

Lipoedema and Pain: What is the role of the psyche?

Results of a pilot study with 150 patients with Lipoedema

Lipödem und Schmerz – Welche Rolle spielt die Psyche?

Ergebnisse einer Pilotstudie mit 150 Patientinnen mit Lipödem-Syndrom

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ABSTRACT

Introduction The present exploratory study is the first so far to investigate the psychological stress in the period before the development of pain symptoms typical for lipoedema.

Methods 150 patients diagnosed with lipoedema syndrome were questioned in semi-structured interviews about psychological stress and were diagnosed with psychological disorders according to ICD-10 criteria. The development of the symptoms typical for lipoedema was recorded in a second interview. Both interviews were blended together in collaboration with the patients, this means Lipoedema-associated pain and psychological stress were related to time.

Result Exactly 80 % of the patients diagnosed with lipoedema show a high level of psychological distress immediately before

the onset of lipoedema-associated symptoms! In this study, mental distress was defined as the presence of a manifest mental disorder (ICD 10 F diagnosis) such as Depression, eating disorder or post-traumatic stress disorder and/or serious psychological distress such as burnout syndrome or chronic stress.

Summary These results contradict a widespread statement that all psychological problems of patients with the diagnosis lipoedema syndrome are caused solely by lipoedema, that lipoedema even causes the patient's mental disorder.

Moreover, depression and posttraumatic stress disorders are significantly related to the maximum pain intensity estimated by patients in everyday life. This demonstrates that it is imperative to rethink lipoedema therapy and to implement a psychosocial pillar in an overall therapy concept.

ZUSAMMENFASSUNG

Einleitung Die vorliegende explorative Studie ist die bislang erste, in der die psychische Belastung im Zeitraum vor Auftreten der Lipödem-assoziierten Schmerzsymptomatik erforscht wird.

Methode 150 Patientinnen mit Lipödem-Syndrom wurden in halbstrukturierten Interviews zu psychischen Belastungen befragt und zu psychischen Störungsbildern nach ICD-10-Kriterien diagnostiziert. In einem zweiten Interviewstrang wurde die Entwicklung der Lipödem-typischen Beschwerden erhoben. Im Anschluss erfolgte gemeinsam mit den Patientinnen das Überblenden beider Interviewbereiche, d. h. Lipödem-assoziierte Schmerzen und psychische Belastungen wurden in einen zeitlichen Zusammenhang gesetzt.

Ergebnis Exakt 80 % der Patientinnen mit der Diagnose Lipödem zeigten eine hohe psychische Belastung unmittelbar im Zeitraum vor der Entstehung Lipödem-assoziiierter Beschwerden! Psychische Belastung wurde in dieser Studie definiert als das Vorliegen einer manifesten psychischen Störung (ICD-10-F-Diagnose), wie z. B. Depression, Essstörung oder posttraumatische Belastungsstörung, oder/und gravierende psychische Auffälligkeit, wie z. B. Burnout-Syndrom oder chronischer Stress.

Zusammenfassung Die Ergebnisse widersprechen damit einem weit verbreiteten Statement, dass alle psychischen Probleme von Patientinnen mit der Diagnose Lipödem-Syndrom ausschließlich durch das Lipödem bedingt seien, ein Lipödem sogar psychisch krank mache.

Depression und Traumafolgestörungen stehen darüber hinaus in signifikantem Zusammenhang mit den von den Patientinnen eingeschätzten maximalen Schmerzstärken im Alltag. Dies macht deutlich, dass die Therapie für Patientinnen mit

der Diagnose Lipödem neu gedacht werden und die psychosoziale Säule zwingend in einem Gesamttherapiekonzept verankert werden muss.

Introduction

Lipoedema is so much more than just having thick painful legs. Lipoedema is a syndrome whose definition includes both a disproportionate distribution of subcutaneous fatty tissue that is more pronounced in the legs (and sometimes also the arms) and pain in the soft tissues of the legs (and/or arms) [1, 2]. Lipoedema-associated pain and restriction of mobility are linked to a physical reduction in the quality of life [3, 4]. However, the results of a study by Frambach et al. also show that the “mental health” of patients with lipoedema is often more severely affected than their “physical health” [3], as measured with the SF-36, an internationally recognised quality of life assessment tool [5]. In other words, patients with a diagnosis of lipoedema suffer more from the psychological aspects than from the somatic symptoms of their disease.

Most women with lipoedema are also overweight or obese [6–9] and are already stigmatised because of their obesity [10]. In addition, many of these patients are lacking in self-acceptance [11]. The current ideals of beauty (encapsulating a slim, long-legged body image) in particular are one reason for this lack of acceptance of one's own body [12].

Lipoedema and psychological stress

The psychological situation of patients diagnosed with lipoedema has already been addressed in several studies [7, 8, 13]. So far, all these publications have given the impression that mental health disorders such as depression or eating disorders would result from the lipoedema; it has been suggested that lipoedema is the underlying cause of the mental health disorders experienced [14]. But is there any scientific evidence for this popular statement?

In general, problems in research fall mainly into two areas: first, there is the risk of overlooking relevant aspects by reducing the complexity. Secondly, statistical relationships in terms of correlation are often wrongly interpreted as causality. With respect to lipoedema, logic tells us there are three possible relationships between severe psychological stress and lipoedema.

1. Lipoedema is indeed the cause of severe psychological stress or mental health disorders (e. g. depression, anxiety, eating disorder)
2. Mental health disorders are independent comorbid conditions of lipoedema.
3. Mental health disorders contribute to the development of the pain experienced in lipoedema.

Psychological stress and pain

Based on surveys that have been carried out, nearly half the women with lipoedema questioned described the pain as severe

(33.9 %) or extremely severe (14.4 %) [8]. Pain is therefore a key symptom in women diagnosed with lipoedema. In other words, the patient with lipoedema is also a Pain patient.

A further and equally challenging question is therefore what effects does the psychological stress of the patient with lipoedema have on her pain perception?

A relationship between psychological stress and pain perception has already been well described in many patients with pain disorders [15–21].

In multimodal pain management, it is a matter of course to ascertain the biopsychosocial factors that are determining and reinforcing chronic pain [22]. Hooten [21] conducted exemplary studies on pain in the neck and lower back (N = 845 and 790). The risk of developing a depressive episode within the following 6–12 months was twice as high to two-and-a-half times higher in people with these painful conditions. Conversely, people who had no pain but high depression scores had a four-fold risk of developing this type of pain. He found a dose-effect relationship: the more severe the depression, the higher the risk of developing pain.

Another question is now whether psychologically stressful experiences in life have an effect on the chronification of pain. In this context, there is also the question of resilience or psychological resistance. What roles do resilience, resources, and other possibilities for coping play in regard to severe psychological stress?

The studies by McLaughlin et al. [23] provide some evidence: violent experiences in childhood predict subsequent pain when the violence has led to the development of a mental health disorder. It is not the event itself that is the deciding factor, but rather the excessive demand to cope with the experience and the subsequent development of a mental health disorder.

The strong neurobiological overlap of the stress-processing system and the pain-processing system can lead to pain being centrally generated due to the dysfunction of the stress-processing system, which is subsumed in the term “stress-induced hyperalgesia” (SIH) [24]. Pain can thereby be modulated or even induced by psychosocial factors [25].

Depression and anxiety disorders also increase the risk of developing chronic pain [21]. One possible explanation is the partial overlap of the neuronal structures that are involved in depression as well as in anxiety and chronic pain.

Beyond the clinical picture of these mental health disorders, catastrophic thoughts and helplessness are also good predictors of the risk that back pain will become a chronic disease [26, 27].

Chibuzor-Hüls et al. considered the following factors to be yellow flags for the chronification of back pain: depressive mood, distress (negative stress), pain-related cognition such as catastrophic thinking, helplessness and hopelessness, fear-avoidance behaviour and passive pain behaviour (marked protective and

avoidance behaviours) [28]. The effects of stress on pain have also been demonstrated in cases of rheumatic disease [29]; particularly in fibromyalgia, there is consistent evidence for the effects of psychosocial factors on pain perception [30, 31].

The perception of other physical symptoms is also influenced by the psyche. The results of a phlebology study [32] show that fear about varicose veins intensifies the feelings of tension and heaviness in the legs even in completely healthy men and women. It is interesting to note that feelings of tension and heaviness in the legs are also typical symptoms of women with lipoedema.

Effects of pain education and psychotherapy on psychological stress and chronic pain

In its scientifically based concept of pain neuroscience education (PNE), the biopsychosocial approach taken by the Neuro Orthopaedic Institute (NOI) recognises that the nervous system is a complex, mobile, plastic, and adaptable organ [33]. Providing patients with knowledge about the relationship between pain, stress, and physical performance leads to a revised conception of pain and is actively used to reduce pain and increase activity [34].

Therapies that are well-researched in the field of interdisciplinary treatment include cognitive behavioural therapy (CBT) [35, 36], which allows a breakthrough in the vicious circle of fear and avoidance, and attention-based acceptance and commitment therapy (ACT), which is used to increase psychological flexibility. Both of these therapies have effects on the severity of pain and improve depression and the quality of life [37, 38].

Eye movement desensitisation and reprocessing (EMDR) is a very promising approach, especially in patients with pain who have a history of trauma [39].

The lipoedema pilot study

Aims of the pilot study

The key questions were:

1. Is lipoedema really the cause of severe psychological stress (including mental health disorders)?
2. Is there a relationship between existing mental health disorders and the pain intensity perceived by patients diagnosed with lipoedema?

Methods

The study protocol meets the requirements of the Declaration of Helsinki in its current version. All subjects gave their informed consent to participation in the study and the analysis of their anonymised data. None of the participants – as indeed no other patient – were withheld treatment due to participating in the study. On the contrary, any psychotherapeutic counselling or therapy sessions required after completion of the study interviews could be carried out on an even more personalised scale thanks to the more detailed diagnostics.

Study design

The present study is a continuation and expansion of the first phase of the study described at the beginning of the series of articles, in Lipoedema – Myths and Facts, Part 1 [40]. In total, 150 patients admitted to the European Centre for Lymphology for inpatient treatment were enrolled in the study with a confirmed diagnosis of lipoedema made by two different doctors with many years of experience in this disease. Patients were enrolled between April 2017 and September 2019, independently of any need for psychotherapy. The criteria for diagnosing lipoedema were defined as follows: a disproportionate increase of fatty tissue in the legs and pain in the affected soft tissues, as the major symptoms. This approach corresponds to the criteria of the European Consensus on the Diagnosis and Treatment of Lipoedema compiled in March 2019 [2].

For the purposes of this study, “psychological stress” was defined as:

- A mental health disorder (ICD-10 F diagnosis such as depression, eating disorder, post-traumatic stress disorder (PTSD), anxiety disorder and panic disorder)
- Signs of mental health issues (ICD-10 Z diagnoses) that did not quite meet the criteria for an “F diagnosis” (serious psychological distress such as burnout, stress, and extreme chronic stress).

A qualified psychotherapist with particular experience in this patient population conducted semi-structured interviews with the patients. The interviews were divided into two sessions and consisted of:

1. ascertaining current mental health disorders according to the ICD-10 criteria [41] and signs of serious mental health issues, as well as determining all such episodes that had occurred in the patient’s past medical history
2. ascertaining the symptoms associated with the lipoedema, including recording the current minimum and maximum pain intensity experienced in everyday life (over the last seven days), as evaluated by the patient using a visual analogue scale (0–10).
3. determining the overlap of the two areas with the patient, i. e. putting the lipoedema-associated pain on the one hand and psychological stress on the other into a temporal relationship.

As there are no questionnaires for establishing psychological stress over a lifetime, we used semi-structured interviews as the explorative method for this new field in women diagnosed with lipoedema. This method was also used to record the current ICD diagnoses. The symptoms that are really clinically relevant were of particular interest. Clinical diagnoses seem to be an appropriate if hard criterion. When previous psychological findings were available, these were included to validate the recorded diagnoses.

The statistical analysis was performed with Excel and support with SPSS from an external source. Two-sided significances are given in the following.

► **Table 1** Description of the sample population: N = 150.

	patients with BMI < 40 kg/m ² n ₁ = 81	patients with BMI ≥ 40 kg/m ² n ₂ = 69	total study population N = 150
age in years	17–62	24–69	17–69
mean age	41.73	45.75	43.58
BMI in kg/m ²	21.98–39.90	40.42–71.52	21.98–71.52
mean BMI	33.20	47.86	39.94
WHtR	0.46–0.73	0.64–0.97	0.46–0.97
mean WHtR	0.61	0.78	0.69

The sample population

One hundred and fifty patients with a diagnosis of lipoedema were enrolled at the start of their inpatient treatment at the European Centre for Lymphology in Hinterzarten.

► **Table 1** shows the age, body mass index (BMI), waist-to-height ratio (WHtR) and their respective mean values, both for the entire study population (N = 150) and for the subgroups n₁ = 81 with BMI < 40 kg/m² and n₂ = 69 with BMI ≥ 40 kg/m². ► **Table 2** shows the distribution of the BMI in the study population: 3.3 % had a normal body weight (BMI 18–25 kg/m²), while 46 % were morbidly obese (Grade III obesity) with a BMI of more than 40 kg/m².

Results of the pilot study

Results with respect to the question: Is lipoedema really the cause of severe psychological stress (including mental health disorders)?

Psychological stress that precedes the development of typical lipoedema pain

We looked at severe psychological stress (mental health disorders and signs of serious mental health issues) within the 12 months directly preceding the onset of the typical symptoms of lipoedema.

In addition, we investigated the patient's whole lifetime, i. e. the entire time before developing lipoedema symptoms as well as the period thereafter.

The results of the diagnostic investigation of mental health disorders (ICD 10 F diagnoses) in the 12 months prior to the onset of lipoedema-associated pain show a strong cluster of depressive diseases that were considered at least a mild depressive episode (► **Table 3**). (Dysthymia, a mild depressive development that does not meet the criteria of a depressive episode, was excluded and counted under "other".) In addition, eating disorders with binge eating were considerably increased in the specified period of time. While the 12-month prevalence of depressive disorders is 8.4 % in the normal population, it was 30.7 % in the lipoedema population studied. The corresponding figures for eating disorders were 0.1 % in the normal population and 18.0 % in the studied patients with lipoedema in the 12 months prior to the development of lipoedema pain.

► **Table 2** Distribution of BMI in the total study population: N = 150.

weight category	BMI in kg/m ²	n	%
normal weight	18.5–25.0	5	3.3
overweight	25.0–29.9	15	10.0
grade 1 obesity	30.0–34.9	25	16.7
grade 2 obesity	35.0–39.9	36	24.0
grade 3 obesity	≥ 40.0	69	46.0

Taking together all the mental health disorders relevant to pain described in the literature, such as depression, anxiety disorders, eating disorders, and post-traumatic stress disorder, 46.7 % of the study sample had one or more of these mental health disorders at the same time. Pain with somatic components in parts of the body other than those later affected by lipoedema occurred in 1.4 % (but not as the primary diagnosis, i. e. other more serious health conditions were present). In this period, 9.3 % showed other primary diagnoses such as dysthymia, chronic fatigue syndrome, borderline personality disorders, and alcohol dependency.

In addition, 24 % of our total population had signs of serious mental health issues that did not meet the criteria of an "F diagnosis" but were coded as "Z diagnoses" (serious psychological distress such as burnout, stress, and extreme chronic stress), which lasted for several months before the start of the painful symptoms.

In this way, exactly 80 % (n = 120) of the women diagnosed with lipoedema showed relevant psychological stress that was already present in the 12-month period before the development of lipoedema-associated symptoms. This included new stress arising in the previous 12 months, as well as the recurrence of psychological stresses that had occurred before start of the 12-month period (e. g. recurrent depressive episodes).

Based on pure logic, the mental health disorders already established in the period before the lipoedema-associated pain developed can in no way be the result of lipoedema, as they were already present beforehand.

► **Table 3** Mental health disorders before the development of typical lipoedema pain, given in % for the subgroups according to BMI and for the total study population (N = 150); some patients with more than one diagnosis.

	patients with BMI <40 kg/m ² n ₁ = 81 in %	patients with BMI ≥ 40 kg/m ² n ₂ = 69 in %	total study population N = 150 in %	comparison of 12-month prevalence in German women [43] in %
depressive disorders	24.7	37.7	30.7	8.4
eating disorders (especially binge eating disorder) [29]	16.0	20.3	18.0	0.1
post-traumatic stress disorder	2.5	4.3	3.3	3.6
anxiety disorders and panic disorders	3.7	5.8	4.7	2.9 2.8
DAET (at least one of the above four categories)	40.7	53.6	46.7	–
pain with somatoform components (secondary diagnosis)	1.2	1.4	1.4	5.0
other primary diagnosis	11.2	7.3	9.3	–
no mental health disorders according to ICD-10: F	48.1	39.1	44.0	–

DAET: the presence of at least one mental health disorder from the four categories given above: depressive disorder, anxiety disorder, eating disorder or post-traumatic stress disorder. In the cases of DAET and "other", it is not possible to make a direct comparison with the 12-month prevalence. Pain with somatoform components appeared only as a secondary diagnosis.

Current mental health disorders (confirmed ICD 10 F diagnoses)

To address the question of whether lipoedema really leads to mental health disorders such as depression, anxiety disorder, eating disorders, and PTSD, the current disorders (i. e. present at the time of the study) were investigated and put into perspective in terms of the lipoedema.

The results of the diagnostic investigation of current mental health disorders given in ► **Table 4** show that 26 % of the 150 patients with lipoedema still suffered from depression, 14.7 % from an eating disorder with binge eating, 5.3 % from PTSD, and 3.3 % from anxiety disorders at the time of the study. It must be noted that some patients had more than one diagnosis.

The percentage of patients with the respective mental health disorders is greater in the subgroup with a higher BMI. In the subgroup with a BMI < 40 kg/m², 25.9 % had a mental health disorder consisting of depression, anxiety disorders, eating disorders, or of traumatic origin (PTSD) – which we have encompassed in the following as DAET – while the corresponding figure for the subgroup with a BMI ≥ 40 kg/m² was 49.3 %.

The percentages of current mental health disorders in the total study population given in ► **Table 4** are somewhat smaller than the figures for those occurring before the onset of lipoedema. This applies to depression, eating disorders, and anxiety disorders. This may be explained by the utilisation of psychotherapy, so that the original mental health disorder was no longer present at the time of the study.

The higher percentage of current PTSD was related to domestic violence and experiencing a crime, not to the existence of lipoedema.

The pilot study interviews explored the possible influence of lipoedema on the development of mental health disorders. The results show that current mental health disorders triggered primarily by lipoedema were identified in only one patient (0.7 %); exacerbation of a – pre-existing – disorder from the added stress of lipoedema occurred in nine cases (6 %).

Definite suicidal thoughts and their background

The patients were specifically asked about suicidal thoughts: 34 patients (22.7 %) admitted to having had suicidal thoughts previously, but not due to the lipoedema. Reasons mentioned were the death of a loved one, experiencing violence, or losing a job. Despite the high level of psychological stress experienced, none of the patients in the present pilot study evinced suicidality purely due to the lipoedema.

Results with respect to the question: Is there a relationship between existing mental health disorders and the pain intensity perceived by patients diagnosed with lipoedema?

The maximum and minimum pain scores in everyday life during the previous seven days were recorded using a visual analogue scale (VAS), as well as their reference to current mental health disorders.

► **Table 4** Current mental health disorders, given in % for the subgroups according to BMI and for the total study population (N = 150); some patients with more than one diagnosis.

	patients with BMI <40 kg/m ² n ₁ = 81 in %	patients with BMI ≥40 kg/m ² n ₂ = 69 in %	total study population N = 150 in %
depressive disorder	18.5	34.8	26.0
eating disorders (especially binge eating disorder) [42]	8.6	21.7	14.7
post-traumatic stress disorder	3.7	7.2	5.3
anxiety disorders and panic disorders	2.5	4.3	3.3
DAET (at least one of the above four categories)	25.9	49.3	36.7
pain with somatoform components ¹)	7.4 ¹	4.3 ¹	6.0 ¹
other primary diagnosis	13.6	10.1	10.6
no mental health disorders according to ICD-10: F	56.8	40.6	49.9 ²

DAET: the presence of at least one mental health disorder from the four categories given above: depressive disorder, anxiety disorder, eating disorder or post-traumatic stress disorder.

¹ the primary diagnosis in n₁: 4.9%; in n₂: 0%; and in N: 2.7%.

² Including 12.7% with binge eating under stress (n₁: 7.4%; n₂: 18.8%).

Presentation of the current maximum and minimum pain scores in everyday life (VASmax and VASmin)

► **Fig. 1** shows the maximum pain intensity in the patients' everyday lives as measured with a visual analogue scale, presented as a percentage of the total study population.

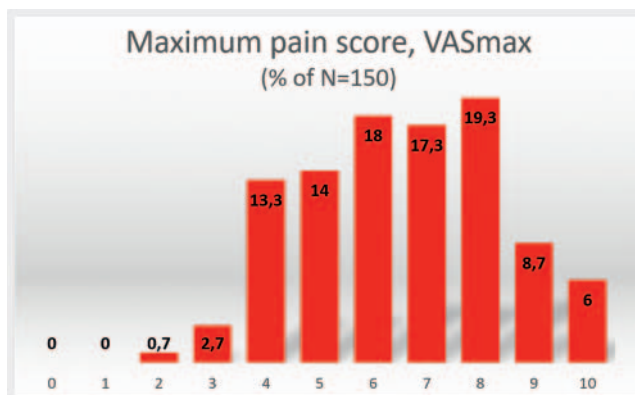
Nearly 70% (69.3%) of the patients gave a VASmax score of 6 or more, while more than half (51.3%) reported a maximum pain score of 7 or more. On a scale of 0–10, VAS 0 means no pain at all while VAS 10 is the most intense pain imaginable.

► **Fig. 2** shows the minimum pain intensity in the patients' everyday lives as measured with a visual analogue scale, presented as a percentage of the total study population. The VASmin showed that 28.7% of all patients were free of pain at least some of the time (VAS 0). Almost one-fifth (18%) of the women studied gave a VASmin of 5 or more. In other words, almost a fifth of the patients with lipoedema never have pain of less than a score of 5 in their daily lives, even for short periods!

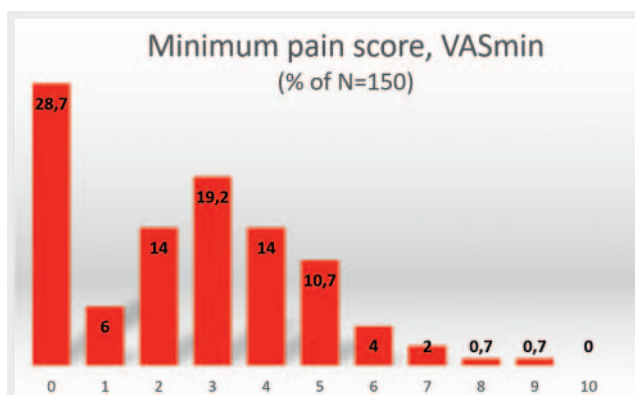
Statistical relationship between the current mental health disorders and the current maximum and minimum pain in everyday life

Patients diagnosed with lipoedema and with current mental health disorders classed as DAET (depression, anxiety disorders, eating disorders, or PTSD) showed a significantly higher VASmax than patients without any of these mental health disorders (with DAET: mean = 6.95 ± 1.64 vs without DAET: mean = 6.32 ± 1.94; p = 0.046) (► **Fig. 3**).

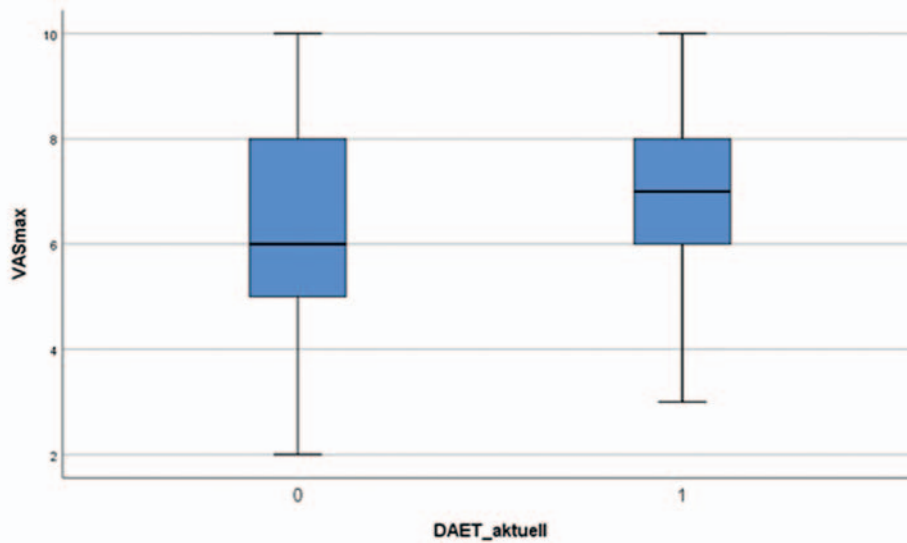
Patients with lipoedema who were suffering from the after-effects of trauma (PTSD) had very significantly higher maximum pain scores than patients who did not have this clinical disorder (with PTSD: mean = 8.38 ± 1.85 vs without PTSD: mean = 6.44 ± 1.80; p = 0.004). (► **Fig. 4**).



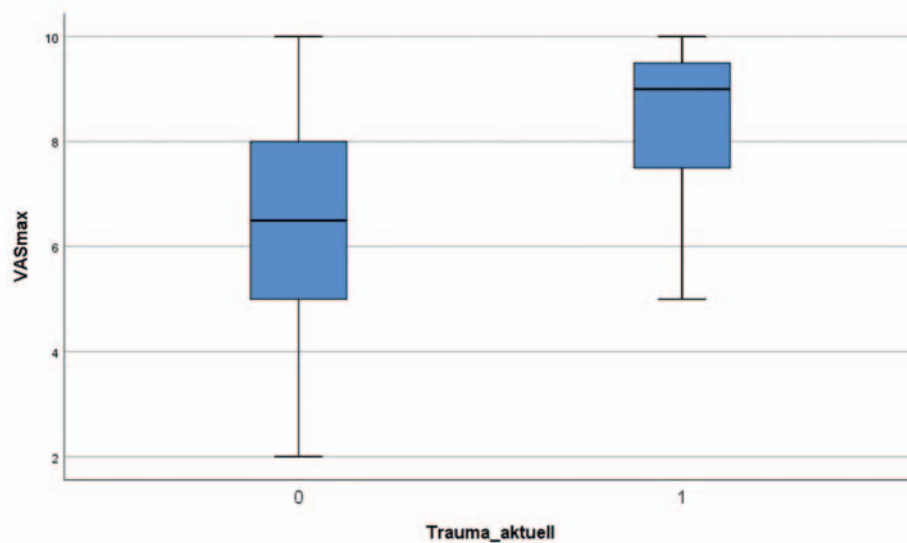
► **Fig. 1** Current maximum pain score, VASmax (0–10) given in %.



► **Fig. 2** Current minimum pain score, VASmin (0–10) given in %.



► **Fig. 3** Current maximum pain scores (VASmax) on a scale of 0–10, in patients with lipoedema: (0) without a DAET disorder or (1) with a DAET disorder (without DAET: median = 6.0; with DAET: median = 7.0).



► **Fig. 4** Current maximum pain score (VASmax) on a scale of 0–10, in patients with lipoedema: (0) without current post-traumatic stress disorder or (1) with post-traumatic stress disorder (without PTSD: median = 6.5; with PTSD: median = 9.0).

Depression (without depression: mean = 6.43 vs. with depression: mean = 6.87) and anxiety disorder (without anxiety disorder mean = 6.54 vs with anxiety disorder mean = 6.80) did not show any significant differences in the maximum pain, although depression had an effect on the minimum pain.

Looking at the level of pain which the patients reported as the absolute minimum in their daily lives, we can say the following: patients with a DAET mental health disorder had significantly higher minimum pain scores than the patients who did not have such problems (with DAET: mean = 3.07 ± 2.30 vs without DAET

mean = 2.18 ± 1.91 , $p = 0.011$). On average, therefore, patients who had a mental health disorder had more pain even when it was at its minimum.

Patients with lipoedema and current depression had a significantly higher minimum pain score than patients without depression (with depression: mean = 3.08 ± 2.30 vs without depression: mean = 2.31 ± 2.00 ; $p = 0.048$). Likewise, there was a highly significant difference in the VASmin of patients with lipoedema who had post-traumatic stress disorder (with PTSD: mean = 5.25 ± 2.36 vs without PTSD: mean = 2.25 ± 1.98 vs.; $p = 0.000$). This means that,

on average, patients with PTSD did not have a pain score less than 5.25 on a scale of 0–10, while patients without PTSD did not have a pain score less than 2.25.

The number of mental health disorders in the past medical history correlated significantly with the current maximum pain intensity in everyday life (Kendall's tau-b = 0.185; $p = 0.006$), i. e. the more concomitant mental health disorders that patients had, the higher the maximum pain experienced in everyday life.

We also looked at whether there was a possible difference in BMI between women with and without mental health disorders: overall, women who currently had an eating disorder had a significantly higher BMI than those who did not (with eating disorder: mean = $44.69 \pm 8.77 \text{ kg/m}^2$ vs without eating disorder: mean = $39.13 \pm 8.65 \text{ kg/m}^2$; $p = 0.006$).

Women with a DAET mental health disorder (depression, anxiety disorders, eating disorders, or PTSD) had a significantly higher BMI than those who did not (with DAET: mean = 41.97 ± 8.76 vs without DAET: mean = 38.77 ± 8.75 , $p = 0.033$). Furthermore, a linear regression showed that the BMI (together with the existence of PTSD before the lipoedema-associated pain developed) was a significant predictor of the VASmax, even though there was less explained variance. (In the model of PTSD prior to lipoedema and BMI: adjusted $R^2 = 0.076$ and $F(2, 147) = 7.151$, $p < 0.001$).

In the classical literature on lipoedema [45–47], oedema was often described as the cause of pain in women with lipoedema, so that we examined a possible influence of lymphoedema on the severity of the pain: patients diagnosed with lipoedema did not differ significantly in the maximum or minimum pain score whether or not they had – usually obesity-related – lymphoedema ($n = 72$ after verifying the diagnostic standards, VASmax in 44 patients without lymphoedema: mean = 6.41 ± 1.87 vs VASmax in 23 patients with lymphoedema: mean = 5.61 ± 1.73 ; $p = 0.093$, not significant; 5 patients had fluid retention) (VASmin in 44 patients without lymphoedema: mean = 2.27 ± 2.02 vs VASmin in 23 patients with lymphoedema: mean = 1.74 ± 2.14 ; $p = 0.317$, not significant). Additional existing lymphoedema therefore had no effects on the perception of pain intensity.

Beyond mental health disorders

The interviews demonstrated the typical problem areas in our patients with lipoedema, namely: self-acceptance, the increase in body weight, and the closely related acceptance of one's own body, as well as coping with the lipoedema-associated pain. Moreover, coping with stress and feelings such as anxiety, anger, and shame are central topics with respect to lipoedema. Some women who have experienced violence and/or been sexually assaulted have a markedly difficult relationship with their own bodies as a result, extending far beyond lipoedema.

On targeted questioning, 52 % of the total study population spoke of experiencing sexual abuse and/or physical violence in the past. We defined violence as multiple episodes of serious violence that led to bruising, e. g. being hit with a stick, belt or other object.

Qualitative part

The following quotations from the interviews provide an impression of what women with lipoedema describe: "I feel very guilty that my body is the way it is."; "Even as a child, I was always fatter than the others."; "I have always struggled with my body, ever since I was abused [in childhood]."; "... and if I ate even something small in between, I had to punish myself and do without at least one meal – sometimes I would then go to bed hungry ..."; "I was absolutely at the end of my tether and right on top of that came this horrible pain in my legs."; "When my husband says that he loves me the way I am, I simply can't believe him."

But the patients' resources also shone through the interviews: "Yes, the pain is often a 7 [on a scale of 0–10], but when you ask me how much I'm suffering, then my answer is more like a 3 [subjective units of disturbance scale of 0–10] ... I have since learnt to deal with it."; "Walking and swimming help me – the next day, I sometimes don't even have any pain for a while."; "In the meantime I have started to dress more fashionably and I am more and more beginning to see myself in a positive light."

Discussion

This pilot study explored a field of research that has previously been overlooked: the psychological situation of women who have been diagnosed with lipoedema immediately before the development of the lipoedema-associated symptoms, as well as the effects of these patients' psychological stress on the pain intensity perceived.

First, we reviewed a great many oft-repeated statements from the literature and the media for scientific evidence, addressing the question:

Is lipoedema really the cause of severe psychological stress?

In our study, we defined psychological stress as the presence of an overt mental health disorder (ICD 10 F diagnosis) or/and signs of a serious mental health issue (serious psychological distress with an ICD 10 Z diagnosis). Exactly 80 % ($n = 120$) of the study patients showed a high level of psychological stress.

However, this psychological stress arose in the 12-month period before the onset of the lipoedema-associated symptoms. On purely logical grounds, something which was already present before the symptoms of lipoedema arose cannot be the consequence of the condition – and that's for sure.

A deterioration in mental health that could be attributed directly to the lipoedema was found in only 6 %, while lipoedema as the main trigger of a mental health disorder was rare, namely in just one person (0.7 %).

In this way, the popular assertions that lipoedema makes people mentally ill or that lipoedema is the cause of all the psychological stress in women who have been diagnosed with lipoedema can be refuted for the vast majority of women with this condition.

With respect to severe psychological stress occurring immediately before the onset of the lipoedema-associated symptoms, the question arises of whether such evident psychological stress possibly has an effect on the development of the pain.

Using data collected retrospectively, we are unable to determine any direct causality, but we can analyse the evidence for possible effects.

A high proportion of women with lipoedema (80 %) not only show serious psychological stress, but also show it immediately before the emergence of the lipoedema-associated symptoms. This increased – and in comparison, with the normal population clearly higher – occurrence (especially of disorders such as depression, eating disorders or PTSD) in the 12 months immediately preceding the lipoedema-associated symptoms, may indicate the following:

With corresponding somatic conditions, psychological factors may contribute to the development of lipoedema-associated pain.

Even if our data do not allow us to prove a causal effect, we can still investigate a possible relationship between psychological factors and lipoedema-associated pain:

Is there a relationship between a patient's mental health disorder and the pain intensity perceived?

As presented above, such effects are known for other “pain conditions”. In particular, depression, anxiety, chronic stress, and trauma are linked to chronic pain.

In the present pilot study, we found that the current mental health disorders of depression, eating disorders, anxiety disorders and PTSD were associated with greater maximum pain. That is to say, in the group of patients who had one of these disorders, the average maximum pain score was higher than in the patients without any of them.

The effects of depression and post-traumatic stress disorder on pain intensity are of particular relevance. Patients who had been diagnosed with lipoedema and depression had a significantly higher minimum pain score than patients without depression. This means that the pain intensity experienced even at relatively good moments remained higher than that experienced by patients with lipoedema but without any depression.

Both PTSD before the development of lipoedema-associated pain and current PTSD had striking effects on the maximum pain currently experienced. But the least pain experienced by the patients with lipoedema and PTSD even at the best times in their daily life also remained significantly higher than the pain experienced by the patients without PTSD. These patients had extremely severe pain in the body regions affected by lipoedema, mostly finding it extremely difficult to be touched in these places. The reason for this could be stress-induced hyperalgesia (as outlined in section 3) after experiencing trauma as extreme stress.

The percentage of patients with anxiety disorders in our sample was relatively low at 3.3 % and showed, possibly for this very reason, no significant effect on the maximum pain. Another explanation for this could be that the disease-related fear relevant to pain was reflected in a full-blown anxiety disorder in only a few cases. Similar observations have also been made in oncology [44].

In the case of eating disorders, there was a subgroup that explained “Eating served to numb the feelings of stress” or “to combat stress.” Binge eating represented an attempt to find a solution for overcoming psychological stress [42] and had the effect of reducing stress and consequently pain in this group of people.

In the classical literature on lipoedema, oedema is readily given as the cause of the feelings of tension, tenderness, and pain in the legs [45–47]. Apart from the fact that the view of “lipoedema as an oedematous condition” has been abandoned in any case [2,

49, 50], the present study shows that additionally existing lymphoedema has no effect on pain intensity in patients with lipoedema.

Diverging briefly to the topic of obesity, a subject that is often ignored in women with lipoedema (► Fig. 5), when we first described our study population it was immediately apparent that 86.7 % of the study population with lipoedema were obese, and that 46 % were even morbidly obese (Grade III obesity with a BMI ≥ 40 kg/m²). Only 3 % of the study population was of normal weight (BMI 18.5 to < 25 kg/m²). The high prevalence of obesity in our inpatients with lipoedema was no different from the figures from other outpatient treatment centres.

Lymphology centres in other countries present similar figures for patients with lipoedema. For example, a much-cited British study by Child and Gordon [6] showed that 8 % had Grade 1 obesity, 27 % Grade 2, and 50 % Grade 3. Only 4 % of the British study population were of normal weight. The study by Dudek [7], surveying women with lipoedema from different countries via the internet also found high BMI values (Study 1 with 113 patients: mean BMI 41.24 kg/m²; Study 2 with 321 patients: mean BMI 42.51 kg/m²).

Integration of the present study results, divided according to the BMI, makes it clear that the patients with lipoedema represent a patient group in which we have to focus on both problem areas – not only the obesity but also the high psychological stress – as well as possible relationships between the two.

As the VASmax for pain also increases with increasing BMI, medical professionals treating women with lipoedema also have to focus on the obesity.

But not all problems are so pronounced that they meet the criteria for mental health disorders (ICD 10 F diagnosis). In the current psychological condition, problems with self-acceptance (in general), acceptance of one's own body (in particular), dealing with lipoedema-associated pain, coping with stress, and “difficult” feelings such as anxiety, anger, and shame due to the lipoedema play an important role. These issues do not necessarily become full-blown mental health disorders but still affect the patient's relationship with her body, how she experiences the pain, and how she copes with it.

Psychotherapy such as cognitive behavioural therapy (CBT) [35, 36], acceptance and commitment therapy (ACT) [37, 38], eye movement desensitisation and reprocessing (EMDR) [39], and “pain neuroscience education” (PNE) [33] has high significance internationally in the treatment of patients with pain, as mentioned in Section 4. It goes almost without saying that patients with lipoedema may also benefit from these approaches.

Limitations

We would very much have liked to have had a control group consisting of patients with pain-free lipohypertrophy, in order to make comparisons with patients whose body image meets the current slim ideal of beauty as little as our patients with lipoedema – however, we almost never see such patients in our clinic. Finding a parallel cohort of women with pain-free lipohypertrophy through general practices proved unfeasible. The inclusion of a control group would have confirmed the findings in this new field



► **Fig. 5** A patient with the diagnoses of lipodema and obesity.

of research to a greater extent. This limitation is the reason why we call the present work still “pilot study”.

Pain is a complex phenomenon with many contributory aspects. In future research, the coarse screen of mental health disorders can be refined to include such entities as disease-related anxiety or fear, which plays an important role in lipodema due to the misinformation that abounds [48].

Only a very small percentage of the anxiety due to misinformation before the lipodema progresses (women with lipodema often express the fear that they may later have to walk with a rollator or end up in a wheelchair) is actually diagnosed as an anxiety disorder. Similar observations have been made in oncology research [44]. This disease-related fear and also catastrophic thinking, the body image, and the belief that the pain can be changed can only be differentiated in a prospective study.

Conclusions and outlook

Eighty per cent of patients who have been diagnosed with lipodema show a high level of psychological stress in the period immediately before the lipodema-associated symptoms develop. Despite all its limitations, the pilot study presented here indicates that with the corresponding somatic conditions, psychological stress may contribute to the development of lipodema-associated pain. In addition, there are relationships between mental health disorders and the pain intensity experienced in everyday life.

This results in new approaches to the interdisciplinary treatment of women with lipodema. A first impression can be gained from the interdisciplinary treatment and follow-up beyond this pilot study of patients at the Centre for Lymphology who currently have PTSD, a group of patients that suffered from particularly intense pain. Even in the first session before the interdisciplinary treatment (sports therapy, compression therapy, and nutritional therapy) began, the input from trauma psychotherapy brought about considerable pain relief, reducing it from an initial VAS score of 8–10 down to 3–4. After the start of the interdisciplinary treatment – and with one to three more psychotherapy sessions – the pain was further reduced to a VAS score of 1–2, and even to 0 in a few cases, although the sports, compression, and nutritional therapies certainly contributed to the pain reduction. Because the number of patients in this subgroup is small, further studies focusing particularly on treatment are needed for us to draw any general conclusions.

In dealing with this condition, it is necessary for us to increase the awareness of doctors, physiotherapists, psychotherapists, and other involved healthcare workers to this frequent and important topic of psychological stress and to take away the shame from the women affected. The psychological perspective views mental health disorders as psychological coping strategies and the mind’s attempts to find a solution, and consciously includes this in planning treatment. The mental disorders identified in the patients of our pilot study are – once recognised – easy to change.

The high level of psychological stress emphasises the importance of integrating the psychosocial therapy pillar into further research and particularly into the interdisciplinary treatment of lipodema.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

- [1] S1-Leitlinie Lipödem. Verfügbar unter http://www.awmf.org/uploads/tx_szleitlinien/037-012L_S1_Lipoedem_2016-01.pdf
- [2] Bertsch T, Erbacher G, Corda D et al. Lipödem – Mythen und Fakten Teil 5. Streitschrift für eine European Best Practice of Lipoedema – Zusammenfassung des Konsensus des European Lipoedema-Forums. *Phlebologie* 2020; 49 (1): 31–50. doi:10.1055/a-1012-7670
- [3] Frambach Y, Baumgartner A, Schmeller W. Lipödem und Lebensqualität. *Vasomed* 2015; 27 (5): 248–249
- [4] Frambach Y, Baumgartner A, Schmeller W. Lipödem – eine „schwere“ Diagnose? *Vasomed* 2016; 5: 2–3
- [5] Bullinger M, Kirchberger I. SF-36 Fragebogen zum Gesundheitszustand. Handanweisung. Göttingen: Hogrefe; 1998
- [6] Child AH, Gordon KD, Sharpe P et al. Lipedema: An inherited condition. *Am J Med Genet Part A* 2010; 152A: 970–976
- [7] Dudek JE, Białaszek W, Ostaszewski P et al. Depression and appearance-related distress in functioning with lipedema. *Psychology, health & medicine* 2018; 23 (7): 846–853. doi:10.1080/13548506.2018.1459750
- [8] Dudek JE, Białaszek W, Ostaszewski P. Quality of life in women with lipedema: a contextual behavioral approach. *Quality of Life Research* 2016; 25: 401–408
- [9] Bosman J. Lipoedema: Poor knowledge, neglect or disinterest? *Journal of Lymphoedema* 2011; 6 (2): 109–111
- [10] Nath R. The injustice of fat stigma. *Bioethics* 2019; 33 (5): 577–590. doi:10.1111/bioe.12560
- [11] Fetzer A, Fetzer S. Lipoedema UK big survey 2014 Research Report. Lipoedema UK. 2016 www.lipoedema.co.uk
- [12] Dudek J. Quality of Life and Psychological Functioning of Patients with Lipedema and Dercum's Disease. FDRS Goals for the Future, Tools for Today. Salt Lake City, 2017. fatdisorders.org. Abrufbar unter: <https://youtu.be/xV-IVc0eVQM>
- [13] Alwardat N, Di Renzo L, Alwardat M et al. The effect of lipedema on health-related quality of life and psychological status: a narrative review of the literature [published online ahead of print, 2019 May 6]. *Eat Weight Disord* 2019; 10: doi:10.1007/s40519-019-00703-x
- [14] Kraus RH. Alles über das Lipödem. Lymphologischer Informationsdienst. Abrufbar unter: <http://www.lipoedemportal.de/lipoedem-folgerscheinungen.htm>
- [15] Linsmayer D, Neidlinger PK, Braus DF. Rheuma und Psyche – Eine Kurzübersicht. *Orthopäde* 2019; 48 (11): 957–962. doi:10.1007/s00132-019-03812-8
- [16] Baerwald C, Manger B, Hueber A. Depression als Komorbidität bei rheumatoider Arthritis. *Z Rheumatol* 2019; 78: 243–248. <https://doi.org/10.1007/s00393-018-0568-5>
- [17] Hofmann P, Hemberger S, Lunzer R et al. Psychische Aspekte der rheumatoiden Arthritis Wie ansprechen? Wie behandeln? Zusammenfassung des Expertenmeetings „Rheuma trifft Psyche“ am 05.11.2015. Abrufbar unter: https://www.pfizermed.at/sites/default/files/rheuma_trifft_psyche.pdf
- [18] Bischoff N, Morina N, Egloff N. Chronischer Schmerz bei Traumatisierung. Komplexität und Herausforderung bei Diagnostik und Therapie. *PiD – Psychotherapie im Dialog* 2016; 17 (4): 69–72. doi:10.1055/s-0042-116706
- [19] Viana MC, Lim CCW, Garcia Pereira F et al. Prior mental disorders and subsequent onset of chronic back or neck pain: findings from 19 countries. *J Pain* 2018; 19 (1): 99–110. doi:10.1016/j.jpain.2017.08.011
- [20] Tegethoff M, Belardi A, Stalujanis E et al. Comorbidity of Mental Disorders and Chronic Pain: Chronology of Onset in Adolescents of a National Representative Cohort. *The Journal of Pain* 2015; 16 (10): 1054–1064. doi:<https://doi.org/10.1016/j.jpain.2015.06.009>
- [21] Hooten WM. Chronic Pain and Mental Health Disorders. 2016 Mayo Foundation for Medical Education and Research, *Mayo Clin Proc* 2016; 91(7): 955–970. Abrufbar unter: [https://www.mayoclinicproceedings.org/article/S0025-6196\(16\)30182-3/pdf](https://www.mayoclinicproceedings.org/article/S0025-6196(16)30182-3/pdf)
- [22] Neustadt K, Kaiser U, Sabatowski R. Das biopsychosoziale Schmerzmodell: Leidfaden Heft 2017; 4: 10.13109/9783666402906.49.
- [23] McLaughlin KA, Basu A, Walsh K et al. Childhood Exposure to Violence and Chronic Physical Conditions in a National Sample of US Adolescents. *Psychosom Med* 2016; 78 (9): 1072–1083. doi:10.1097/PSY.0000000000000366
- [24] Egloff N, Bischoff NS, Kipfer S et al. Stressinduzierte Hyperalgesie. Ein pathogenetisches Modell zum klinischen Verständnis funktioneller Schmerzsyndrome. *Ärztliche Psychotherapie und psychosomatische Medizin* 2016; 11 (3): 130–137
- [25] Roth G, Egle UT. Neurobiologie von Schmerz und Stress. *Ärztliche Psychotherapie u. Psychosomatische Medizin* 2016; 11: 120–129
- [26] Briest J, Bethge M. Der Einfluss von Katastrophisieren auf den Effekt von Depressivität auf Schmerz und körperliche Funktion. *Der Schmerz* 2017; 2: 159–166
- [27] Neubauer E, Junge A, Pirron P et al. HKF-R 10 – screening for predicting chronicity in acute low back pain (LBP): a prospective clinical trial. *Eur J Pain* 2006; 10 (6): 559–566. doi:10.1016/j.ejpain.2005.08.002
- [28] Chibuzor-Hüls J, Casser HR, Birklein F et al. DNP – Der Neurologe & Psychiater 2020; 21 (2): 54–62
- [29] Baerwald C. Einfluss von geringem und schwerem Stress auf eine Rheumaerkrankung. Deutsche Rheuma Liga. Abrufbar unter: <https://www.rheuma-liga.de/stress>
- [30] Häuser W, Bohn D, Kühn-Becker H et al. Is the association of self-reported childhood maltreatments and adult fibromyalgia syndrome attributable to depression? A case control study. *Clin Exp Rheumatol* 2012; 74: 59–64
- [31] Afari N, Ahumada SM, Wright LJ et al. Psychological trauma and functional somatic syndromes: a systematic review and meta-analysis. *Psychosom Med* 2014; 76: 2–11
- [32] Blaettler W, Amsler F, Mendoza E. The relative impact on leg symptoms of fears of getting varicose veins and of great saphenous vein reflux. *Phlebology* 2012; 1–6. doi:10.1258/phleb.2012.011158
- [33] Moseley GL, Butler DS. Fifteen Years of Explaining Pain: The past, Present and Future. *The Journal of Pain* 2015; 16 (9): 807–813
- [34] Louw A, Zimney K, Puentedura EJ et al. The efficacy of pain neuroscience education on musculoskeletal pain: A systemic Review of the literature. *Physiother Theory Pract* 2016; 32 (5): 332–355
- [35] Probst T, Jank R, Nele Dreyer N et al. Early Changes in Pain Acceptance Predict Pain Outcomes in Interdisciplinary Treatment for Chronic Pain. *J Clin Med* 2019; 8: 1373. doi:10.3390/jcm8091373
- [36] Liedl A, Knaevelsrud C. PTBS und chronische Schmerzen: Entstehung, Aufrechterhaltung und Zusammenhang – Ein Überblick. *Schmerz* 2008; 22: 644–651. doi:10.1007/s00482-008-0714-0
- [37] Hughes LS, Clark J, Colclough JA et al. Acceptance and Commitment Therapy (ACT) for Chronic Pain: A Systematic Review and Meta-Analyses. *Clin J Pain* 2017; 33 (6): 552–568. doi:10.1097/AJP.0000000000000425
- [38] Veehof M, Trompetter H, Bohlmeijer E et al. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cognitive Behaviour Therapy* 2016; 45 (1): 5–31. doi:10.1080/16506073.2015.1098724
- [39] Gerhardt A, Leisner S, Hartmann M et al. Front Psychiatry (Impact factor: 4.58) 2016 [Epub ahead of print]. Eye Movement Desensitization and Reprocessing (EMDR) Versus Treatment as Usual for Non-Specific Chronic Back Pain Patients with Psychological Trauma: A Randomized Controlled Pilot Study.
- [40] Bertsch T, Erbacher G. Lipödem – Mythen und Fakten Teil 1. *Phlebologie* 2018; 47: 84–92

- [41] Dilling H, Mombour W. Internationale Klassifikation psychischer Störungen: ICD-10 Kapitel V (F) – Klinisch-diagnostische Leitlinien. Hogrefe. 2015
- [42] Gemeinsame S3-Leitlinie „Diagnostik und Therapie der Essstörungen“, 2. überarbeitete Version Frühjahr 2018. Abrufbar unter: https://www.awmf.org/uploads/tx_szleitlinien/051-026l_S3_Esstoeerung-Diagnostik-Therapie_2020-03.pdf
- [43] Jacobi F, Höfler M, Siegert J et al. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: The Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). *Int J Methods Psychiatr Res* 2014; 23 (3): 304–319. doi:10.1002/mpr
- [44] Dinkel A, Krensreiter K, Marten-Mittag B et al. Comorbidity of fear of progression and anxiety disorders in cancer patients. *Gen Hosp Psychiatry* 2014; 36 (6): 613–619. doi:10.1016/j.genhosppsych.2014.08.006
- [45] Schmeller W, Meier-Vollrath I. Das Lipödem: Neue Möglichkeiten der Therapie. *Schweiz Med Forum*. 2007; 7: 151
- [46] Schmeller W, Meier-Vollrath I. Lipedema. Abrufbar unter: <https://www.lipedema-simplified.org/downloads/Lipoedema-schmeller.pdf> S. 297
- [47] Rapprich S, Dingler A, Podda M et al. Liposuction is an effective treatment for lipedema – results of a study with 25 patients. *Journal of the German Society of Dermatology* 2011; 9 (1): 33–40. doi:10.1111/j.1610-0387.2010.07504.x
- [48] Mendoza E. Beitrag als Diskussionsgrundlage zum Thema: Fehlinformation im Internet und Konsequenzen für Patienten und uns Ärzte im täglichen Arbeitsfeld am Beispiel des Lipödems. *Phlebologie* 2020; 49 (2): 115–116. doi:10.1055/a-1124-5079
- [49] Bertsch T, Erbacher G. Lipödem – Mythen und Fakten Teil 2. *Phlebologie* 2018; 47 (3): 120–126. doi:10.12687/phleb2418-3-2018
- [50] Hirsch T, Schleinitz J, Faerber G. Ist die Differentialdiagnostik des Lipödems mittels hochauflösender Sonografie möglich? *Phlebologie* 2018; 47: 182–187. doi:10.12687/phleb2431-4-2018