes. Our results showed that DXA can be used as a method to estimate arm volume, and that the increased volume in nonpitting arm lymphedema is predominantly due to fat.

Materials and Methods

Eighteen female patients with secondary upper limb lymphedema participated in the study (Table 1). All had undergone mastectomies with lymph node excision: 16 patients had unilateral modified radical mastectomies and 2 patients had partial mastectomies. Radiotherapy was given to 15 patients and chemotherapy to 4. None of the patients had a generalized disease or any local wound problems after the operation. All the lymphedemas were of the nonpitting type.

Previous treatment of the patients’ lymphedema included a variety of conservative therapies such as manual lymph drainage, compression pumping, bandaging with semi-elastic rolls, and home exercises. None of the 18 patients felt that the previous conservative treatments had been successful, as the treatment had not completely reduced the excess volume in their arms.

The volume of both arms was measured by a water displacement technique called plethysmography (PG), which has been thoroughly described in previous reports.11,12 The hand and the whole arm up to the axilla, equivalent to the area measured by DXA, were included in the PG measurement.8 The contralateral arm was also measured for comparison. The displaced water was weighed on a balance to the nearest 5 grams, corresponding to a volume of 5 ml. The excess arm volume or ‘edema volume’ was defined as the difference in volume between the lymphedematous and the normal arm.

Dual-energy X-ray absorptiometry (DXA; DPX-L version 3.2, Lunar, Madison, WI) accurately estimates soft tissue composition.13–15 We used DXA to measure the soft tissue composition of both the lymphedematous and the normal arm of each patient; the hand and the whole arm up to the axilla, which is equivalent to the area measured by PG, were included in the DXA estimation. Using the standard LUNAR total body software, the fat mass, lean mass, and bone mineral content (BMC) were determined for each arm.13,14 The measured tissue weight was then transformed into an estimated volume using the known densities of fat (0.9167 g/ml = 0.92 g/cm3),16 muscle (1.0615 g/ml = 1.06 g/cm3),17,18 and bone (3.15 g/cm3).19 The coefficient of variation (CV%) was estimated by repeating the DXA measurements twice in 16 arms. The CV was 2.5% for total arm tissue, 1.2% for fat tissue, 4.2% for lean body mass, and 4.9% for BMC.

Each patient was examined while dressed in short arm and short leg underwear in a recumbent position with her arms slightly abducted. Foam rubber was placed between the upper arms and the torso to prevent direct contact. A region of

| Table 1. Characteristics of 18 Women with Unilateral Nonpitting Arm Lymphedema After Breast Cancer Treatment in Whom Conservative Treatment Was Unsuccessful |
|----------------------------------|-----------------|-------------------|
| Number of patients              | 18              | Interval between breast cancer operation and investigation (years) |
| Age at cancer operation         | 49              | Mean              |
| Mean                             | 34–77           | Range             |
| Interval between breast cancer operation and onset of lymphedema (years) | 1.8 | Mean |
| Mean                             | 0–6             | Range             |
| Duration of lymphedema (years)  | 11              | Height (cm)       |
| Mean                             | 2–38            | Mean              |
| Age at investigation (years)     | 62              | Range             |
| Mean                             | 41–80           | Weight (kg)       |
| Mean                             |                  | Mean              |
| Range                            |                  | Range             |
| BMI (kg/m2)                      | 29              | BMI (kg/m2)       |
| Mean                             | 24–39           | Mean              |
| Range                            |                  | Range             |
interest (ROI) was defined that included the upper extremities from the armpit and distally. This region corresponded to the region measured by PG, and is the same region that is generally included when liposuction is performed on the arm.

All PG measurements were performed by two investigators, a physiotherapist (GO) and an occupational therapist (KO). DXA was performed according to the manufacturer’s recommendations. A single technician performed all the

FIG. 1. Regression analysis of the mean total volume of the lymphedematous arms as measured by plethysmography (PG) and by dual-energy X-ray absorptiometry (DXA). \[ \beta = 1.015 \text{ (95\% CI: 0.970–1.061), } r = 0.996, p < 0.0001 \].

FIG. 2. Regression analysis of the mean excess arm volume as measured by plethysmography (PG) and by dual-energy X-ray absorptiometry (DXA) \[ \beta = 0.884 \text{ (95\% CI: 0.814–0.955), } r = 0.988, p < 0.0001 \].
measurements, and a single researcher (HB) conducted the software analyses. During the study period, daily calibration of the PG machine was performed using the Lunar phantom.

Statistics

Data are presented as mean and range or mean and standard deviation (SD). The Student’s *t*-test was used to compare the values for the lymphedematous and the normal arm of each patient. Linear regression analysis was performed to obtain the coefficient of correlation (*r*) and the coefficient of regression (*β*) with a 95% confidence interval (95% CI); the constant was set to zero when volumes were analyzed. A *p* value of < 0.05 was considered statistically significant.

Ethics

The study was approved by the Ethics of Human Investigation Committee at Lund University, Sweden, and by the Radiation Protection Committee of Malmö University Hospital, Sweden. Written informed consent was obtained from the patients. The study was performed in accordance with the principles set forth in the Helsinki declaration.

Results

The total mean volume of the lymphedematous arms was estimated by DXA to be 3873 ml (range, 2809–5802) and by PG to be 3962 ml (range, 2780–2780). There was a high correlation between the methods [*β* =1.015 (95% CI: 0.970–1.061), *r* = 0.996, *p* < 0.0001] (Fig. 1).

The mean excess arm volume of the lymphedematous arms was estimated by DXA to be 1422 ml (range, 735–2603) and by PG to be 1275 ml (range, 620–1920). This corresponds to a mean increase of 58% (range, 30–83) as measured by DXA and 47% (range, 29–66) as measured by PG. There was a high correlation between the methods when estimating the excess arm volume [*β* = 0.884 (95% CI: 0.814–0.955); *r* = 0.988, *p* < 0.0001] (Fig. 2, Table 2).

DXA analysis of the specific tissues showed that there was 73% (range, 43–111) greater volume due to fat, 47% (range, 13–81) greater volume due to muscle, and 7% (range, −12–32) more bone volume in the lymphedematous arm compared to the healthy arm (Fig. 3).

The excess volume in the lymphedematous arm comprised 55% fat (range, 32–81), 45% muscle (range, 18–68), and 0.2% bone (range, −0.4–1.1) (Fig. 4).

### Table 2. Dual-Energy X-Ray Absorptiometry (DXA) Estimation of Total Arm Volume and Volume of Fat, Muscle, and Bone in Lymphedematous and Normal Arms of 18 Women with Unilateral Nonpitting Arm Lymphedema

<table>
<thead>
<tr>
<th>Volumes</th>
<th>Normal arm (ml)</th>
<th>Swollen arm (ml)</th>
<th>Excess volume (ml)</th>
<th>Increased volume in the diseased arm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>1040 (632–1452)</td>
<td>1810 (1090–2998)</td>
<td>770 (421–1579)</td>
<td>73 (43–111)</td>
</tr>
<tr>
<td>Muscle</td>
<td>1377 (1054–2108)</td>
<td>2027 (1551–3236)</td>
<td>650 (186–1127)</td>
<td>47 (13–81)</td>
</tr>
<tr>
<td>Bone</td>
<td>35 (24–43)</td>
<td>37 (28–51)</td>
<td>2 (-4–11)</td>
<td>7 (-12–32)</td>
</tr>
</tbody>
</table>

Table 2. DXA was performed on 18 women with unilateral nonpitting arm lymphedema. Data is given as mean (range).

FIG. 3. The mean (SD) volume of the arm and of fat, lean body mass (muscle), and bone in the lymphedematous (Lymph) and healthy arms (Normal) as estimated by dual-energy X-ray absorptiometry (DXA).
The duration of the lymphedema did not correlate with the excess volume of the arm as measured by PG \(\beta = -10.1\) (95% CI: −33.5–13.3); \(r = 0.222, p < 0.375\) or by DXA \(\beta = -12.5\) (95% CI: −39.1–14.0); \(r = 0.242, p < 0.333\). There was also no correlation between the duration of the lymphedema and the DXA-estimated excess in terms of fat volume \(\beta = -6.08\) (95% CI: −24.1–11.9); \(r = 0.176, p < 0.485\) (Fig. 5), muscle volume \(\beta = -6.27\) (95% CI: −22.0–9.46); \(r = 0.207, p < 0.410\) (Fig. 6) or bone volume \(\beta = -0.172\) (95% CI: −0.358–0.014); \(r = 0.440, p < 0.067\)

There was a significant correlation between the total excess volume of the lymphedematous arm and the excess muscle volume, both when total excess volume was estimated by PG \(\beta = 0.507\) (95% CI: 0.437–0.577); \(r = 0.966, p < 0.0001\) and by DXA \(\beta = 0.456\) (95% CI: 0.397–0.515); \(r = 0.970, p < 0.0001\). There was also a significant correlation between the total excess volume of the lymphede-

![FIG. 4.](image_url)

**FIG. 4.** The total mean (SD) excess arm volume and the proportion of fat, muscle, and bone as estimated by dual-energy X-ray absorptiometry (DXA). The percentage values indicate the increased volume in the lymphedematous arm compared to the unaffected arm.

![FIG. 5.](image_url)

**FIG. 5.** No correlation was found between the duration of the lymphedema and the excess fat in the lymphedematous arm as measured by DXA.
matous arm and the excess fat volume, both when total excess volume was estimated by PG ($\beta = 0.595$ (95% CI: 0.507–0.683); $r = 0.961, p < 0.0001$) and by DXA ($\beta = 0.542$ (95% CI: 0.484–0.601); $r = 0.979, p < 0.0001$). In addition, there was a significant correlation between the total excess volume of the lymphedematous arm and the excess bone volume, both when the total excess volume was estimated by PG ($\beta = 0.0017$ (95% CI: 0.0005–0.0030); $r = 0.572, p < 0.0001$) and by DXA ($\beta = 0.0004$ (95% CI: 0.0000–0.0008); $r = 0.419, p < 0.0001$).

**FIG. 6.** No correlation was found between the duration of the lymphedema and the excess muscle in the lymphedematous arm as measured by DXA.

**FIG. 7.** No correlation was found between the duration of the lymphedema and the excess bone in the lymphedematous arm as measured by DXA.
0.05] and by DXA [$\beta = 0.0016$ (95% CI: 0.0005–0.0027); $r = 0.593$, $p < 0.05$].

Conclusions

Clinical findings of hypertrophy of adipose tissue in a lymphedematous arm following breast cancer treatment has long been neglected.20,21 Previous reports in patients with nonpitting lymphedema treated with liposuction have indicated that, on average, the aspirate consisted of 68% to 93% fat, 32% interstitial fluid, and 7% lymph, depending on whether a tourniquet was used.8,22 A study using computed tomography reported excess of fat volume of 81%.22 This is similar to the 73% greater fat volume in the lymphedematous arm compared to the healthy arm that we found in this study.

This study was performed to evaluate whether DXA could be used to estimate the excess fat, muscle, and bone tissue in the diseased lymphedematous arm. The high correlation of DXA with the PG technique, usually regarded as the gold standard for arm volume measurements, suggests that DXA can be used to estimate the excess volume. However, the DXA measurements must first be transformed into volume values using known tissue densities. Compared to PG, which can only estimate volume, DXA measurements can also estimate the volumes of the various tissues in the arm. This could be of great clinical relevance in order to objectively evaluate different treatment strategies. Excess adipose tissue, for example, could also indicate a higher risk of treatment failure when using conservative treatment strategies; liposuction might be indicated in such a case. DXA measurements could also be used preoperatively to estimate the amount of excess adipose tissue that should be emoved by liposuction.

The DXA measurements also showed that the increased volume of lymphedematous arms was not only the result of excess adipose tissue. We also found that there was a substantially greater volume due to increased lean body mass (predominantly muscle) and, to some part, bone in the affected arm compared to the healthy arm. In addition, the increase in arm volume correlated with the excess volumes of all three compartments (i.e., fat, muscle, and bone). No other studies have reported increased amounts of muscle and bone tissue in a lymphedematous arm. One hypothesis that could explain this is that the greater weight of the affected arm leads to a higher mechanical load on both the muscle and the skeleton, resulting in increased muscle and bone mass.23–25 It is also interesting to note that in individuals with lymphedema for 2–38 years (Table 1), there was no correlation between the duration of lymphedema and the amount of excess adipose (Fig. 5), muscle (Fig. 6), or bone tissue (Fig. 7). This indicates that the increase in soft tissue volume develops when the lymphedema appears or soon thereafter.

Most of the increased soft tissue volume in the affected arm was due to increased fat. This explains the clinical finding that liposuction can be used to effectively treat longstanding nonpitting arm edema. Furthermore, DXA seems to be an excellent method for preoperatively evaluating the amount of fat tissue to remove during liposuction. Future prospective studies are needed to evaluate whether the preoperative DXA estimation of excess fat volume correlates with the amount of fat actually removed during surgery.

In summary, this study indicates that the excess volume in breast cancer-related chronic arm lymphedema is due to both excess fat and muscle tissue. The excess soft tissue can develop either when the lymphedema becomes clinically significant or can occur within a year or two. The DXA technique can be used to objectively monitor soft tissue increases and may identify individuals who have a poor prognosis with conservative treatment. DXA may also be used to estimate the amount of fat that should be removed in patients subjected to liposuction.

Acknowledgments

The authors thank Jan-Åke Nilsson, statistician at the Clinical and Molecular Osteoporosis Research Unit, Department of Orthopaedics, Malmö University Hospital, who supervised the statistical analyses.

Disclosure Statement

No competing financial interests exist.

References


Address reprint requests to:
Håkan Brorson, M.D., Ph.D.,
Department of Plastic and Reconstructive Surgery
Lund University
Malmö University Hospital
SE-205 02 Malmö, Sweden
E-mail: hakan.brorson@med.lu.se