Is the differential diagnosis of lipoedema by means of high-resolution ultrasonography possible?

T. Hirsch[1]; J. Schleinitz[2]; M. Marshall[3]; G. Faerber[4]

[1]Praxis für Innere Medizin und Gefäßkrankheiten, Halle; [2]Praxis für Allgemeinmedizin und Phlebologie, Lützen; [3]Tegernsee; [4]Zentrum für Gefäßmedizin, Hamburg

Keywords

Lipoedema, lipohypertrophy, secondary lymphoedema, sonography, mattress phenomenon

Summary

Introduction: The current German guidelines on treating lipoedema recommend using flat-knitted compression material and manual lymphatic drainage as well as liposuction. Differentiating lipoedema from obesity and asymptomatic lipohypertrophy frequently proves difficult. However, a reproducible and objective differential diagnosis is the foundation of an expedient and cost-effective treatment. Material and Methods: As part of a multi-centre registry study (5 centres) ultrasound scans were performed between 1/2016 and 5/2017 on the legs (n=294) of a total of 147 patients with lipoedema (n=136), lymphoedema (n=20), lipoedema with secondary lymphoedema (n=30), lipohypertrophy (n=42) and obesity (n=30), as well as healthy individuals (n=36). Measurements were performed on the thickness of the cutis and subcutis of the lower and upper leg and on their compressibility. An analysis of the sonomorphology was also conducted. Results: Special sonomorphological properties that allow lipoedema to be differentiated from other disease entities and from healthy individuals have yet to be consistently and conclusively identified. The compressibility of the cutis-subcutis complex is completely unspecific and does not allow for any conclusions to be drawn concerning lipoedema. It has not been possible to detect fluid retention in patients with "painful lipohypertrophy" so that the description of the disease as lipoedema is misleading and should be reconsidered.

Schlüsselwörter

Lipödem, Lipohypertrophie, sekundäres Lymphödem, Sonografie, Matratzenphänomen

Zusammenfassung

Einleitung: Die aktuelle deutsche Leitlinie zur Behandlung des Lipödems empfiehlt neben der Therapie mit flachgestrickten Kompressionsmaterialien und manueller Lymphdrainage auch die Liposuktion. Die Abgrenzung zu Adipositas und asymptomatischer Lipohypertrophie stellt dabei häufig ein differenzialdiagnostisches Problem dar. Eine reproduzierbare und objektivierbare Differenzialdiagnostik ist aber die Grundlage für eine zielführende und wirtschaftliche Behandlung. Material und Methoden: Im Rahmen einer multizentrischen Registerstudie (5 Zentren) wurden im Zeitraum von 01/2016 bis 05/2017 die Beine (n=294) von Patientinnen mit Lipödem (n=136), Lymphödem (n=20), Lipödem mit sekundärem Lymphödem (n=30), Lipohypertrophie (n=42) und Adipositas (n=30) sowie von Gesunden (n=36) sonografisch untersucht. Es wurden Messungen der Dicke von Kutis und Subkutis an den Unter- und Oberschenkeln sowie von deren Komprimierbarkeit durchgeführt. Zusätzlich erfolgte eine Analyse der Sonomorphologie. Ergebnisse: Spezielle sonomorphologische Eigenschaften, die ein Lipödems von den anderen Krankheitsentitäten bzw. vom Gesunden abgrenzen lassen, konnten bislang nicht übereinstimmend und überzeugend herausgearbeitet werden. Die Komprimierbarkeit des Kutis-Subkutis-Komplexes ist vollkommen unspezifisch und lässt keinen Rückschluss auf die Diagnose Lipödem zu. Der Nachweis von Flüssigkeitseinlagerungen bei Patienten mit einer „schmerzhaften Lipohypertrophie" gelingt nicht, sodass die Krankheitsbezeichnung Lipödem irreführend ist und überdacht werden sollte.

Correspondence to:
Dr. med. Tobias Hirsch
Praxis für Innere Medizin und Gefäßkrankheiten
Venen Kompetenz-Zentrum®
Leipziger Straße 5
06108 Halle (Saale)
Tel. +49–345–50 33 03
Fax +49–345–50 33 04
E-Mail: info@gefaessmedizin-hirsch.de
www.gefaessmedizin-hirsch.de

Ist die Differenzialdiagnostik des Lipödems mittels hochauflösender Sonografie möglich?
Phlebologie 2018; 47: 182–187
https://doi.org/10.12687/phleb2431-4-2018
Received: 18. Juni 2018
Accepted: 19. Juni 2018

Introduction

Lipoedema is a chronic, often progressive disease characterised by a disproportionately high distribution of subcutaneous fat in the extremities. With rare exceptions, the disease affects women. In contrast to asymptomatic lipohypertrophy, which should be regarded as a morphologically normal variant of no pathological character, patients with lipoedema suffer from frequent episodes of orthostatic oedema and an increased tendency to bruise (1).

However, the main feature of the disease is pain, hence the names such as "lipohy-

perplasia or lipohypertrophia dolorosa", "lipalgia" or "painful column leg" also used in older terminology. Patients feel increased pain on contact or palpation of the affected areas of the arm or leg. Spontaneous pain is also often reported.

The current German guidelines for the treatment of lipoedema recommend compression therapy as first-line treatment. To relieve pain in refractory cases and if lymphostasis is also present, manual lymph drainage (MLD) and/or intermittent pneumatic compression (IPC) can be added. If symptoms persist despite this intensified conservative treatment, liposuction is recommended as a further step (2).

Although the definition of the disease appears clear, because of the frequently encountered mixed forms, differential diagnosis to distinguish lipoedema from obesity, lipohypertrophy and also from lymphoedema is often a challenge. In addition to lipoedema and lipohypertrophy, there are transitional forms that can arise in connection with changes in weight or the hormonal situation. Weight gain has an adverse effect on the course of the disease, not only through increasing the leg mass, but also due to the role of fat tissue in the intrinsic production of oestradiol (3).

Misdiagnosis leads to a waste of resources through the superfluous prescribing of compression stockings and MLD. Furthermore, liposuction is misunderstood as a method for weight reduction. But this corresponds neither to the aim of the procedure nor the recommendation of the guidelines.

Dubious reports in the media, but also the incorrect diagnosis by doctors treating them due to confusion of disease entities, lead to false hopes among overweight patients, to say nothing of unnecessary financial burdens.

This situation gives rise to the need to develop a procedure for a verifiable and reproducible diagnosis that can then enable the correct therapeutic consequences to be drawn from it. This is not only important in relation to liposuction (which is not generally covered by the statutory health insurance schemes; a situation that will not change until a completed independent study on liposuction is submitted following a decision by the G-BA), but also in relation to the waste of resources through the non-indicated – because futile – prescribing of MLD in lipohypertrophy.

Material and methods

Between 01/2016 and 05/2017, five German centres of vascular medicine (Hamburg, Wunstorf, Halle [Saale], Lützen, Munich) investigated the legs (n=294) of 147 consecutive female subjects and reported the following diagnoses based on the clinical findings: lipoedema (n=136), lipoedema with secondary lymphoedema (n=30), lymphoedema (n=20), painless lipohypertrophy (n=42) and obesity (n=30). Healthy women (n=36) were included for comparative purposes. The main exclusion criterion was a predominant phlebogenic oedema component in the context of chronic venous insufficiency, diagnosed using digital photoplethysmography (DPPG) and duplex ultrasonography of the leg veins. The presence of oedema of cardiac or nephrogenic genesis on the basis of the medical history and clinical findings, also led to exclusion.

The principal aim of the investigations was to identify specific morphological features that might be suitable for the exclusive characterisation of lipoedema and to distinguish it from the differential diagnosis of the above-mentioned conditions.

Another aim was to determine whether morphological diagnosis needed specific device requirements and technical settings on the ultrasound machines routinely used in clinical practice.

As well as measuring the thickness of the cutis-subcutis complex, an answer was sought to the question of whether an impaired compressibility can be considered as a correlate for the observation that on palpation the skin of lipoedema patients appears to show a coarser consistency, which is associated with the so-called "mattress phenomenon".

In addition, the possibility of using the findings described in previous ultrasound studies of lipoedema for the differential diagnosis of the above-mentioned disease entities was to be investigated. Of particular interest was a reported uniformly increased echogenicity and echo-rich septa, with the absence of anechoic gaps (4, 5).

The investigations were carried out with linear transducers (frequency 10–13 MHz) and the following ultrasound scanners: GE Logiq E MK 7, GE Logiq P, Esaote My Lab Six. The penetration depth with all scanners was set at 4 cm with 2 foci (3/3).

For the best possible match of the image quality of the different scanners at the different centres, test images of the forearms of the participating investigators were recorded (scanner GE Logiq E Mk 7, 12 MHz linear transducer, Hirsch Practice) at a subsequent joint conference of the authors on 03.12.2016. The image then served as a reference for matching the scanner settings used in the individual study centres.

The specified points of measurement are shown in ▶ Figure 1.

In addition to the sonomorphological evaluation, anatomical features such as jodhpur (riding breeches) deformity and/or the location of flabby skin folds could be recorded.

The following parameters were measured: cutis and subcutis thickness, maximum compressibility with the transducer (▶ Fig. 2).

Results

Sonomorphological features

After the terminology for the ultrasound characteristics had been specified according to the above-mentioned criteria, the study protocol planned to send the recorded scans to an independent expert with no knowledge of the clinically confirmed diagnosis and the other measurements, who was to classify the scans according to the above morphological criteria.

This approach did not lead to a usable result, for which the authors believe several factors were responsible. Despite the use of the most modern models of the various scanner brands and the best possible matching of their configurations, the technical differences in the images were too great to enable a critical comparison. This meant that the established image criteria could not be applied to all the devices.

The echogenicity of the interstitial structures varied too widely depending on

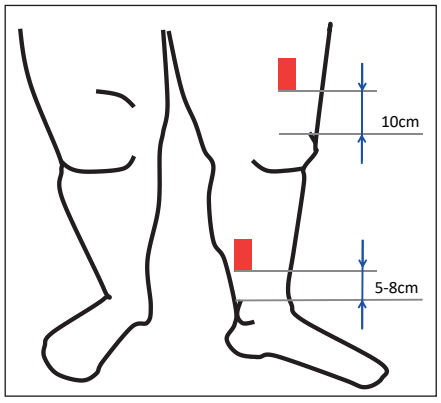

Fig. 1 Measurements were made with the transducer used longitudinally. Due the low variation in anatomy, the region 5–8 cm proximal to the medial malleolus proved particularly suitable.

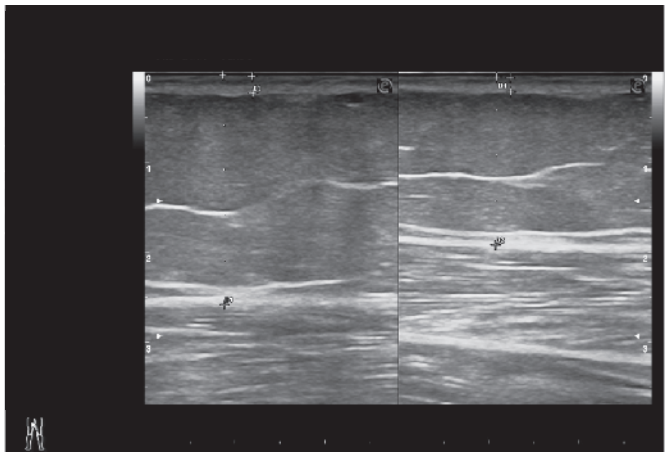

Fig. 2 Compressibility of the cutis-subcutis complex was measured first on minimal contact of the transducer (left) and then after maximum compression (right).

the scanner used. The matching of the device settings we had aimed for could not be implemented satisfactorily with the differing brands. Furthermore, the characteristics of the transducer and the sono-optic resolution depended on the depth of penetration. It was found that despite standardising the measuring points on the legs of subjects, the characteristics specified by consensus could not be differentiated in a reproducible manner.

Nevertheless, some knowledge could be gained. The general observation of a septa-rich subcutis, as described in the literature for a diagnosis of lipoedema (3, 4), could not be confirmed. Instead, the imaging was decisively dependent on the positioning angle and the axial rotation of the transducer, but did not correlate with the clinically diagnosed disease picture. It was clear that even the septa which, together with superficial skin changes, were expected to have been a possible correlate for a palpatory "mattress phenomenon" were completely non-specific in this study and were not related in any way to the clinical findings. The same applied to the "enhanced diffuse echogenicity" that has likewise been described for lipoedema (6). This sono-morphological feature could not be clearly characterised either or allocated to the individual diseases and/or to the normal state. Whereas the demonstration of larger hypoechoic images in the case of an also clinically predominant oedema was not difficult, it was not consistently possible with the smaller ones, described in the reference findings as "fine granular". In particular, no assessment applicable to all scanners or all scanner types could be achieved.

Tissue thickness and compressibility

The compressibility of the cutis-subcutis complex was determined by placing the transducer at the described points of measurement firstly with minimum contact and then, in a second step, with maximum compression of the tissue. The cutis and subcutis were measured before and after compression and the result given in percent. The same lack of sharpness as with the other morphological properties applied to the measurement of cutis thickness: the different scanners produced different imaging properties of the adjacent structures that rendered comparability impossible. In addition, the cutis thickness was highly variable.

The thickness of the cutis-subcutis complex and compressibility proved relatively unambiguous to measure, since the systematic error through the device-dependent resolution no longer mattered. Measurement in the distal lower leg region was particularly suitable because this region showed a smaller range of morphological variation in the adjacent structures. As expected, the thickness of the cutis-subcutis complex was less in the healthy control group and greater in the obese group than in the subjects with lipoedema and lipohypertrophy – which did not show relevant differences from each other (▶ Table 1).

The literature contains frequent reports of a coarser consistency of the skin in lipoedema and this was to be investigated by ultrasound in the compression test. Compressibility in the healthy control group (no pain, no disproportionality) varied from 3.2% to 32.6% in the ankle region and from 2.2% and 43.9% in the thigh. Obese sub-

Tab. 1 Demographic data and measurement values of the individual disease entities and of the control group

	Age (years)	BMI (kg/m2)	Cutis-subcutis complex (cm)	Compressibility (%)
Lipoedema (n=136)	39.27 ± 12.65	29.83 ± 6.75	2.2 ± 0.8	22.2
Lipohypertrophy (n=42)	42.94 ± 12.22	30.74 ± 7.49	1.9 ± 0.7	22.7
Obesity (n=30)	41.44 ± 11.67	46.04 ± 10.08	2.7 ± 0.9	25.6
Healthy (n=36)	50.88 ± 17.73	22.44 ± 3.24	1.0 ± 0.4	12.7

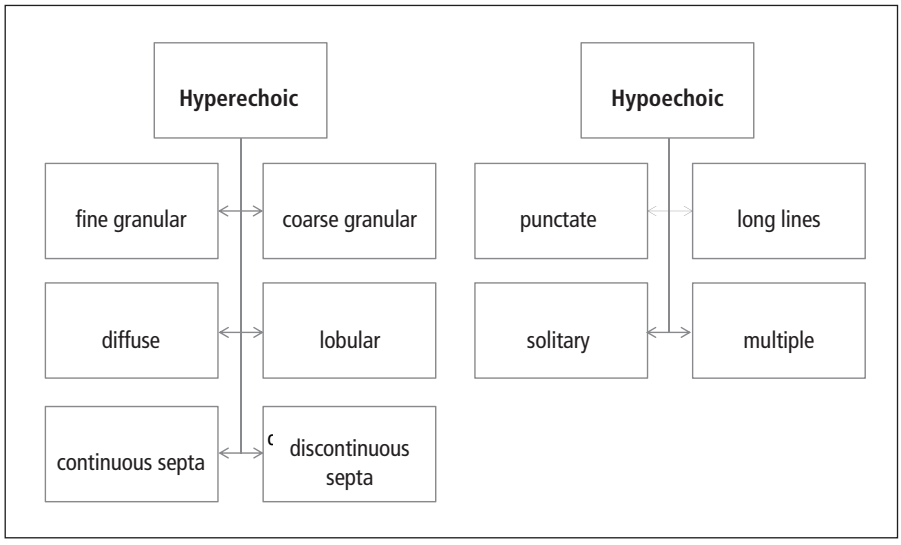

Fig. 3 Terminology system for sonomorphology

jects were characterised by a softer skin-subcutaneous complex and showed a greatly increased deformability (4.5% to 42.9%), Patients with painless lipohypertrophy showed a far greater variability (<5% to 48%) and did not differ from lipoedema patients (▶ Table 1, ▶ Figs. 5a and b).

Discussion

B-mode, Doppler and duplex ultrasonography are particularly important diagnostic instruments in vascular medicine. Whereas Doppler and duplex ultrasonography give very precise information about flow rates and characteristics of the blood, B-mode ultrasound is an excellent

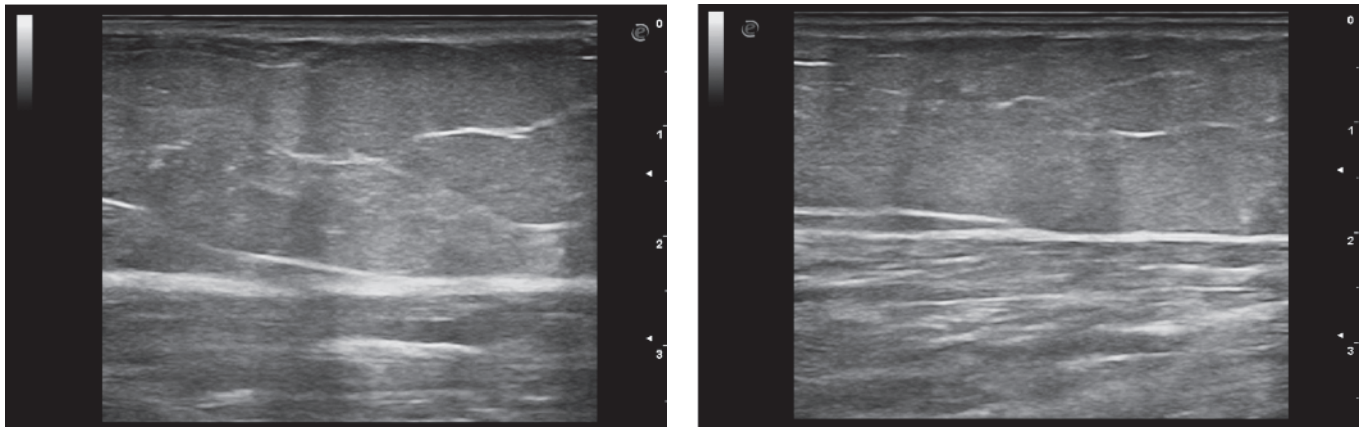

Fig. 4 a) Example 1: fine granular, lobular, hyperechoic tissue texture with continuous septa, multiple punctate hypoechoic parts; b) Example 2: fine, sometimes also coarse granular, diffuse, hyperechoic tissue texture with discontinuous, short septa, solitary hypoechoic parts in the septa.

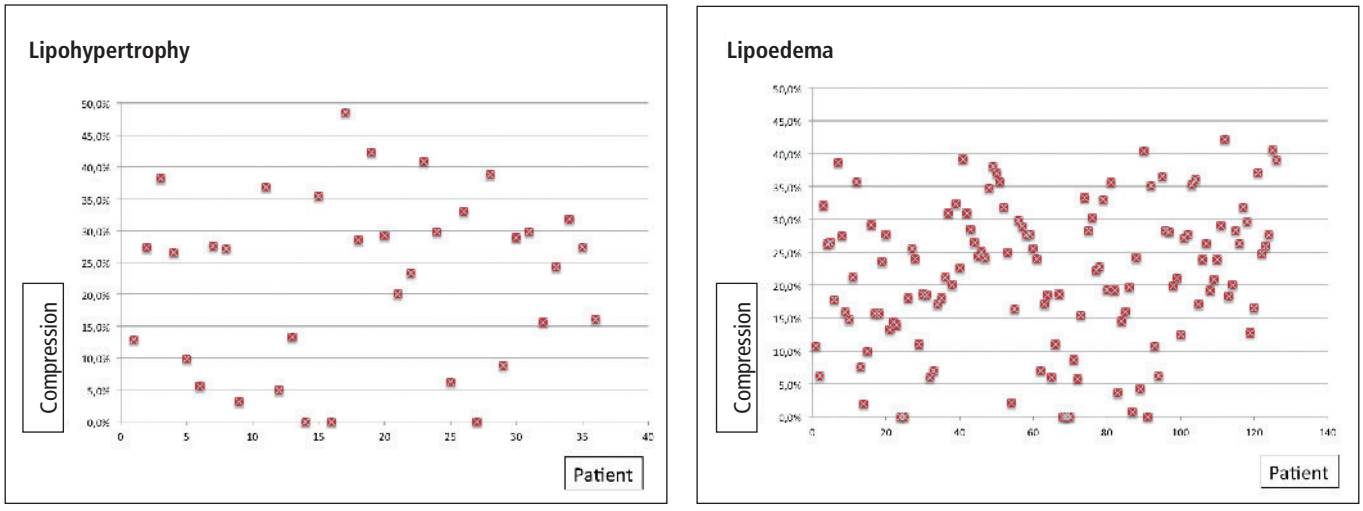

Fig. 5 The compressibility of the tissue varies considerably both in lipohypertrophy and in lipoedema and shows no specific features.

technique for distinguishing between solid structures and liquid compartments. For example, blood-filled vessels, fluid-filled cysts and effusions can be clearly identified through the absence of internal echoes. This is how oedema, which is represented by typical, three-dimensional anechoic tissue clefts, can be demonstrated in the skin and subcutaneous tissues (3, 4). However, as Becker et al. proved in a study in 38 subjects, it is not possible to draw any conclusions regarding the aetiology of oedema from the ultrasound scan. In that study, the authors attempted to distinguish lymphoedema from cardiogenic, phlebogenic and hepatogenic oedema (7). Naouri et al. compared the dermal echogenicity of patients with lipoedema (n=16) with that of patients with lymphoedema (n=22, control group n=16) and concluded that it was possible to differentiate lymphoedema and lipoedema with high-resolution ultrasonography, because the latter showed identical echogenicity to the healthy control group (8). Whereas the cutis thickness in the group with lymphoedema did not differ from that in the lipoedema group, the tissue of patients with lymphoedema was hypoechoic.

The intention of the present study was to examine whether differences in the echogenicity and/or ultrasound characteristics between lipoedema on the one hand and painless lipohypertrophy and obesity and healthy subjects on the other, could be demonstrated in the routine setting of a practice specialising in vascular medicine.

As reported by Naouri et al., we found it impossible to differentiate between the cutaneous/subcutaneous scan of a lipoedema patient and a normal subject or the findings of lipohypertrophy or of obesity. In particular, it was not possible to visualise the oedema component of lipoedema. This is ultimately not possible until a lymphostatic overload occurs, with the manifestation of anechoic tissue gaps. Using MRI, Lohrmann et al. (9) demonstrated a widening of the lymphatic vessels to >3 mm in patients with lipo-lymphoedema, whereas these were only measurable in pure lipoedema with calibres of up to 2 mm. They assessed these changes in calibre as signs of an incipient lymphostatic decompensation in lipoedema. However, we could not demonstrate this morphological feature in our ultrasound study.

Taking all the recorded results as a whole, the authors conclude that to date, confirmation of the diagnosis of lipoedema and its differential diagnosis is not possible using high-resolution ultrasonography. This is due to technical differences and characteristics of current scanners and the continued absence of a generally standardised and recognised investigation procedure. At present it is of considerable significance that it is not reliably possible to distinguish physiologically hypoechoic (liquid) structures from pathological ones.

Limitations

Ultrasound devices that cover the entire spectrum of vascular medicine diagnoses and which are routinely employed in a practice setting were used in this study. It is conceivable that computerised processing of high-resolution ultrasound signals, as is used for elastography when diagnosing breast and prostate cancer, would provide more information (10). Likewise, the use of higher frequency (15–20MHz) linear transducers offers advantages with regard to resolution and additional information. Expectations placed on ultrasound technology that were previously raised in older papers have not yet been fulfilled (11).

The clinical mixed pictures cause problems in the clinical differentiation of disease entities. Pure lipoedema in women of normal weight is a comparatively rare condition, and for this reason it was not possible to undertake a comparative subgroup analysis of only women of normal-weight with painless lipohypertrophy versus subjects with painful lipoedema. The specific comparison of just lipoedema and lipohypertrophy (BMI 25–30 kg/m^2) would be worthwhile in a further study. The additional use of higher-frequency transducers (20 MHz) for imaging would have to be investigated.

Conclusions

1. To date, the qualitative differentiation of the anatomical and pathomorphological features of lipoedema from those of painless lipohypertrophy, obesity and the skin/subcutaneous tissue of healthy persons using sonographic imaging is not possible to a satisfactory degree. Due to the large individual variation in findings and the likewise considerable differences in ultrasound scanners and their configuration, it is also currently impossible to obtain reproducible results that would enable the individual disease entities to be clearly distinguished.
2. Contrary to expectations, the compressibility of the cutis-subcutis complex is entirely non-specific. No sonographic correlate for clinical phenomena such as the mattress phenomenon could be established.
3. Although ultrasound enables accumulations of interstitial fluid to be demonstrated, it does not provide any indications of oedema aetiology.
4. Since it was not possible to demonstrate fluid accumulations in patients with "painful lipohypertrophy", the description of this disease as "lipoedema" is misleading and should be re-considered.

At the present time, it must be assumed that in routine care, essentially only the medical history and clinical findings are available for confirming the diagnosis of lipoedema and its differential diagnosis.

Acknowledgement

The authors are grateful to Dr. med. Christine Schwahn-Schreiber, Otterndorf for support in the inclusion of patients and in the processing of data and to Dr. med. Andrea Liebhold, Munich for participating in patient recruitment.

Conflict of interests

The authors declare that there is no conflict of interests

References

1. Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the dis-

proportional fatty deposition syndrome – systematic review. Clin Obes 2012; 2(3–4): 86–95.
2. Reich-Schupke S, Schmeller W, Brauer WJ et al. S1 guidelines: Lipedema. J Dtsch Dermatol Ges 2017; 15(7): 758–767.
3. Faerber G. Adipositas und chronische Inflammation bei phlebologischen und lymphologischen Erkrankungen. Phlebologie 2018; 47: 55–65.
4. Marshall M. Differentialdiagnostische Abgrenzung des Lipödems gegenüber dem Lymph- und Phlebödem mittels hochauflösender (Duplex)-Sonographie. Lymphol 1996; 20: 79–86.
5. Marshall M, Schwahn-Schreiber C. Lymph-, Lip- und Phlebödem. Differenzialdiagnostische Abklärung mittels hochauflösender Duplexsonografie: Gefässchirurgie 2008; 13: 204–212.
6. Mendoza E. Lipohyperplasie und Lipödem. In: Mendoza E (Hrsg). Duplexsonographie der oberflächlichen Beinvenen. 2. Aufl. Berlin, Heidelberg: Springer 2013, 265.
7. Becker M, Schilling T, von Beckerath O, Kröger K. Sonography of subcutaneous tissue cannot determine causes of lower limb edema. Vasa 2015; 44(2): 122–128.
8. Naouri M, Samimi M, Atlan M, et al. High-resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema. Br J Dermatol 2010; 163(2): 296–301.
9. Lohrmann C, Foeldi E, Langer M. MR imaging of the lymphatic system in patients with lipedema and lio-lymphedema. Microvasc Res 2009; 77(3): 335–339.
10. Sommerfeld HJ, Garcia-Schürmann JM, Schewe J et al. Prostatakarzinomdiagnostik durch Ultraschallelastographie – Vorstellung eines neuartigen Verfahrens und erste klinische Ergebnisse. Urologe 2003; 42(7): 941–945.
11. Dimakakos PB, Stefanopoulos T, Antoniades P, Antoniou A, Gouliamos A, Rizos D. MRI and ultrasonographic findings in the investigation of the lymphedema and lipedema. Int Surg 1997; 82: 414–416.