

## ORIGINAL ARTICLE

# Disease progression and comorbidities in lipedema patients: A 10-year retrospective analysis

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**Abstract**

Multiple associated comorbidities have been described for lipedema patients. Disease diagnosis still remains challenging in many cases and is frequently delayed. The purpose of this study was to determine the most common comorbidities in lipedema patients and the impact of surgical treatment onto disease progression. A retrospective assessment of disease-related epidemiologic data was performed for patients who underwent liposuction between July 2009 and July 2019 in a specialized clinic for lipedema surgery. All patients received a standardized questionnaire regarding the clinical history and changes of lipedema-associated symptoms and comorbidities after surgery. 106 patients who underwent a total of 298 liposuction procedures were included in this study after returning the questionnaire fully filled-in. Multiple comorbidities were observed in the assessed collective. The prevalence for obesity, hypothyroidism, migraine, and depression were markedly increased in relation to comparable nonlipedema populations. Despite a median body mass index (BMI) of 31.6 kg/m<sup>2</sup> (IQR 26.4–38.8), unexpected low prevalence of diabetes (5%) and dyslipidemia (7%) was found. Diagnosis and initiation of guideline-appropriate treatment were delayed by years in many patients. After surgical treatment (medium follow-up 20 months, IQR 11–42), a significant reduction of lipedema-associated symptoms was demonstrated. Lipedema occurs with a diversity of associated comorbidities. Therefore, on the basis of available data, the authors suggest the necessity of a multimodal therapy concept for a comprehensive and holistic treatment. Despite a commonly increased BMI, lipedema patients appear to have an advantageous metabolic risk profile.

**KEYWORDS**

comorbidities, epidemiology, lipedema, lipoedema, subcutaneous adipose tissue

## 1 | INTRODUCTION

Lipedema predominantly affects women and commonly manifests in phases of hormonal changes such as puberty, pregnancy, or menopause.<sup>1</sup> As routine consultations to physicians of different specialties are made especially in these periods, sufficient knowledge about lipedema in everyday clinical practice is of special importance for primary diagnosis. Although lipedema was first described in

1940 by Allen and Hines, the disease received little attention for decades.<sup>2,3</sup> Due to current health policy efforts and increasing media coverage, awareness has been markedly increased.<sup>1</sup> Nevertheless, there is still a considerable uncertainty regarding the correct diagnosis. This often results in an unsatisfactorily long interval between the appearance of the first symptoms and the initiation of adequate therapeutic measures for both, the patient and the health care professional.<sup>4,5</sup>

Morphological changes involve a disproportionate fat distribution between the trunk and extremities, due to a circumscribed, bilateral, symmetrically localized increase in subcutaneous fat tissue. Mostly affected are the lower extremities and buttocks region.<sup>6</sup> Involvement of the arms is described in up to 80%.<sup>7,8</sup> Typically, hands and feet are sharply spared from the areas of fat tissue growth ("cuff sign"). Clinical symptoms of the disease are summarized in Table 1. The leading symptom is an increased pain perception in the affected areas with progression throughout the day. With increasing stages of lipedema, secondary development of lymphedema might occur.

The disease is classified into three clinical stages, which progress with increasing fibrotic remodeling of the subcutaneous tissue.<sup>9</sup> The severity classification is based on a physical examination of the skin and subcutaneous tissue quality primarily through palpation (Figure 1).<sup>10</sup>

The cause of the disease has not yet been clarified. Family clusters indicate a genetic component with a possibly x-chromosomal dominant inheritance pattern and incomplete penetrance.<sup>11-13</sup> Regulatory candidate genes from genome-wide association studies have not yet been identified sufficiently.<sup>14,15</sup>

Estrogen in particular is considered to play a key role in regulating pathogenesis.<sup>16</sup> Affected men with lipedema were only described as isolated cases in the existing literature, whereby hormonal changes due to hypogonadism or liver dysfunction with consecutively increased estrogen levels or reduced testosterone levels were assumed to be associated.<sup>11,17</sup> However, detailed pathophysiological mechanisms for possible hormone receptor alterations have not yet been demonstrated.<sup>16,18</sup>

Cornerstones of the conservative treatment consist in a promotion of a healthy lifestyle and the use of combined decongestive therapy (CDT). Manual lymphatic drainage (MLD), compression therapy, exercise therapy and skin care form the pillars of CDT and are currently the standard therapy for lipedema.<sup>9</sup> Psychological support is often necessary.<sup>19</sup> If adequate symptom reduction is not achieved

after at least 6 months of CDT, the indication for surgical treatment (lymph sparing liposuction) can be considered.<sup>1,20</sup> Randomized controlled studies on the benefits of liposuction for lipedema are currently not available, but a number of selected observation studies have described evidence of permanent symptom reduction by removal of the pathological adipose tissue.<sup>21-25</sup> Furthermore, a reduction of menstrual disorders after surgical treatment has been reported.<sup>5</sup>

Current publications have described a large number of associated comorbidities for patients with lipedema.<sup>5,7,8,10</sup> A major topic of discussion is the high proportion of obesity in lipedema patients and its influence on therapy guidelines.<sup>9,26</sup> The widely postulated "diet resistance" of lipedema adipose tissue has so far not been substantiated with evidence. In addition, it remains unclear to what extent a progression of lipedema causes a consecutive weight gain.<sup>27</sup> Despite the often significantly increased BMI, lipedema patients seem to have a lower risk for diabetes mellitus, arterial hypertension or hyperlipidemia compared to a reference population.<sup>7</sup> Furthermore, there is an ongoing discussion about lipedema and an often-associated psychosocial impairment. The presumed causal influence of lipedema on the cause of mental illnesses has recently been questioned.<sup>28</sup> In addition, an elevated prevalence of hypothyroidism and migraine in lipedema patients has been reported.<sup>5,21</sup>

Original articles on the subject of lipedema with a special focus on clinical course and associations with comorbidities have so far hardly been published. In the present work, relevant comorbidities and the disease-related medical history of surgically treated patients were collected from the patient collective of a specialized clinic for lipedema surgery over the past 10 years and retrospectively evaluated. The objective of this study is the systematic processing of this data and a critical reflection in the context of the currently existing literature.

## 2 | MATERIALS AND METHODS

Between July 2009 and July 2019, a total of 147 lipedema patients underwent a multi-stage liposuction treatment at a specialized clinic for lipedema surgery. Diagnosis was made based on the criteria of Buck and Herbst (Table 1).<sup>6</sup> A validation of the diagnosis, as well as the exclusion of possible differential diagnoses, was carried out for each patient according to the four-eyes principle by a specialized external lymphologist. All patients received preoperative conservative therapy for at least 6 months. Liposuction was performed under general anesthesia under inpatient conditions. In order to protect the lymphatic system, surgery was carried out in "wet technique" with infiltration of a maximum of 6000 mL of tumescent solution (1 mL of adrenaline 1:1000 in 1000 mL of NaCl). Liposuction was performed using power-assisted (PAL) and water-jet-assisted systems (WAL).<sup>20,29,30</sup>

Between December 2019 and February 2020, all patients received a standardized questionnaire on the clinical history of lipedema with a special focus on family history, disease progression and comorbidities. In order to investigate the influence of lymph

**TABLE 1** Clinical criteria for the diagnosis of lipedema

Almost exclusive occurrence in women
Bilateral and symmetrical disproportional fat hypertrophy of the extremities
Sharp margination and sparing of hands and feet ("cuff phenomenon")
Involvement upper extremity in approx. 30%
Negative stemmer sign <sup>a</sup>
Feeling of heaviness and tension in the affected extremity
Pain and tenderness on pressure
Easy bruising
Stable limb circumference with weight loss or caloric restriction
Symptom intensification during the day
Telangiectasia/visible vascular drawings around fat depots
Skin hypothermia

<sup>a</sup>Positive stemmer sign: it is not possible to lift the skin fold between the second and third toes.

**FIGURE 1** Lipedema stages. Stage I: Thickened subcutis, soft, small palpable nodules, skin surface still smooth. Stage II: Thickened subcutis, soft, larger nodes, uneven skin surface, wavy. Stage III: Thickened subcutis, indurated, large nodules with pronounced sclerosis, deforming fat lobes



sparing liposuction on the manifestation of comorbidities and disease-related symptoms, the questionnaire focused on pre- and postoperative changes. Out of 147 operated patients, 106 were included in this study after returning the postoperative questionnaire fully filled-in.

A comorbidity was confirmed, when

1. the condition was clinically symptomatic (ie, occurrence of migraine attacks) and/or diagnostic tests proved abnormal marker levels (eg, elevation of triglycerides and/or cholesterol in blood for dyslipidemia or elevated blood pressure measures for hypertension) and
2. the condition required medical consultation and/or treatment within the last 12 months.

In case of doubt, diagnosis of comorbidities was confirmed by the primary care physician. Since the BMI has only a limited informative value regarding the differentiation between lipedema and obesity,<sup>7,14,31,32</sup> the presence of obesity was defined as WHO definition stage II (BMI  $\geq 35$  kg/m<sup>2</sup>).

Statistical analysis was performed using GraphPad Prism version 8.3 (GraphPad Software, Inc., San Diego, California). The D'Agostino-Pearson omnibus normality test was used to verify the non-Gaussian distribution of the data. Group differences in the pre / postoperative comparison were assessed using the nonparametric Wilcoxon matched-pairs signed-rank test. Group differences in the frequency of comorbidities depending on the stage were assessed using the Mann-Whitney test (two groups) or the Kruskal-Wallis test (more than two groups). A *P* value of  $<.05$  was considered significant in two-group comparisons and adjusted in multiple-group comparisons.

### 3 | RESULTS

All included patients were female. A total of 298 liposuctions were performed in 106 examined patients. In 46.3% (*n* = 138) the

treatment costs for surgical intervention were covered by the statutory health insurance. In median, three operations per patient were necessary, which spanned a surgical treatment period of 8 months (interquartile range [IQR] 4-14 months). The follow-up survey was carried out between 6 and 115 months after the last liposuction with a median follow-up of 20 months (IQR 11-42 months). The median follow-up period after the first operation was 34 months (IQR 18-57 months).

#### 3.1 | Family history

A total of 77 patients (73%) reported a positive family history regarding lipedema. Most frequently affected was the mother (*n* = 40; 38%), followed by grandmother (*n* = 18; 17%), aunt (*n* = 8; 8%), sister (*n* = 6; 6%) and cousin (*n* = 5; 5%).

#### 3.2 | Onset, development and morphology

The majority of affected lipedema patients reported a disease onset during puberty (*n* = 62; 59%) or pregnancy (*n* = 22; 21%). Other potential onset triggers such as contraceptives (*n* = 4; 4%), menopause (*n* = 2; 2%) or others (*n* = 6; 6%), were stated less frequently.

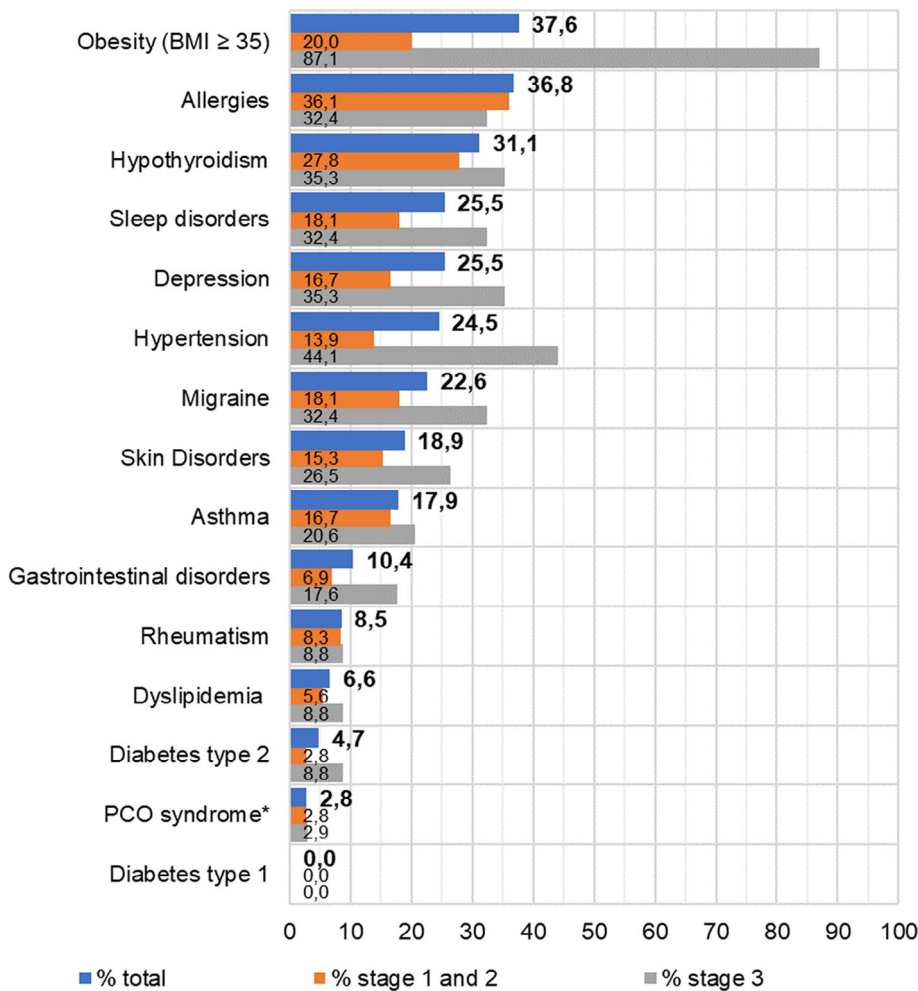
For 88% of those affected, the time period between lipedema onset and the correct diagnosis was several years. The longest period specified was almost 50 years. In median, final diagnosis took 10 years (IQR 5-20 years). The median interval between diagnosis and initiation of specific therapeutic measures was 5 months (IQR 1-24 months). In 13% of all cases (*n* = 14), despite a correct diagnosis, it took more than 3 years until appropriate therapeutic measures were started.

Typical lipedema-associated complaints in the upper extremity occurred in 61% of the examined collective. The involvement of the arms was observed to be significantly higher in stage 2 and 3 lipedema (*p* = 0,0335) (Table 2). In cases of involvement of the upper

	Total	Stage I	Stage II	Stage III
n (percentage)	106	11(10.4%)	61(57.6%)	34(32.1%)
Involvement upper extremity (percentage)	65(61.3%)	5(45.5%)	34(55.7%)	26(76.5%)
Age(IQR)	41(30-51)	30(26-34)	41(31-51)	47(32-52)

Abbreviation: IQR, Interquartile range.

**TABLE 2** Baseline characteristics by stage



**FIGURE 2** Prevalence of common comorbidities in lipedema, percentage. PCO syndrome, polycystic ovary syndrome

extremities, complaint onset in arms was stated concurrent to general disease onset in 71% of the cases (n = 45).

For other concomitant diseases, no significant group differences could be observed.

### 3.3 | Prevalence comorbidities

93 of the examined patients (88%) indicated at least one concomitant illness. The most common comorbidities are shown in Figure 2.

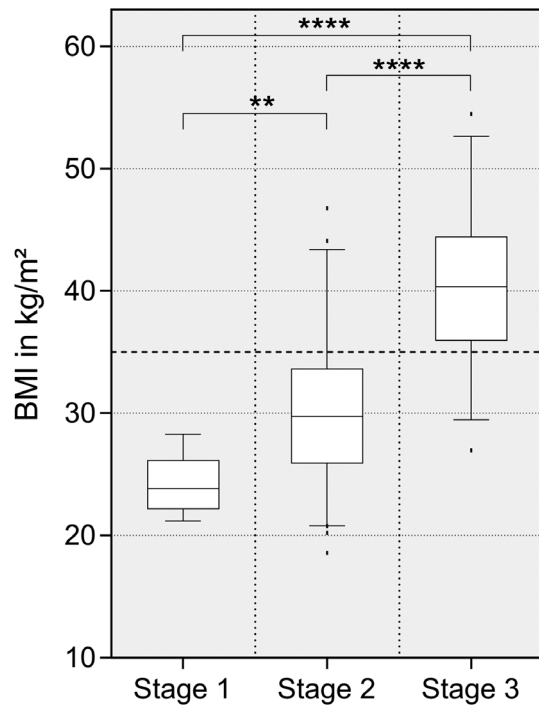
Despite a median body mass index of 31.6 kg/m<sup>2</sup> (IQR 26.4-38.8), unexpected low prevalence of diabetes (5%) and dyslipidemia (7%) were found.

For the comorbidities obesity ( $P < .0001$ ) and arterial hypertension ( $P = .0030$ ), significant group differences in the prevalence were found when comparing stage 1 and 2 vs stage 3 patients.

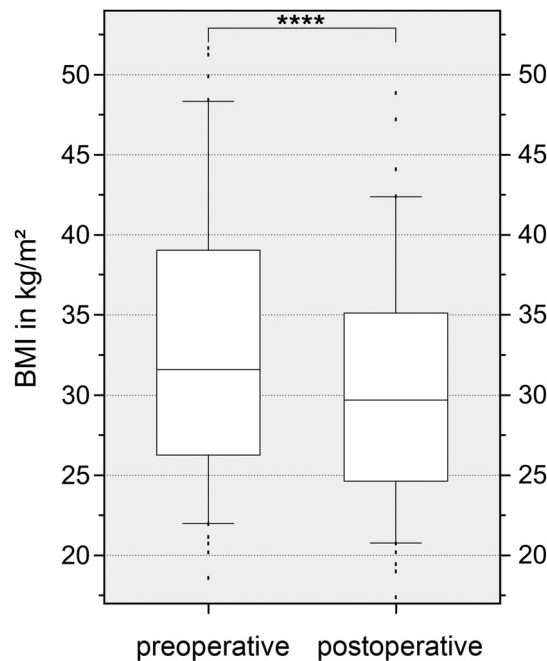
### 3.4 | Lipedema and obesity

Overall, obesity was the most common comorbidity (37.6%, n = 38). The median BMI was 31.6 kg/m<sup>2</sup> (IQR 26.4-38.8 kg/m<sup>2</sup>). The higher the stage of the disease, the higher was the median BMI preoperatively (Figure 3). Only five patients with stage 3 lipedema (15%) had a BMI ≤35 kg/m<sup>2</sup>.

After the multistage surgical treatment and a median follow-up time of 20 months (IQR 11-42 months), a significant median reduction of the BMI of 2.7 kg/m<sup>2</sup> (IQR 1.1-5.2 kg/m<sup>2</sup>) could be observed ( $P < .0001$ ) (Figure 4). This corresponds to a median percentage

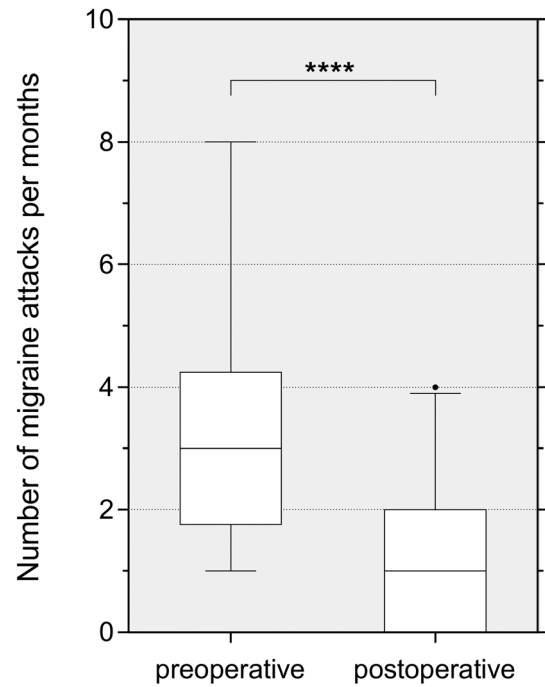


**FIGURE 3** Body mass index before surgery in different lipedema stages as box plots with the median, IQR (25-75%), and whiskers (5-95%). \*\*Statistically significant ( $P = .0201$ ). \*\*\*\*Statistically significant ( $P < .0001$ )



**FIGURE 4** Body mass index before and after surgery as box plots with the median, IQR (25-75%), and whiskers (5-95%). \*\*\*\*Statistically significant ( $P < .0001$ )

reduction of the BMI of 8.7% (IQR 3.6-14.0%). The absolute ( $P < .0001$ ) and percentage ( $P = .0007$ ) difference were significantly higher for stage 3 patients than for those with stage 1 and 2.



**FIGURE 5** Change in number of migraine attacks per month: preoperative and postoperative as box plots with the median, IQR (25-75%), and whiskers (5-95%). \*\*\*\*Statistically significant ( $P < .0001$ )

### 3.5 | Lipedema and menstrual cycle

Of all premenopausal lipedema patients, 18% ( $n = 19$ ) complained about menstrual bleeding that is abnormal and/or irregular in frequency, duration, and/or intensity. Postoperatively, a normalization of the menstrual cycle could be achieved in 53% of these patients ( $n = 10$ ).

### 3.6 | Lipedema and hypothyroidism

31% of all examined lipedema patients ( $n = 32$ ) were treated for hypothyroidism. Although a significantly lower BMI with a consequently reduced basal metabolism could be demonstrated after surgery (Figure 4), no significant change in the L-thyroxine dosage could be determined ( $P = .0945$ ).

### 3.7 | Lipedema and migraine

A diagnosed migraine was reported in 23% of the examined patients ( $n = 24$ ). The number of migraine attacks per month was significantly reduced after surgical treatment (Figure 5,  $P = .0002$ ). Postoperatively, a total of 67% ( $n = 16$ ) reported an improvement in intensity or frequency of attacks, and 12.5% ( $n = 3$ ) of all patients had no migraines at all after the operation.



### 3.8 | Lipedema and skin disorders

19% of those affected ( $n = 20$ ) reported suffering from lipedema-associated dermatoses requiring treatment before the operative intervention. In 90% ( $n = 17$ ) of these patients, an improvement in the symptoms could be achieved by liposuction.

### 3.9 | Surgical outcome on lipedema symptoms

The mean lipoaspirate volume per operation was 6355 mL ( $\pm 2797$  mL) with a mean total aspirate volume per patient of 17 887 mL ( $\pm 10 341$  mL) throughout the entire surgical treatment. The complication rate was low with a total of four superficial wound infections (1.3%) and two seromas (0.7%), as well as one case of mild postoperative bleeding (0.3%) which did not necessitate a blood transfusion. All complications could be treated conservatively.

The leading symptom "pain" was preoperatively classified as "strong" for all parameters asked ("spontaneous pain", "pressure pain", "feeling of tension"; median VAS score: 80). Surgical therapy resulted in a significant reduction in pain perception ( $P < .0001$ ).

Sick leave due to lipedema could be reduced in the examined cohort after surgical intervention. 58% of the patients ( $n = 62$ ) stated that they needed fewer or no more medical sickness certificates due to lipedema-related symptoms after the last operation.

The subjective quality of sex life improved significantly in the VAS score evaluation after liposuction ( $P < .0001$ ). With a median overall satisfaction of 90 in the VAS score 0 to 100, 99% of all patients included in this study would recommend the multi-stage surgical therapy concept.

## 4 | DISCUSSION

The variety of associated comorbidities and symptoms in lipedema patients underline the need for a multimodal therapy concept for a comprehensive and holistic treatment of the disease.

The present data demonstrate that the number and extent of comorbidities increase with advancing stage. The chronically progressive course of the disease leads to a progressive tissue fibrosis and thus to aggravation in the local findings.<sup>9</sup> Therefore, the earliest possible diagnosis is of crucial importance for optimal long-term therapy. In this context, the primary healthcare provider or the treating dermatologist plays a key role in the disease management. The indicated periods of several years between disease onset and diagnosis could be significantly reduced by an increased awareness of lipedema. Earlier diagnosis and treatment may possibly avoid a frequently complained stigmatization of lipedema sufferers as obese with a resulting strain on the doctor-patient relationship.

Given the high prevalence of several comorbidities, lipedema should always be treated in an interdisciplinary manner. The high prevalence of obesity has already been shown in several publications and was recently critically discussed.<sup>7,14,21</sup> Based on the currently

available studies, it cannot be conclusively assessed whether the pathological lipedema adipose tissue is actually "diet-resistant".<sup>8</sup> It further remains unclear whether a progression of lipedema leads to an increase in BMI or vice versa.<sup>27</sup> Therefore—regardless of the BMI at diagnosis—early nutritional therapy is advisable to avoid the development of severe obesity with progressing lipedema.<sup>9</sup> When obesity is present in lipedema sufferers, guideline-based therapy by the respective specialist disciplines should be obligatory and regularly controlled before considering surgical intervention.<sup>9</sup>

Despite the significantly increased BMI compared to the normal population in the examined collective, typical concomitant diseases of the metabolic syndrome were underrepresented. Considering the median BMI of 31.6 kg/m<sup>2</sup> and a proportion of diabetes mellitus of only 4.7% in the investigated cohort, the prevalence differs significantly from representative comparative collectives, where a prevalence of 12 to 25% was reported.<sup>33,34</sup> The results of the examined patients in this study are congruent with data from similar cohorts.<sup>7,32</sup> Possible changes in the insulin response of lipedema adipose tissue could be the starting point for further research into pathophysiology.

In comparative obese female populations without lipedema, levels of triglycerides were increased by over 33.5%.<sup>35,36</sup> In view of the median BMI of 31.6 kg/m<sup>2</sup> of the patients in this study, the proportion of sufferers with the comorbidity hyperlipidemia was comparatively low (6.6%). Similar data have already been published.<sup>7</sup> Future studies should investigate whether the gynoid fat distribution pattern or the biochemical properties of lipedema adipose tissue actually have a protective value with regard to insulin response and cardiovascular risk.<sup>7</sup>

The prevalence of people with depression (25.5%) described in the present work corresponds to the previously published literature.<sup>3,5,8,19</sup> Compared to the healthy, female population (12-month prevalence 6.6-10.2%),<sup>37-40</sup> this is considerably higher. To what extent mental disorders may be regarded as secondary effects of lipedema<sup>9</sup> or whether there is a contradicting causal connection<sup>28</sup> cannot be assessed on the basis of the present data. In case of doubt, a psychological co-assessment should be recommended.<sup>9</sup> In order to reduce psychosocial side effects, lipedema sufferers should be given options for an active disease management and strategies for accepting the disease and adapting lifestyle should be shown. The causal relationship between obesity and depressive symptoms, which is still being discussed, should also be viewed critically. Publications that were able to show correlations between obesity and mental illnesses often showed a possible help-seeking bias.<sup>41</sup> A cross-sectional study with a representative cohort, however, could not explicitly show a significant connection between BMI and mental illness.<sup>42</sup>

The link between lipedema and hypothyroidism, which has been reported in recent publications, was also observed in the present collective.<sup>5,8</sup> The demonstrated prevalence of 31% is higher than in comparative populations (0.5-2.0%).<sup>43</sup> To what extent there is a causal connection, or whether hypothyroidism could only be epiphenomenon of obesity<sup>44</sup> remains unclear. However, since no significant change in the necessary L-thyroxine dose was observed despite successful reduction of body weight and BMI, the authors believe that hormonal dysregulation in the context of lipedema can be assumed.

Currently, there are no hypotheses regarding pathophysiological cause of the observed increased prevalence of patients with migraines (22.6%) in the context of lipedema compared to the (female) German nonlipedema population (15.6%).<sup>4,5</sup> The significant postoperative improvement in migraine symptoms reported in this study has already been demonstrated in other publications.<sup>5</sup> It is currently difficult to estimate to what extent the symptom improvement can be reduced to a simple reduction in BMI<sup>4,6</sup> or whether other regulatory mechanisms are more important.

With careful patient selection, several observational studies indicated that the surgical therapy was able to improve lipedema-associated symptoms (pain perception, tension sensation, hematoma tendency, quality of life) as well as objectively measurable parameters such as leg circumference or extent of conservative therapy.<sup>21-25</sup> The results of this retrospective analysis underline this data. In addition, an improvement in menstrual irregularities could be observed. In any case, the conclusions of the prospective, multicenter, randomized, controlled study commissioned by the German Federal Joint Committee (G-BA) to compare the conservative vs the operative treatment are eagerly awaited.<sup>47</sup>

This study has some limitations. First, the relatively low number of patients included, as well as the methodological design of the study (retrospective study based on a self-reported questionnaire without a matched control group) does not allow firm conclusion to the general population. Second, no pathophysiological evidence for a possible link between lipedema and the reported diseases has been provided so far. Furthermore, although relatively highly represented in this population, none of the comorbidities were invariably associated with lipedema.

## 5 | CONCLUSION

Lipedema occurs with a diversity of associated comorbidities. Therefore, on the basis of available data, the authors suggest the necessity of a multimodal therapy concept for a comprehensive and holistic treatment of the disease.

Despite a commonly increased BMI, lipedema patients appear to have an advantageous metabolic risk profile. Further research into pathophysiology should therefore focus on a possible protective value of lipedema adipose tissue with regard to the insulin response or the cardiovascular risk.

### CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

### AUTHOR CONTRIBUTIONS

Study conception and design: Mojtaba Ghods, Philipp Kruppa. Acquisition of data: Iakovos Georgiou, Jeremias Schmidt, Philipp Kruppa. Analysis and interpretation of data: Philipp Kruppa. Drafting of manuscript: Philipp Kruppa. Critical revision: Mojtaba Ghods, Iakovos Georgiou, Jeremias Schmidt.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Philipp Kruppa, upon reasonable request.

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