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The significance of reducing upper limb fat content in improving breast cancer-related upper limb lymphedema

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ABSTRACT

Problem considered: To investigate the potential association between reducing upper limb body fat content through nutritional guidance and breast cancer-related upper limb lymphedema improvement.
Methods: A retrospective study was carried out on patients with breast cancer-related upper limb lymphedema who underwent nutritional guidance from June 2016 to December 2018, aiming to explore the potential correlation between alterations in body fat mass and the improvement of lymphedema.
Results: Following nutritional guidance, patients exhibited a significant reduction in both body mass index (BMI) and total body fat mass ($p < 0.05$). Although there was no significant change in the circumference of the affected forearm, the extracellular water ratio demonstrated a non-significant declining trend. Exploratory analysis indicated that the group with relatively notable lymphedema improvement experienced a more pronounced reduction in body fat mass on the healthy side ($p = 0.049$), and a positive correlation was observed between changes in body fat mass on the healthy side and the improvement of lymphedema on the affected side ($p = 0.013$). However, these subgroup analyses are data-driven and exploratory, and their findings should be interpreted with caution due to the risks of multiplicity and false-positive results; they require validation in prospective studies.
Conclusion: Weight reduction through nutritional guidance may be associated with alleviation of lymphedema, particularly as the reduction in body fat mass on the healthy side appeared to correlate with lymphedema improvement in exploratory analyses. In addition to routine lymphedema evaluation, measuring body fat mass on the healthy side could be explored as a supplementary indicator for assessing the effectiveness of nutritional guidance in future studies.

Breast cancer can be effectively managed through a combination of treatment modalities, including surgery, chemotherapy, and radiotherapy. Nevertheless, some patients may develop upper limb lymphedema as a complication following these treatments. Lymphedema is a sequelae resulting from factors such as axillary lymph node dissection, radiotherapy, or the administration of docetaxel. It manifests as the accumulation of protein-rich interstitial fluid that fails to be reabsorbed by the lymphatic vessels.[1] Once this condition arises, it tends to progress chronically and is challenging to cure, posing a significant challenge for breast cancer survivors. Mild lymphedema has a relatively minor impact on daily life. However, compared to unaffected individuals, patients with lymphedema endure greater physical discomfort due to limb swelling and mental distress, such as depression, leading to a decline in their quality of life (QOL).[2,3] Hence, it is crucial to prevent the onset of lymphedema and to prevent its exacerbation post-diagnosis. Research indicates that obesity is a risk factor for breast cancer-related upper limb lymphedema.[4,5] Previous reports have suggested an association between weight reduction and edema symptom improvement.[6,7] In light of this, since 2016, our hospital's clinical dietitians have been part of the multidisciplinary lymphedema care team, offering specialized nutritional guidance to patients with lymphedema.

At present, there have been no reports regarding the involvement of nutrition managers in the care of patients with lymphedema. Moreover, the correlation between edema and changes in body fat remains ambiguous. Based on this, this study investigates the potential correlation between alterations in body fat and improvements in edema among patients with breast cancer-related upper limb lymphedema who undergo weight-loss nutritional guidance.

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1. Materials and methods

1.1. Research subjects

This study performed a retrospective investigation on patients with breast cancer-related upper limb lymphedema who sought treatment at the Breast Diagnosis and Treatment Center of the *** Hospital of *** Medical University between June 2016 and December 2018, and who received nutritional guidance for weight loss due to a Body Mass Index (BMI) of $\geq$25 kg/m^2 or a body fat percentage of $\geq$28%. The exclusion criteria were as follows: patients initially diagnosed at stage I or below according to the International Society of Lymphology staging system (Table 1); patients who received surgical treatment for lymphedema during the observation period; patients who developed cellulitis; **patients receiving treatment for other cancers during the nutritional guidance/observation period**; **patients receiving docetaxel during the nutritional guidance/observation period**; **patients receiving postoperative radiotherapy during the nutritional guidance/observation period**; and patients for whom the necessary clinical information for analysis could not be obtained. **Concurrent endocrine (hormonal) therapy was permitted.**

1.2. Method

1.2.1. Nutritional guidance

Based on authoritative guidelines related to the diagnosis and treatment of obesity, the target energy intake (in kilocalories, kcal) is set at 25–27 kcal per kilogram of standard body weight. The weight loss target is set at a 3% decrease in body weight within 6 months. Guidance includes using the 24-h recall method to investigate dietary intake, informing patients of the target energy intake, providing nutritional guidance based on the behavioral change model, setting goals, investigating physical activity levels, and confirming body composition.

1.2.2. Assessment of lymphedema

The improvement of edema was assessed by evaluating the circumferential change at a point 5 cm below the elbow fossa joint of the affected forearm after 6 months of nutritional guidance implementation. For exploratory analysis, the 25th percentile of circumferential change was used as a cutoff to categorize patients into two groups: those with relatively good improvement and those with relatively poor improvement. This classification is data-driven and should be interpreted as exploratory.

1.2.3. Investigation and measurement items

Treatment history (surgical method, axillary lymph node dissection, radiotherapy, hormone therapy, docetaxel treatment), clinical presentation (age, gender, recurrence status, height, weight, BMI, body fat mass, body fat percentage, extracellular water ratio, circumference of the affected forearm), lymphedema treatment-related information (disease stage, frequency of visits to the lymphedema care clinic, number of nutritional guidance sessions, time from onset of lymphedema to the start of nutritional guidance, time from onset of lymphedema to the first visit to the lymphedema care clinic). Disease stage is assessed at the initial consultation. Body composition is measured using the InBody720 (Biospace).

Table 1
Disease staging classification by the international lymphatic society: Guidelines for the diagnosis and treatment of lymphedema (2020 Edition)[8].

Disease stage	Symptoms during disease stage
Phase 0	Impaired lymphatic transport without overt potential for edema or asymptomatic morbidities
Phase I	Early-stage swelling with high protein content in interstitial fluid; improves with elevation
Phase II	Swelling persists despite elevation; pitting edema present, progressing to fibrosis
Phase III	Elephantiasis with skin changes and fat deposition; non-pitting

1.3. Statistical analysis

We utilized the Wilcoxon signed-rank test to investigate the alterations in clinical manifestations (including the circumference of the affected forearm, extracellular water ratio, body weight, BMI, body fat percentage, and body fat mass) after six months of implementing weight loss nutritional guidance. The Mann-Whitney *U* test was applied to compare the disparities between the good and poor edema reduction groups concerning lymphedema treatment aspects (such as the number of medical visits, frequency of nutritional guidance sessions, and body weight at the initiation of nutritional guidance) as well as clinical manifestations (including age, circumference of the affected forearm, extracellular water ratio, body weight, BMI, body fat percentage, and body fat mass). Similarly, the Mann-Whitney *U* test was employed to compare the variations in the circumference of the affected forearm between the group experiencing a reduction in body fat on the affected side and the group without such a reduction. Meanwhile, Spearman's rank correlation coefficient was used to assess the correlation between changes in body fat mass on both the affected and unaffected sides and alterations in the circumference of the affected forearm. Data processing was performed using SPSS 19.0 software, with statistical significance defined as $p < 0.05$. This study has received approval from the Ethics Committee of *** Hospital of *** University (IRB number: ***).

2. Results

2.1. Enrolled population

During the specified period, a total of 60 patients received nutritional guidance. Exclusions comprised 7 patients with disease stages below Stage I, 8 patients undergoing surgical treatment for lymphedema during this timeframe, 4 patients with cellulitis, 4 patients **receiving treatment for other cancers during the nutritional guidance period**, and 10 patients with incomplete clinical data, leaving 27 patients as the final cohort. **No patients were receiving docetaxel or radiotherapy at the time of or during the nutritional guidance period.** Among them, 3 patients (11%) exhibited signs of recurrence; however, their general condition remained stable, and they were deemed suitable by physicians for weight-loss nutritional guidance. Potential edema-inducing treatments **with a history prior to study inclusion** included: axillary lymph node dissection in 26 patients (96%), **a history of** radiotherapy in 19 patients (71%), and **prior** docetaxel treatment in 13 patients (48%). **Regarding hormonal therapy, as of the start of nutritional guidance, 4 patients (15%) had no treatment history, 17 patients (63%) were receiving ongoing treatment, and 6 patients (22%) had completed treatment.**

2.2. Alterations in upper limb edema before and after nutritional guidance

The median (range) of nutritional guidance sessions was 3 (2–5) (Table 2). Following the implementation of nutritional guidance, significant reductions were observed in the subjects' body weight, BMI, and total body fat mass. Although the circumference of the affected forearm, used as an indicator for edema improvement, did not show significant changes, the extracellular fluid ratio on the affected side demonstrated a non-significant decreasing trend. Twelve patients (44%) successfully reached their weight loss goals (Table 3). For exploratory purposes, the 25th percentile change in the circumference of the affected forearm was −0.6 cm, which was used as a threshold to classify patients into a well-improved group (n = 8) and a poorly-improved group (n = 19) (Fig. 1). A comparative analysis between the two groups revealed notable differences in body weight, attainment of weight loss goals (75% vs. 31%,

Table 2
Clinical and pathological conditions of patients.

Factors	Number of cases (n = 27)
Gender (Female)	27 (100%)
Age (years)	59 (41–81)
Recurrence (none/yes)	24/3 (89%/11%)
Surgical approach (total mastectomy/breast-conserving)	23/4 (85%/15%)
Axillary lymph node dissection (no/yes)	1/26 (4%/96%)
Lymphedema stage (stage IIa/IIb/III)	25/2/0 (93%/7%/0%)
Number of visits to the lymphatic care room	3 (2–16)
Nutrition guidance (frequency)	3 (2–5)
Time from lymphedema onset to nutritional guidance (months)	12 (0.5–215)
History of radiotherapy (none/past history)	**8/19 (30%/70%)**
Hormonal therapy history (none/ongoing/completed)	4/17/6 (15%/63%/22%)
History of docetaxel treatment (none/past history)	**14/13 (52%/48%)**

Table 3
Comparison of body measurements before and after 6 months of nutritional guidance: median (range).

Factor	Before guidance	After 6 months	P value
Circumference of affected forearm (cm)	27 (22.2–33)	26.6 (22.3–35)	0.549
Extracellular water ratio			
total body	0.390 (0.379–0.406)	0.390 (0.380–0.405)	0.339
unaffected side	0.383 (0.374–0.390)	0.381 (0.375–0.390)	0.229
affected side	0.390 (0.378–0.421)	0.388 (0.372–0.422)	0.211
Weight (kg)	69.5 (55–103.9)	65.2 (52.7–93.6)	0.001*
BMI (kg/m^2)	28.5 (23.4–43.2)	27.6 (23.5–38.9)	<0.001*
Body fat percentage (%)	38 (22.9–50.7)	37 (27.1–48.6)	0.339
Body fat mass (kg)			
whole body	25.5 (15.1–52.7)	23.8 (15.8–45.5)	0.016*
unaffected side	1.9 (0.9–5.6)	1.7 (0.9–4.3)	0.1
affected side	1.8 (0.9–5.6)	1.7 (1.0–4.3)	0.199

Note: Wilcoxon signed-rank test.

P = 0.035), and changes in body fat mass on the unaffected side (−0.20 kg vs. −0.01 kg, p = 0.049). The extracellular fluid ratio on the affected side, BMI, body fat percentage, body fat mass, and reduction rate of body fat mass on the affected side exhibited a more pronounced but non-significant trend of change in the well-improved group. Furthermore, no significant differences were found between the two groups in terms of the number of visits to the lymphatic care room and the frequency of nutritional guidance sessions (Table 4).

2.3. Correlation between changes in body fat mass and forearm circumference

With the cutoff value set at 0, a comparison was made between the groups with and without changes in body fat mass on the affected side regarding the variations in forearm circumference on the affected side. No significant difference was observed (Table 5). Although there was no significant correlation between changes in body fat mass on the affected side and changes in forearm circumference on the affected side (p = 0.054), a correlation was observed between changes in body fat mass on the unaffected side and changes in forearm circumference on the affected side (p = 0.013) (Fig. 2).

3. Discussion

Through a retrospective analysis, this study found that nutritional guidance was associated with significant reduction in BMI and total body fat mass in patients with breast cancer-related upper limb lymphedema. It is particularly noteworthy that the reduction of body fat mass on the unaffected side correlated with the improvement of lymphedema on the affected side in our exploratory analysis. This observational finding supports further investigation into the role of weight management in lymphedema treatment and suggests a potential direction for future research regarding auxiliary assessment approaches.

Obesity has been confirmed by multiple studies as one of the important risk factors for breast cancer-related lymphedema. The mechanisms may include mechanical compression of lymphatic vessels by adipose tissue, hindering lymphatic return, and inflammatory factors secreted by adipocytes exacerbating local inflammation and fibrosis processes [9–12]. In this study, although there was no significant change in local body fat mass on the affected side, the reduction of systemic and

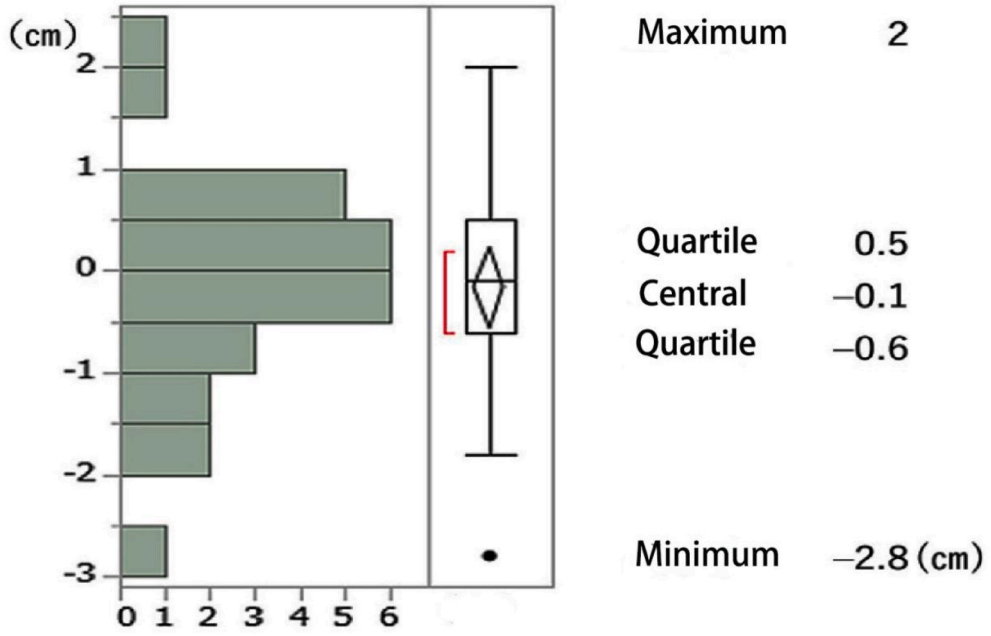

Fig. 1. Changes in circumference of the affected forearm.. *(Interpretation should note the exploratory nature of the threshold and that overall group change was not statistically significant.)*

Table 4
Comparison between groups classified by exploratory improvement threshold (median (range)).

Factors	Well-improved (n = 8)	Poorly-improved (n = 19)	P value
Age (years)	56 (41–81)	61 (45–77)	0.873
Lymphedema stage (IIa/IIb/III)	7/1/0	18/1/0	0.529
Number of visits to lymphatic care room	4 (2–12)	3 (2–16)	0.782
Time from onset to nutritional guidance (months)	14 (2–77)	10.8 (0.5–215)	0.252
Nutritional guidance (frequency)	3 (3–5)	4 (2–5)	0.31
Weight at baseline (kg)	68.7 (55–103.9)	69.5 (62.7–74.6)	0.915
BMI at baseline (kg/m^2)	28.4 (23.4–43.2)	28.7 (25.2–31.4)	0.831
Δ Circumference of affected forearm (cm)	−1.25 (−2.8 to −0.6)	0.2 (−0.4 to 2)	0.001*
Δ Extracellular water ratio			
total body	0 (−0.007 to 0.005)	−0.001 (−0.005 to 0.009)	0.893
unaffected side	−0.002 (−0.009 to 0.01)	0 (−0.008 to 0.006)	0.915
affected side	−0.003 (−0.02 to 0.004)	0 (−0.011 to 0.01)	0.092
Δ Weight (kg)	−3.6 (−14.6 to 0.2)	−1.6 (−10.9 to 5.1)	0.043*
Δ Weight (%)	−5.5 (−18.3 to 0.3)	−2.2 (−14.8 to 6.9)	0.046*
Achieved −3% weight loss (yes/no)	6/2	6/13	0.035*
Δ BMI (kg/m^2)	−1.5 (−6.2 to 0.2)	−0.6 (−4.4 to 1.9)	0.062
Δ Body fat percentage (%)	−1.9 (−8.5 to 2.6)	0.1 (−10.3 to 11.1)	0.094
Δ Body fat mass (kg)			
whole body	−2.5 (−11.6 to 0.6)	−0.7 (−10.7 to 5.9)	0.084
unaffected side	−0.2 (−1.35 to 0.19)	−0.01 (−0.96 to 0.57)	0.049*
affected side	−0.11 (−1.31 to 0.13)	−0.04 (−1.17 to 0.61)	0.242

Note: Δ denotes change from baseline. Mann-Whitney *U* test and chi-square test.

Table 5
Comparison of changes in body fat mass and forearm circumference on the affected side, median (range).

Factors	Fat loss group (n = 16)	Fat retention group (n = 11)	P value
Δ Circumference of affected forearm (cm)	−0.2 (−2.8 to 1.6)	0.1 (−1.8 to 2.0)	0.400

contralateral body fat was accompanied by improvement in edema severity in the exploratory subgroup, suggesting a potential link between systemic weight loss and enhanced lymphatic function that warrants further study. The lack of significant change in local body fat mass on the affected side may be due to fibrosis of adipose tissue as the disease progresses and duration extends,[1] which could limit the responsiveness to weight loss interventions. The duration from the onset of edema to the commencement of nutritional guidance for the target patients in this study ranged from 0.5 to 215 months, and some patients may have progressed to late stage II or stage III during the period from initial diagnosis to the commencement of nutritional guidance.

It is noteworthy that the exploratorily defined group with good improvement in edema showed a more pronounced reduction in body fat on the unaffected side ($p = 0.049$), and there was a significant correlation between changes in body fat on the unaffected side and changes in circumference on the affected side ($p = 0.013$). However, these findings originate from exploratory, data-driven subgroup analyses and carry risks of multiplicity and false-positive results; they must be validated prospectively. This finding suggests that changes in body fat on the unaffected side might reflect systemic metabolic changes influencing lymphedema, especially when local tissue on the affected side has undergone fibrosis. However, this interpretation is preliminary and requires validation.

Compared with the study by Shaw et al. in the UK,[6] the average BMI of the subjects in this study was lower, suggesting that even patients with mild to moderate obesity might potentially experience edema improvement with weight reduction. However, due to the small sample size in this study and the significant variation in the duration of edema among patients (0.5–215 months), some patients may have progressed to later stages, with irreversible local tissue changes, which may explain the lack of significant correlation between changes in body fat mass on the affected side and edema improvement.

Importantly, the clinical relevance of the observed circumferential changes (−0.6 cm threshold) must be interpreted cautiously, as the overall cohort did not show a statistically significant reduction in forearm circumference, and changes in extracellular water were not significant. Whether these modest changes translate into meaningful improvements in symptoms, function, or quality of life remains unclear and warrants further study.

Furthermore, the considerable heterogeneity in time since lymphedema onset, disease stage, and treatment history among participants must be acknowledged. The retrospective design and lack of multivariable adjustment limit the ability to control for potential confounding factors. Thus, the observed associations should be considered exploratory and hypothesis-generating.

From a clinical practice perspective, this study supports the notion of further integration of nutritional guidance into the multidisciplinary

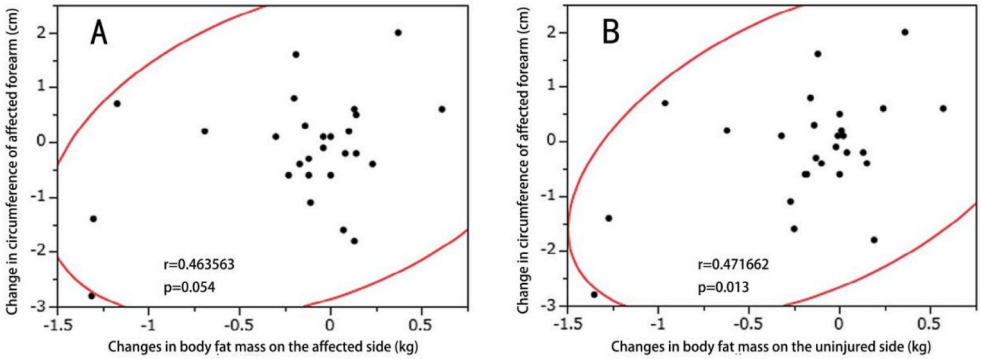

Fig. 2. Correlation between changes in circumference of the affected forearm and changes in body fat mass.. (Interpretation should be cautious given the exploratory nature of the subgroup analyses, the risk of false-positive findings from multiple comparisons, and the lack of a statistically significant overall effect on forearm circumference.)

management of lymphedema, particularly for overweight patients, which could be explored in future trials. Early weight management might potentially help prevent or delay lymphedema progression. Our hospital has established a resident nutritionist system and is developing perioperative nutritional management pathways, which may enhance supportive care for breast cancer survivors.

In summary, this pilot observational study suggests that weight reduction through nutritional guidance may be associated with improvement in breast cancer-related upper limb lymphedema, with reductions in body fat mass on the unaffected side potentially correlating with edema improvement in exploratory analyses. These subgroup findings are hypothesis-generating and require confirmation. These findings should be interpreted cautiously due to the small sample size, retrospective design, exploratory nature of key analyses, and lack of clinical outcome validation. Future multi-center prospective studies are needed to confirm these associations, define clinically meaningful outcomes, and establish optimal weight management strategies for different lymphedema stages.

4. Conclusion

In summary, this retrospective study observed an association between weight reduction through nutritional guidance and improvement in breast cancer-related upper limb lymphedema, particularly with respect to reductions in body fat mass on the unaffected side in exploratory analyses. The subgroup findings based on a data-driven improvement threshold are preliminary and require prospective validation to mitigate risks of false discovery. Measurement of body fat mass on the unaffected side may be considered for exploration as an auxiliary indicator in clinical assessment in future research. Individualized nutritional strategies should consider disease duration and stage, while further research is needed to establish causal relationships and clinical utility.

Consent to participate

Written informed consent was obtained from the patient for publication.

Ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was waived by the Institutional Review Board of the First Affiliated Hospital of Gannan Medical University.

Ethical approval statement

This study was conducted in accordance with the principles of the Helsinki Declaration. This experiment has been approved by the Ethics Committee of the First Affiliated Hospital of Gannan Medical University (Ethics Number: GYYFY201600212).

Author contributions

All authors contributed substantially to the manuscript's development, including conceptualization, writing, and editing. Conceptualization and design: Zhi-yong Liu, Ran Chen; part of the treating team and data collection and data analysis: Zhi-yong Liu, Ran Chen; revision of the manuscript drafts: Zhi-yong Liu, Ran Chen. The submitted version of the manuscript has been approved by all authors, who have also agreed to take responsibility for any aspect of the work.

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Data availability

The data supporting the findings of this study are available within the article. Further details can be provided by the corresponding author upon reasonable request.

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