

Disability and emotional symptoms in women with lipedema: A comparison with overweight/obese women

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2024

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Funding sources

This study was supported by Wrocław Medical University grant (No. SUB.C100.21.091). The funder accepted the study protocol and had no role in the collection, analysis, interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

Conflict of interest

None declared

Received on August 9, 2023

Reviewed on October 14, 2023

Accepted on January 13, 2024

Published online on February 13, 2024

Cite as

Chachaj A, Jeziorek M, Dudka I, et al. Disability and emotional symptoms in women with lipedema: A comparison with overweight/obese women [published online as ahead of print on February 13, 2024]. *Adv Clin Exp Med*. 2024. doi:10.17219/acem/181146

DOI

10.17219/acem/181146

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Abstract

Background. Lipedema is characterized by the painful abnormal deposition of adipose tissue in the lower limbs and is often misdiagnosed as obesity. Considering the numerous bothersome physical symptoms of lipedema, women with lipedema may have greater disability and emotional problems than women with lifestyle-induced obesity.

Objectives. Our study aims to assess disability, anxiety and depression symptoms in women with lipedema compared to women with overweight/obesity.

Materials and methods. Women with lipedema (n = 45, with a mean age of 41 years) and women who are overweight/obese (n = 43, with a mean age of 44.95 years) were asked to complete the following questionnaires: The World Health Organization Disability Assessment Schedule (WHO-DAS II), Beck's Depression Inventory – II (BDI-II), and The Hospital Anxiety and Depression Scale (HADS).

Results. Despite the higher BMI in the overweight/obesity group, the group with lipedema was more disabled in numerous domains of the WHO-DAS II questionnaire, including Life activities – domestic, work and school responsibilities and Participation in society. When the influence of BMI was adjusted, a difference in the domain of Mobility was also present. The study groups did not differ in anxiety and depression symptoms.

Conclusions. We showed that behavioral impairment was the main factor affecting functioning in women with lipedema. Emotional symptoms did not differentiate the study groups. Leg volumes and adipose tissue pain intensity were associated with greater disability in women with lipedema, and should be considered in managing women with this condition and in future research estimating the effectiveness of lipedema treatment.

Key words: lipedema, obesity, disability, depression, adipose tissue

Background

Lipedema is a chronic and progressive condition that gradually leads to a disproportionate body. It occurs almost exclusively in women and is characterized by the painful abnormal deposition of adipose tissue in the lower extremities and, in $\frac{1}{3}$ of cases, also within the arms. The term “lipedema” was initially coined by Hines and Allen in 1940.¹ Women with lipedema typically have characteristic bilateral and symmetrical “column” legs with sparing of the feet with a cuff sign at the ankle and masses of nodular fat within the adipose tissue in later stages of the disease. In most cases, lipedema is accompanied by pressure-induced or spontaneous pain in the affected areas of adipose tissue and a tendency for easy bruising.^{2–4}

The incidence of lipedema was estimated at 11%.^{2,5} There are no known biomarkers for diagnosing lipedema. Therefore, the recognition of lipedema is clinical and based on established criteria.^{5,6}

The etiology of lipedema is not well understood. The onset of lipedema is usually during hormonal changes, such as puberty, pregnancy or menopause. This suggests a link with female sex hormone fluctuations.⁷ Genetic inheritance is also possible.^{2,5} Women with lipedema often have first-line women relatives with lipedema.⁸

Histological examination of adipose tissue demonstrated that lipedema results from both adipocyte hypertrophy and hyperplasia.⁹ Excessive accumulation of adipose cells probably leads to hypoxia, resulting in adipocyte necrosis and macrophage recruitment.¹⁰ Moreover, adipose tissue in lipedema compared to control was demonstrated to be associated with greater fibrosis,^{9,11} inflammation, angiogenesis, and microangiopathy.¹²

Lipedema is a relatively common disease, but is still underrecognized and often misdiagnosed by clinicians as lifestyle-induced obesity.¹³ As a result, patients are recommended to follow a low-calorie diet and increase physical activity.¹⁴ However, this treatment generally has little to no effect on leg volumes.¹¹ Even bariatric surgery does not significantly decrease the areas affected by lipedema despite weight reduction.¹⁵ The lack of a diagnosis can make the patients feel helpless.¹⁶ This contributes in a very significant way to the deterioration of the mental state of patients and to further psychological consequences, such as self-esteem issues, anorexia nervosa, bulimia, depression, self-harm, and suicidal thoughts.^{13,14,16,17} The chronic pain of adipose tissue, easy bruising, and complications or comorbidities of lipedema such as obesity, secondary lymphedema (lipolymphedema), joint degeneration and, in extreme cases, mobility difficulties may also affect the mental state of the patient. According to the findings of the study conducted by Erbacher and Bertsch in a 150-person group of women with lipedema, 36.7% presented at least 1 symptom of psychological disorder, with depression and anxiety in 26% and 3.3% of patients, respectively.¹⁸ The incidence of depression in women with

lipedema in other studies was estimated to be 31–59%.^{19,20} Each of these aspects contributes to a poor quality of life (QoL) in patients with lipedema, as was demonstrated in numerous studies.^{19,21–23} Moreover, depressive and anxiety symptoms often coexist, resulting in more severe impairment.²⁴

In light of recent findings, there might be a biochemical connection between neural and endocrine mechanisms associated with the adipose tissue and emotional state of women with lipedema. The adipose tissue is rich in nociceptive neurons,²⁵ and it was indicated that chronic pain may result in changes in brain activity involved in emotional regulation.^{26,27} Chronic pain as a repeating negative stimulus on the central nervous system may also lead to the generation of neurovisceral hyperactivity.²⁸ It was also demonstrated that adipose tissue is an active endocrine organ capable of producing various signaling molecules, including cytokines and proinflammatory hormones – the adipokines, such as leptin, tumor necrosis factor alpha (TNF- α), interleukin (IL)-6, resistin, and visfatin, in addition to many others.²⁹ These molecules can have an effect both locally and throughout the body, with a potentially wide range of impact.²⁹ Considering that depression and anxiety can be caused by neural mechanisms associated with signaling molecules,³⁰ adipose tissue potentially might directly impact a person’s emotional state. Interestingly, neuroimaging and brain stimulation represent a promising new approach to diagnosing and individualizing the treatment of emotional disorders in the future.³¹ A recently published study on mice revealed that essential oils could benefit neuroprotection and decrease depressive symptoms.³² So far, no studies have evaluated the use of essential oils in treating lipedema. However, it should be noted that the low-carbohydrate high-fat diet (LCHF), which is rich in vegetable oils, has been shown to not only decrease leg volume in lipedema but also alleviate pain in adipose tissue.^{33,34} Therefore, the addition of further essential oils may enhance the effects of the LCHF diet. Searching for new methods of treating lipedema is especially desirable since there is no cure for this entity.

Lipedema management is still symptom-based and aims to reduce patient discomfort, disability and disease progression.¹¹ Treatment includes a conservative approach and surgical interventions. The conservative treatment consists of a diet, especially a LCHF diet,^{33,34} physical activity, complex decongestive therapy, and intermittent pneumatic compression.^{11,35–37} Surgical treatment involves the removal of excess fatty tissue through liposuction.^{38,39}

The co-occurrence of lipedema and obesity and the influence of one on the deterioration of the other has long been known.⁴⁰ Increased body weight is also associated with disability, depression and reduced QoL.^{41–43} However, to our knowledge, no study has compared a woman’s physical and emotional status with lipedema to those with lifestyle-induced obesity.

Objectives

Our study was designed to assess the differences in disability, anxiety and depression symptoms in women with lipedema compared to women with lifestyle-induced overweight/obesity. Considering the numerous bothersome physical symptoms of lipedema (above all, body disproportion and pain in the affected areas of adipose tissue), we hypothesized that women with lipedema may have a greater disability in many life areas and emotional problems compared to women with lifestyle-induced overweight/obesity.

Materials and methods

Study design

Our study was a part of the project in which we implemented the LCHF diet for 7 months in women with lipedema and women with lifestyle-induced overweight/obesity to assess the diet's laboratory and clinical (both physical and emotional) effects. Most of the project results are yet to be published, except for 1 study on the lymphoscintigraphic alterations in the lower limbs⁴⁴ and 1 paper on the impact of the LCHF diet on blood parameters.³⁴

In this study, women diagnosed with lipedema ($n = 45$, with a mean age of 41.00 ± 13.32 years) and women with lifestyle-induced overweight/obesity ($n = 43$, with a mean age of 44.95 ± 13.90 years) who agreed to complete self-administered questionnaires evaluating disability, anxiety and depression symptoms were included. The women in both study groups were recruited from January 2021 to May 2022, and each woman's participation in the study was voluntary. The woman's consent to use the LCHF diet was not an inclusion criterion for this study. The LCHF diet was not implemented by 11 women (24%) in the group with lipedema and by 13 women (30%) in the overweight/obese group. The questionnaires were completed before starting the LCHF diet.

Women with lipedema were the patients from the Outpatient Angiology Clinic. Lipedema was recognized in women by an angiologist, based on established clinical criteria of lipedema,¹ and was classified into 4 clinical stages and 5 types of disease.^{5,11,45}

The overweight/obese women were, in part, patients from the Outpatient Angiology Clinic, but the majority were volunteer employees of the hospital where the study was conducted.

The patients in both study groups were assessed in medical and demographical aspects and completed self-administered questionnaires. Women with lipedema were additionally asked about the intensity of pain within the lower legs on a graduated scale from 0 (no pain at all) to 10 (full of pain).²⁶

Ethical approval was provided by the Local Bioethical Committee (approval No. KB-690/2017). All women gave informed written consent before inclusion in the study, following the principles outlined in the Declaration of Helsinki.

Inclusion and exclusion criteria

Diagnosis of lipedema was stated according to the criteria established by Wold et al.¹ The minimal inclusion criteria to fulfill for the group with lipedema was a body disproportion, i.e., excessive accumulation of adipose tissue in the lower limbs compared to the upper body and the presence of at least 1 of 2 clinical symptoms: 1) pressure-induced or spontaneous pain of adipose tissue and 2) tendency for easily bruising.

The inclusion criterion for the overweight/obesity group was a body mass index (BMI) above 25 kg/m^2 . The exclusion criteria for both study groups were the presence of lymphedema, edema in the course of other diseases, such as chronic venous insufficiency, heart failure, chronic kidney disease and hepatic insufficiency, abnormal thyroid-stimulating hormone (TSH) level, diabetes, depression, neoplasms, pregnancy, a period of at least 6 months after pregnancy, and diagnosis of depression or anxiety in the past.

Questionnaires

The self-administered questionnaires listed below were used to assess disability, anxiety and depression symptoms in both study groups.

WHO-DAS II

The World Health Organization's Disability Assessment Scale II (WHO-DAS II) is a generic assessment instrument developed by the WHO to provide a standardized method for measuring health and disability.⁴⁶ Importantly for our study, the questionnaire provides a metric of the impact of any health condition in terms of disability related to many life areas and interactions between the person and the environment.⁴⁶

The WHO-DAS II questionnaire covers 6 disability domains: 1) Cognition - understanding and communicating (6 questions), 2) Mobility - moving and getting around (5 questions), 3) Self-care - attending to one's hygiene, dressing, eating and staying alone (4 questions), 4) Getting along - interacting with other people (5 questions), 5) Life activities - domestic, work and school responsibilities (8 questions), and 6) Participation-joining in community activities, participating in society (8 questions). In addition, the WHO-DAS II questionnaire includes a question about the subjective assessment of health (domain H1) and questions about the impact of disability on everyday activity (domains H2-H5). The questionnaire evaluates the last 30 days preceding the survey. The questionnaire can be self-administered or conducted by an interviewer. It comprises 36 items and uses a 5-point Likert scale for responses, ranging from "none" (0 points) to "extreme" (4 points).⁴⁶ The results of the domains were summed up and converted into a percentage value of disability for each domain separately, according to the formulas given below:

Domain 1 = (D1.1+D1.2+D1.3+D1.4+D1.5+D1.6)/24*100

Domain 2 = (D2.1+D2.2+D2.3+D2.4+D2.5)/20*100

Domain 3 = (D3.1+D3.2+D3.3+D3.4)/16*100

Domain 4 = (D4.1+D4.2+D4.3+D4.4+D4.5)/20*100

Domain 5.1 = (D5.1+D5.2+D5.3+D5.4)/16*100

Domain 5.2 = (D5.5+D5.6+D5.7+D5.8)/16*100

Domain 6 = (D6.1+D6.2+D6.3+D6.4+D6.5+D6.6+D6.7+D6.8)/32*100

The higher calculated scores indicate a more elevated level of disability in each domain. The questions H1 and H2 were calculated directly according to the 5-point Likert-type scale of answers, as written above (0–4 points for each question). The answers to the questions H3–H5 represented a given number of days and constituted a direct value in the calculations.

Beck Depression Inventory-II

Beck Depression Inventory-II (BDI-II) is one of the most widely used psychometric questionnaires designed to measure depression symptoms and their severity in persons aged ≥ 13 years.^{47,48} The questions are related to cognitive, somatic, affective, and vegetative symptoms of depression in the past 2 weeks. Each item has a set of 4 responses, ranging in intensity.^{47,48}

Beck Depression Inventory-II is a self-report and consists of 21 questions that must be answered on a scale from 0 (not at all) to 3 (very much). The number of points for all answers should be added, and the total score is used to determine the severity of depression symptoms.^{47,48}

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a questionnaire commonly used by doctors in a variety of settings, including primary care, hospital and psychiatry. It was designed to initially identify patients with anxious and depressive states who need further psychiatric evaluation.

The Hospital Anxiety and Depression Scale is a self-report questionnaire consisting of 14 items, divided into 2 subscales: HADS-A (anxiety) and HADS-D (depression), with a set of 4 responses for each question ranging from 0 (no impairment) to 3 (severe impairment). The questionnaire estimates the past week. The total score ranges from 0–21 for anxiety and 0–21 for depression, with a greater score indicating more severe symptoms. According to Pais-Ribeiro et al., the interpretation of scores 0–7 represents “normal”, 8–10 – “mild”, 11–14 – “moderate”, and 15–21 “severe” symptoms.⁴⁹ The HADS does not include somatic symptoms of emotional distress that may be caused by the illness itself.⁵⁰

Statistical analyses

Results are presented as mean values \pm standard deviations (M \pm SD) or median and quartiles Q1 and Q3 when the data distribution was normal or non-normal,

respectively. The conformity of the distribution in the given variable to the normal distribution was verified using the Shapiro–Wilk test and homogeneity of variances with Levene’s test (Supplementary Table 1). If the distribution was statistically significantly different from normal, a non-parametric Mann–Whitney U test was applied, otherwise – the student’s t-test. For categorical variables, Fisher’s exact test was used when the variable had only 2 categories and the χ^2 test when there were more categories for the variable. As the distribution of many variables differs from a normal one, a robust analysis of covariance (ANCOVA) test (using a function ‘rlm’ from the R-package “MASS”) was used to compare the results of WHO-DAS II, BDI-II and HADS questionnaires between the study groups adjusted for the influence of BMI. For the same reason, the relationships between variables from the questionnaires and leg volume and adipose tissue pain intensity (both defined as predictors) were analyzed using the ‘rlm’ function for each parameter from the questionnaire separately. As the ‘rlm’ is resistant to skewed data distribution and the presence of outliers, no assumptions were checked. Differences were considered statistically significant when $p < 0.05$.

All statistical analyses were performed using GraphPad Prism 9 for Windows (GraphPad Software, Inc., San Diego, USA), Statistica v. 13 (TIBCO Software Inc., Palo Alto, USA) and using the R-package “MASS” (Venables and Ripley 2002; Springer, New York, USA) in the R-environment 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Medical and demographic parameters

The basic medical and demographic characteristics of the study participants are presented in Table 1. The study groups did not differ statistically significantly in age. However, the overweight/obesity group had higher weight, BMI, waist circumferences, and waist-to-hip ratio (WHR).

Differences in the parameters from the questionnaires between the study groups

The WHO-DAS II questionnaire was filled in by all the study participants, which means that there were no missing data. The BDI-II questionnaire was not completed by 2 women from the lipedema group (4.4%) and 1 woman from the overweight/obesity group (2.3%). The HADS questionnaire was not filled in by 2 women from the overweight/obesity group (4.7%). The reason for not completing all the questionnaires by the study participants was probably a lack of time, absent-mindedness or fatigue with filling in many forms. The data were missing completely

Table 1. Medical and demographic characteristics of the study participants

Parameter		Lipedema group (n = 45)	Overweight/ obesity group (n = 43)	Statistics	
				Z/ χ^2 /t; df	p-value
Age [median (Q1, Q3)]		38.00 (31.50, 49.50)	45.00 (33.00, 54.00)	-1.56	0.120*
Number of years spent studying at school, college or university [median (Q1, Q3)]		17.00 (14.00, 19.00)	17.00 (14.00, 19.00)	-0.19	0.856*
Current marital status	single	15 (33.33%)	10 (23.26%)	5.50; 5.00	0.358**
	currently married	17 (37.77%)	21 (48.84%)		
	in separation	0	1 (2.33%)		
	divorced	4 (8.89%)	7 (16.28%)		
	widowed	4 (8.89%)	1 (2.22%)		
	cohabiting with a partner	5 (11.11%)	3 (6.98%)		
Current main work status	employed	25 (55.56%)	33 (73.33%)	9.37; 7.00	0.227**
	own business	4 (8.89%)	4 (8.89%)		
	voluntary work	2 (4.45%)	0		
	student	3 (6.67%)	2 (4.44%)		
	home maker	2 (4.45%)	0		
	retired	5 (11.11%)	4 (8.89%)		
	disabled	0	0		
	no occupation	1 (2.22%)	0		
	other	3 (6.67%)	0		
Height [cm], M \pm SD		166.28 \pm 7.32	165.5 \pm 6.15	0.51; 86.00	0.614***
Weight [kg], M \pm SD		84.08 \pm 16.73	94.57 \pm 16.39	2.97; 86.00	0.004***
BMI [kg/m ²], M \pm SD		30.53 \pm 6.24	34.41 \pm 5.05	3.19; 86.00	0.002***
Age at the onset of lipedema/obesity [median years (Q1, Q3)]		23.00 (15.00, 33.50)	28.00 (12.00, 39.00)	0.00	1.000*
Arterial hypertension, yes (%)		9 (20.0%)	11 (25.58%)	-	0.615****
Insulin resistance, yes (%)		11 (24.44%)	16 (37.21%)	-	0.249****
Hypothyroidism (compensated with supplementation, yes (%))		8 (17.78%)	10 (23.26%)	-	0.602****
BMI [kg/m ²]	normal	11 (24.44%)	0	14.38; 4.00	0.006**
	overweight	8 (17.78%)	10 (23.26%)		
	1 st class obesity	17 (37.78%)	15 (34.89%)		
	2 nd class obesity	5 (11.11%)	11 (25.58%)		
	3 rd class obesity	4 (8.89%)	7 (16.28%)		
	extreme obesity (>50 kg/m ²)	0	0		
Waist circumference [cm], M \pm SD		95.33 \pm 12.86	108.48 \pm 11.07	5.13; 86.00	<0.001***
Hip circumference [cm], M \pm SD		113.41 \pm 11.36	115.4 \pm 11.15	0.83; 86.00	0.411***
WHR (mean waist-to-hip ratio)		0.8403 \pm 0.08	0.9423 \pm 0.08	6.28; 86.00	<0.001***
Legs volume [median mL (Q1, Q3)]	right leg	12204 (10448, 14785)	11690 (9639, 13263)	-1.43	0.155*
	left leg	12541 (10613, 14725)	11742 (9767, 13054)	-1.77	0.078*
	mean volume of both legs	12428 (10492, 14806)	11735 (9486, 13315)	-1.55	0.123*
Stage of lipedema	I	22 (48.89%)	-	-	-
	II	21 (46.67%)	-	-	-
	III	2 (4.44%)	-	-	-
Type of lipedema	1 (buttocks)	0	-	-	-
	2 (buttocks, hips and thighs)	6 (13.33%)	-	-	-
	3 (from hips to ankles)	21 (46.67%)	-	-	-
	4 (arms and legs)	10 (22.22%)	-	-	-
	5 (calves)	0	-	-	-
Family history of lipedema, yes (%)		32 (71.11%)	-	-	-
Pain of adipose tissue (spontaneous or on pressure, yes (%))		41 (91.11%)	0	-	<0.001****
Intensity of pain of adipose tissue (from 1 (minimal pain) to 10 (maximal pain) M \pm SD		4.64 \pm 2.69	-	-	-
Easy bruising, yes (%)		44 (97.78%)	11 (24.44%)	-	<0.001****

Statistically significant results (p < 0.05) are in bold; *Mann–Whitney U test; ** χ^2 test; ***student's t-test; ****Fisher's exact test. M \pm SD – mean \pm standard deviation; Q1 – 1st quartile; Q3 – 3rd quartile.

at random and consequently did not affect the obtained results.

There were statistically significant differences between the lipedema group and the overweight/obesity group in the WHO-DAS II questionnaire regarding domain 5.1 (Life activities – domestic responsibilities, leisure), 5.2. (Life activities – work and school), 6 (Participation – joining in community activities, participating in society), H2 (the impact of difficulties DAS1–DAS6 on life), and H3 (number of days in the previous 30 days in which difficulties DAS1–DAS6 were present).

Since the groups differed regarding BMI, the calculations were done after adjusting the effect of BMI. With the BMI adjustment, the differences between the groups

in domain 2 (Mobility – moving and getting around), 5.1 (Life activities – domestic responsibilities, leisure), 6 (Participation – joining in community activities, participating in society), H2 (the impact of difficulties DAS1–DAS6 on life), and H3 (number of days in the previous 30 days in which difficulties DAS1–DAS6 were present) could be observed. The difference between the study groups in domain 5.2. (Life activities – work and school) after adjusting for the effect of BMI was close to statistical significance ($p = 0.071$; Robust ANCOVA test).

The study groups did not differ in anxiety and depression symptoms evaluated with the BDI-II and HADS questionnaires. Study group comparisons with the questionnaires used in the study are presented in Table 2.

Table 2. Study groups comparison with questionnaires WHO-DAS II, BDI-II and HADS

Scale		Lipedema group (n = 45)		Overweight/obesity group (n = 43)		Statistics		Statistics adjusted for the influence of BMI***	
		Me (Q1, Q3)/ M \pm SD	Std. err.	Me (Q1, Q3)/ M \pm SD	Std. err.	Z/t; df	p-value	Z	p-value
Domain 1	Cognition – understanding and communicating	12.50 (4.17, 25.00)	1.90	8.33 (0.00, 25.00)	2.29	-1.22	0.224*	1.48	0.139
Domain 2	Mobility – moving and getting around	15.00 (0.00, 32.50)	2.78	5.00 (0.00, 20.00)	2.64	-1.71	0.088*	2.58	0.010
Domain 3	Self-care – attending to one's hygiene, dressing, eating and staying alone	0.00 (0.00, 6.25)	1.39	0.00 (0.00, 6.25)	0.96	-0.04	0.969*	0.13	0.898
Domain 4	Getting along – interacting with other people	10.00 (5.00, 22.50)	2.28	0.00 (5.00, 20.00)	2.32	-1.66	0.097*	1.48	0.138
Domain 5.1	Life activities – domestic responsibilities	18.75 (0.00, 28.13)	3.34	0.00 (0.00, 18.75)	3.10	2.01	0.044*	2.54	0.011
Domain 5.2	Life activities – work and school	12.50 (0.00, 25.00)	3.42	0.00 (0.00, 18.75)	2.86	-1.99	0.047*	1.81	0.071
Domain 6	Participation in society – joining in community activities	21.88 (12.50, 31.25)	2.22	12.50 (3.13, 21.88)	1.81	-3.18	0.001*	3.15	0.002
Domain H1	Overall health assessment in the last 30 days	1.00 (1.00, 2.00)	0.14	1.00 (1.00, 2.00)	0.10	-0.05	0.966*	0.54	0.586
Domain H2	The impact of difficulties DAS1–DAS6 on life	1.00 (1.00, 2.00)	0.14	1.00 (0.00, 1.00)	0.14	-3.24	0.001*	2.98	0.003
Domain H3	Number of days in the past 30 days in which difficulties DAS1–DAS6 were present	5.00 (4.50, 17.50)	1.55	0.00 (0.00, 4.00)	1.30	-4.30	<0.001*	4.13	<0.001
Domain H4	Number of days in the past 30 days in which there was a total inability to carry out usual activities or work because of any health condition	0.00 (0.00, 1.50)	0.44	0.00 (0.00, 0.00)	0.64	-0.96	0.342*	1.14	0.254
Domain H5	Number of days in the past 30 days in which there was a reduction in usual activities or work because of any health condition	0.00 (0.00, 4.50)	1.04	0.00 (0.00, 2.00)	0.85	-1.23	0.222*	1.52	0.128
BDI-II		11.00 (7.00, 16.00)	1.02	8.00 (3.00, 14.25)	1.17	-1.52	0.130*	1.51	0.132
HADS-A		9.16 \pm 3.59	0.53	8.10 \pm 3.35	0.52	1.41; 84	0.162**	0.98	0.327
HADS-D		5.00 (3.00, 8.00)	0.50	6.00 (3.00, 8.00)	0.48	-0.72	0.474*	0.04	0.970

*Mann–Whitney U test; **student's t-test; ***robust analysis of covariance (ANCOVA) test (see the "Statistical Analysis" section for detail). Statistically significant results ($p < 0.05$) are in bold. Missing data: in WHO-DAS II: no missing data; in BDI-II: in the lipedema group – 4.4%, in the overweight/obesity group – 2.3%; in HADS-A and HADS-D: in the lipedema group – no missing data, in the overweight/obesity group – 4.7%. M \pm SD – mean \pm standard deviation; Q1 – 1st quartile; Q3 – 3rd quartile.

Statistically significant relationships in the lipedema group

Statistically significant relations between leg volume/pain intensity and parameters from the questionnaires used in the study of the group with lipedema were as follows: 1) between leg volumes and domain 3 (Self-care – attending to one's hygiene, dressing, eating and staying alone), 5.1 (Life activities – domestic responsibilities), 5.2 (Life activities – work and school), H1 (Overall health assessment in the last 30 days), and H5 (Number of days in the past 30 days in which there was a reduction in usual activities or work because of any health condition); 2) between pain intensity and domain 2 (Mobility – moving and getting around) and H5 (Number of days in the past 30 days in which there was a reduction in usual activities or work because of any health condition). Relationships between leg volume and pain intensity and parameters from the questionnaires in the group with lipedema are presented in Table 3.

Discussion

Our study is the first to compare disability, anxiety and depression symptoms in women with lipedema to women with lifestyle-induced overweight/obesity.

Despite the lower BMI in the lipedema group than in the overweight/obesity group, the lipedema group reported worse functioning in numerous domains of the WHO-DAS II questionnaire, including domestic, work and school responsibilities and participation in society. Both groups did not differ statistically significantly in depression or anxiety symptoms. After adjusting for BMI, the differences between the study groups were observed in domestic responsibilities, participation in society and mobility. Therefore, our study strongly indicates that lipedema is a much more disabling condition than overweight/obesity. However, obesity is also a limiting condition in many aspects of life. In the study of Sirtori et al., BMI values in patients with obesity have been shown to correlate with the severity of public distress as measured by the impact of weight on the QoL (IWQoL-Lite) questionnaire and, to a lesser extent, with the participation domain of the WHO-DAS II questionnaire.⁴³

Appropriate physical activity and diet are essential medical recommendations in lipedema treatment.¹¹ However, in simple overweight/obesity, a reduced diet usually results in weight loss. In lipedema, more aggressive management is needed to decrease leg volumes, including using a ketogenic diet^{33,34} or liposuction.^{38,39}

The disproportionate distribution of fat between the upper and lower body, as seen in lipedema, can cause sensations of heaviness, fatigue and discomfort in the lower limbs. Most women with lipedema also suffer from pressure-induced or spontaneous pain in the affected adipose tissue areas.^{2–4} Understandably, such legs can cause

difficulty in standing, moving and walking long distances. It was evidenced in our study by the difference in scores of domain 2 in the WHO-DAS II questionnaire (Mobility – moving and getting around) between the lipedema and the overweight/obesity groups after adjusting for BMI. Mobility difficulties may explain the reduced ability to perform domestic, work and school responsibilities in women with lipedema compared to women with overweight/obesity, as was also shown in our study (difference in the domain 5.1 and 5.2 scores of the WHO-DAS II questionnaire).

The recommendation to increase physical activity in the treatment of lipedema in many women with severe lipedema may be challenging to implement. Moreover, many women with lipedema also suffer from orthostatic edema, which worsens during warm weather and exercise.⁵¹ Therefore, when recommending increased physical activity, the type of physical activity should be adapted to the degree of edema.¹¹ Compression therapy is effective in preventing orthostatic edema and should be recommended to be worn during physical activity.¹¹

The worse functioning of women with lipedema in domain 6 of the WHO-DAS II questionnaire (Participation in society) and also in 5.2 (Life activities – work and school) compared to the overweight/obesity group may indicate that women with lipedema do not accept their appearance and disease. Our results may also suggest that women with lipedema do experience a lack of acceptance and understanding from other people, including medical personnel.¹⁴ Despite the growing awareness of lipedema diagnosis in society and among doctors, patients with lipedema still face a lack of understanding. They are often unfairly accused of being lazy in their efforts to achieve a healthy body weight. A study by Dudek et al. indicates that the appearance-related distress of patients with lipedema contributes to a deterioration in QoL.⁵² In the other research by Dudek et al., it was demonstrated that women who were more open to experiencing both pleasant and painful emotions and were more engaged in their lives reported higher QoL scores.²² Therefore, it seems that in caring for women with lipedema, it is essential to pay attention to how much the disease isolates an individual patient from society. It can be assumed that social isolation not only decreases the QoL of women with lipedema but also worsens the course of the disease in the aspects of self-care (including body weight), as well as compliance with medical recommendations, i.e., proper diet maintenance and regular use of compression therapy.

As we expected, women with lipedema and a greater volume of legs and adipose tissue pain were more disabled. Leg volume was associated with worse physical functioning, less self-care, and disability in domestic and professional activity. Adipose tissue pain was associated with greater difficulties in mobility. Previous studies demonstrated that the pain of adipose tissue is the main parameter affecting QoL in women with lipedema.^{3,19} The etiology of pain in lipedema is unclear. Histological studies suggest that

Table 3. Robust multivariable linear models of relationships between variables from questionnaires and their predictors (legs volume and adipose tissue pain intensity) in the group with lipedema

Explained variable	Predictor	Coeff.	SE	Z	p-value
Domain 1 Cognition – understanding and communicating	intercept	0.07	7.31	0.01	0.992
	leg volume	0.00	0.00	1.52	0.128
	pain intensity	0.96	0.74	1.31	0.191
Domain 2 Mobility – moving and getting around	intercept	-12.27	8.32	-1.47	0.141
	leg volume	0.00	0.00	1.76	0.078
	pain intensity	3.75	0.84	4.47	<0.001
Domain 3 Self-care – attending to one's hygiene, dressing, eating and staying alone	intercept	-6.87	2.47	-2.78	0.005
	leg volume	0.00	0.00	3.29	0.001
	pain intensity	0.40	0.25	1.61	0.108
Domain 4 Getting along – interacting with other people	intercept	4.07	7.51	0.54	0.588
	leg volume	0.00	0.00	1.11	0.268
	pain intensity	0.14	0.76	0.18	0.856
Domain 5.1 Life activities – domestic responsibilities	intercept	-15.64	10.47	-1.49	0.135
	leg volume	0.00	0.00	2.65	0.008
	pain intensity	1.95	1.05	1.85	0.064
Domain 5.2 Life activities – work and school	intercept	-17.76	10.51	-1.69	0.091
	leg volume	0.00	0.00	2.63	0.009
	pain intensity	2.02	1.06	1.91	0.056
Domain 6 Participation in society – joining in community activities	intercept	8.82	8.49	1.04	0.299
	leg volume	0.00	0.00	1.20	0.229
	pain intensity	1.07	0.85	1.25	0.212
Domain H1 Overall health assessment in the last 30 days	intercept	0.02	0.51	0.04	0.971
	leg volume	0.00	0.00	2.31	0.021
	pain intensity	0.07	0.05	1.46	0.145
Domain H2 The impact of difficulties DAS1–DAS6 on life	intercept	0.42	0.46	0.91	0.365
	leg volume	0.00	0.00	1.75	0.080
	pain intensity	0.05	0.05	1.11	0.268
Domain H3 Number of days in the past 30 days in which difficulties DAS1–DAS6 were present	intercept	1.09	5.85	0.19	0.853
	leg volume	0.00	0.00	1.07	0.284
	pain intensity	0.69	0.59	1.18	0.239
Domain H4 Number of days in the past 30 days in which there was a total inability to carry out usual activities or work because of any health condition	intercept	0.00	0.00	-0.48	0.631
	leg volume	0.00	0.00	0.91	0.361
	pain intensity	0.00	0.00	0.85	0.398
Domain H5 Number of days in the past 30 days in which there was a reduction in usual activities or work because of any health condition	Intercept	-4.50	1.82	-2.48	0.013
	leg volume	0.00	0.00	2.91	0.004
	pain intensity	0.42	0.18	2.31	0.021
BDI-II	intercept	7.13	3.67	1.94	0.052
	leg volume	0.00	0.00	0.68	0.496
	pain intensity	0.27	0.37	0.73	0.467
HADS-A	intercept	11.88	2.20	5.40	<0.001
	leg volume	0.00	0.00	-1.14	0.254
	pain intensity	-0.08	0.22	-0.38	0.702
HADS-D	intercept	1.11	1.95	0.57	0.570
	leg volume	0.00	0.00	1.85	0.065
	pain intensity	0.18	0.20	0.90	0.366

Statistically significant results ($p < 0.05$) are in bold. Coeff. – coefficient; SE – standard error of the coefficient; Z – test value.

the inflammatory process and hypoxia may be responsible for this symptom.¹¹ Another potential mechanism involves nerve compression in the septa, surrounding the growing fatty lobules within adipose tissue.⁵³

However, while the volume of lipedema and the pain intensity influenced daily functioning in our study, surprisingly, they did not affect the severity of depressive and anxiety symptoms. Similarly, the lower limbs' circumference and pain intensity were not associated with the severity of emotional symptoms. These consistent findings suggest that behavioral impairment is the primary factor influencing functioning in women with lipedema compared to women with overweight/obesity, and emotional symptoms do not play a significant role. However, these results are puzzling, as other studies have shown significantly higher levels of depressive and anxiety symptoms in groups of patients with lipedema.^{18–20}

Considering that no published study assessing depressive and anxiety symptoms in women with lipedema has used the HADS or BDI-II questionnaire, it is impossible to directly compare the results of our research with those from other centers. Nevertheless, Dudek et al. demonstrated that more than half of the women with lipedema (59.2%) reported a heightened level of depressive symptoms,²¹ and the greater intensity of depressive symptoms had a significant impact on women's QoL.⁵² Al-Wardat et al. showed that women with lipedema had significant difficulties with emotion regulation associated with anxiety symptoms.⁵⁴ Clarke et al. revealed that women with lipedema in stages 3–4 compared to stages 1–2 were more likely to report depression, emotional lability, eating disorders, as well as feeling lonelier, more fearful, more likely to stay at home and less likely to have visited a psychologist.⁵⁵ Similarly, in the study by Erbacher and Bertsch, the percentage of women with lipedema and mental health disorders (such as depression, anxiety disorders, eating disorders, or post-traumatic stress disorder (PTSD)) was significantly greater in the subgroup with a BMI ≥ 40 kg/m² than with a BMI < 40 kg/m² (49.3% compared to 25.9%, respectively).¹⁸

The lack of difference between our study groups in severity of anxiety and depressive symptoms can be explained by the fact that in the previous studies, the lipedema group was only compared to healthy individuals,⁵⁴ while our results demonstrate the comparison of lipedema to lifestyle-induced overweight/obesity group. Moreover, the majority of women in our lipedema group (96%) were in the 1st and 2nd stages of the disease. It might also be suspected that the long-term lack of diagnosis of enlarged, heavy and painful legs may result in the symptoms of depression and anxiety. Women with lipedema in our study had the diagnosis of lipedema before participation in this study and most of them hoped that the condition of their legs would improve after implementing the LCHF diet. Additionally, most women in the study groups who decided to participate in our study were ready to follow a rigorous LCHF diet. The hypothetical presence of depression or anxiety

symptoms might be associated with reduced motivation and might make it difficult to take on such a challenge. Therefore, perhaps the planned intervention in our study prompted to participate in our research women who did not have symptoms of depression or anxiety.

Our findings have not only theoretical but also practical implications for women with lipedema for healthcare providers. Leg volumes and adipose tissue pain intensity were the factors associated with worse functioning of women with lipedema, and they should be taken into account in the management of women with this condition. The experience of the authors of this publication indicates the high effectiveness of the LCHF diet in reducing not only BMI but also leg volumes and pain of adipose tissue,^{33,34} i.e., the impact of the LCHF diet on parameters in our study that were demonstrated to be disabling to the functioning of women with lipedema. Complete decongestive therapy (CDT) and physical exercises have also been demonstrated to significantly improve leg volume, alleviate pain and positively affect function of patients with lipedema.⁵⁶ Another treatment of proven effectiveness in this regard is liposuction.^{57,58}

Leg volumes and adipose tissue pain intensity should also be estimated in further regular control visits of women with lipedema after intensive treatment. Maintaining body weight and leg volume in the long term may be difficult for women with lipedema. Therefore, it is necessary to educate and motivate them to undertake appropriate diet and physical activity.

Limitations

The limitations of this study may result from the difficulty in distinguishing lipedema from obesity, especially in patients with poorly expressed symptoms of lipedema or with greater obesity. However, the group selection criteria used in our study and the examination of all women by angiologists experienced in the diagnosis and treatment of women with lipedema significantly reduced the possibility of incorrect classification into the study groups.

It is also possible that the planned implementation of the LCHF diet in women enrolled in our study may have an impact on depressive and anxiety symptoms. Firstly, by decreasing these possible symptoms and giving hope for improvement in women in both study groups, and secondly, by the effect on the recruitment of women who were mainly ready to follow a rigorous LCHF diet, i.e., probably without signs of depression or anxiety.

Additionally, the number of women in both study groups was too small to distinguish the subgroups of patients according to the stage and type of lipedema or degree of obesity with BMI or additional symptoms, especially pain of adipose tissue. Our study evaluated the relationship between leg volumes and adipose tissue pain intensity and parameters from questionnaires in the lipedema group. However, the direct comparison of specific subgroups of patients might be very informative.

Conclusions

Our study indicates that behavioral impairment is the main factor affecting functioning in women with lipedema, and emotional symptoms did not differentiate patients with lipedema and lifestyle-induced overweight/obesity. Despite the lower BMI in the lipedema group compared to the overweight/obesity group, the lipedema group reported worse functioning.

Legs volume and adipose tissue pain intensity were the most disabling factors in women with lipedema, and they should be taken into account when planning treatment for women with this condition. It is important to consider these factors in future research assessing the effectiveness of lipedema treatment.

Lipedema requires a complex and multidirectional treatment. In light of our findings, it seems that patient education and social support might improve QoL of women with lipedema. Further research in this field should be conducted on a larger patient cohort to identify subgroups based on the stage and type of lipedema, degree of obesity and accompanying clinical symptoms.

Supplementary data

The Supplementary materials are available at <https://doi.org/10.5281/zenodo.10427200>. The package includes the following files:

Supplementary Table 1. The results of normal data distribution and variance homogeneity tests.




Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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