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High-resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema

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Summary

Background Lipoedema is an accumulation of fat abnormally distributed in the lower limbs, and lymphoedema is oedema caused by a deficiency of the lymphatic system. High-resolution ultrasound operating at 20 MHz makes it possible to characterize dermal oedema.

Objectives The purpose of our study was to demonstrate that high-resolution ultrasound imaging of the skin can differentiate lipoedema from lymphoedema.

Methods Sixteen patients with lymphoedema (22 legs), eight patients with lipoedema (16 legs) and eight controls (16 legs) were included. Patients with lipolymphoedema were excluded. Ultrasound examinations were carried out with a real-time high-resolution ultrasound device on three different sites for each lower limb. The images were then anonymized and examined by an independent dermatologist who was blind to the clinical diagnosis. A new series of images was examined by three dermatologists to check interobserver agreement.

Results A significant difference in dermal thickness was observed between patients with lymphoedema and those with lipoedema and between patients with lymphoedema and controls. No significant difference in dermal thickness was shown between patients with lipoedema and controls at the thigh or ankle. Dermal hypoechogenicity was found in at least one of the three sites in 100% of patients with lymphoedema, 12·5% of cases with lipoedema and 6·25% of the controls. Hypoechogenicity affected the entire dermis in all cases of lymphoedema except one. In cases of lipoedema and controls, hypoechogenicity was localized at the ankle and prevailed in the upper dermis. The expert correctly diagnosed all lower limbs with lymphoedema. No cases of lipoedema were diagnosed as lymphoedema. Exact interobserver agreement was excellent (0·98).

Conclusions High-resolution cutaneous ultrasonography makes it possible to differentiate lymphoedema from lipoedema. Obtaining a reliable diagnosis through high-resolution cutaneous ultrasonography might be valuable for improving the treatment of lipoedema and lymphoedema.

Lipoedema is an infrequently recognized disease that almost exclusively affects women.[1] It is characterized by bilateral, symmetrical lower extremity enlargement related to deposition of subcutaneous fat from the buttocks to the ankles, usually starting after puberty.[2,3] Feet are usually spared. Palpation of the lower limb can cause pain. Many patients with lipoedema have a family history of similarly enlarged legs, suggesting a genetic basis. Although obese patients may be over-represented among those with lipoedema (85% in the principal series),[4] individuals of normal weight are also frequently affected. The term lipolymphoedema is increasingly used to describe the superadded oedema which occurs on a background of lipoedema.[5]

Lymphoedema is a particular type of oedema caused by a deficiency of the lymphatic system resulting in an accumulation of protein-rich fluid in the dermis and the hypodermis.[3,6,7] Lymphoedema initially presents as unilateral painless swelling that usually starts on the dorsal aspect of the foot

including nonpitting oedema of the toe (Stemmer sign). Later stages include increased volume of lower limbs with nonslack oedema, sometimes leading to elephantiasis. Primary lymphoedemas are a heterogeneous group of genetic diseases with known mutations of the *FLT4* gene (previously known as *VEGFR3*) in Milroy disease[8] and of the *FOXC2* gene in lymphoedema associated with distichiasis,[9] resulting in functional abnormality of the lymphatic system. Lymphoedema is found in both sexes, but women are more often affected than men.[6] It can be found at any age. Two-thirds of all cases are unilateral.[6] Prevalence is estimated at 1 in 6000. Secondary lymphoedema more frequently occurs after radical lymph node surgery and/or radiotherapy of lymph nodes, but may follow changes caused by trauma, infection, inflammation or obesity.

Most cases of lymphoedema and lipoedema are diagnosed on history and clinical findings. However, it is sometimes difficult to distinguish the two conditions, even for skilled practitioners.[7,10,11] Clinical criteria were proposed by Wold *et al.*,[4] but there is currently no objective exploration routinely available to differentiate the two conditions. However, it is necessary to make the correct diagnosis as the treatments of the two conditions are different. Manual lymphatic drainage combined with multilayer lymphoedema bandaging or elastic compression is the main treatment of lymphoedema. These treatments are also frequently prescribed in cases of lipoedema because of a false diagnosis, but they are ineffective, costly, burdensome and sometime painful in this disorder. On the other hand, surgery may be indicated in some cases of lipoedema and can aggravate true lymphoedema.

Lymphoscintigraphy is currently the main procedure used to assess lymphoedema.[12,13] However, it is time-consuming and costly, and requires intradermal injection of radionuclide. High-resolution cutaneous ultrasonography is a noninvasive procedure, routinely used for more than 20 years in dermatology, and it can demonstrate dermal oedema.[14–18] Some studies have identified particular aspects of lymphoedema with high-resolution ultrasonography.[15,16] We hypothesized that a normal ultrasonographic dermal appearance in lipoedema is normal because it results from the deposition of subcutaneous fat and not from dermal accumulation of fluid. The purpose of our study was to demonstrate that high-resolution ultrasound imaging of the skin can differentiate lipoedema from lymphoedema.

Patients and methods

Criteria for subject selection

From November 2005 to November 2007, all the patients referred to our department for lymphoedema or lipoedema were offered high-resolution cutaneous ultrasonography. We also offered high-resolution cutaneous ultrasonography of the lower limbs to other patients hospitalized in our department to form a control group.

The inclusion criteria for patients with lymphoedema were swollen legs, nonpitting oedema, foot involvement, presence of Stemmer sign and abnormalities of lymphatic vessels as demonstrated on lymphoscintigraphy carried out for initial assessment of the disease. The inclusion criteria for patients with lipoedema were swollen legs and at least four of the six following clinical criteria: family history of lipoedema; obesity; lack of lower limb injury; absence of Stemmer sign; symmetrical involvement of both lower limbs; and spontaneous or provoked pain of the lower limbs. For the controls the inclusion criteria were legs clinically demonstrated as not swollen and no exclusion criteria.

The exclusion criteria were lipolymphoedema, skin diseases affecting the skin structure (elastic tissue disease, scleroderma, etc.), inflammatory skin disease, clinical signs of venous incontinence, history of renal, hepatic or cardiac failure, and treatment with corticosteroids.

Ultrasound imaging

Examinations were performed by a single operator (M.N.). Real-time 20-MHz high-resolution ultrasound imaging equipment (Dermcup® 2020; Atys Médica, Soucieu en Jarrest, France) was used with an axial resolution of 80 μm and lateral resolution of 200 μm, an acquisition speed of 15 frames s^{-1} and a field of view 6 mm wide by 5 mm deep. A standard echographic gel was used as a coupling agent between the skin surface and the probe. Minimal pressure was applied to preserve the thickness and echogenicity of the skin. The linear probe was held manually, and maintained perpendicular to the skin surface on three different sites for each lower limb: thigh (front of the thigh, halfway between the iliac spine and the knees), lower leg (lateral external side of the leg, halfway between the knee and the malleolus) and ankle (area just above the malleolus externally).

Ultrasound analysis

Thickness was measured by a single operator (M.N.) perpendicular to the surface, from the skin surface to the deepest point of dermal echogenicity, using an electronic calliper. At least three sonometric thicknesses were measured for each site, and the mean depth was used. In cases of an unclear lower limit of the dermis, the gain was increased until the limit was easily identifiable.

Images were then recorded with a gain between 22 and 24 dB, anonymized and reread by a dermatologist (L.M.) who is experienced in ultrasound imaging of the skin and who was blind to the clinical diagnosis. He checked for the presence of dermal hypoechogenicity, defined as an unusually clear appearance of the dermis, on each of the three sites, and the localization of hypoechogenicity within the dermis (superficial dermal oedema or oedema affecting the whole dermis). He also characterized the pattern of the dermohypodermal junction. The junction was defined as unclear when it was difficult to identify, and dermal echogenicity decreased gradually, rather than suddenly, to reach hypodermic hypoechogenicity. It was defined as crenulated in the case of

intrusion of hypodermic hypoechogenic areas into echogenic dermal areas.

L.M. then made a diagnosis for each lower limb based only on the ultrasound images, without clinical examination and blind to the identities of the patients.

One year later, a series of 54 randomly ordered ultrasound images was examined blind to clinical diagnosis by three observers (M.S., M.N. and L.M.) to check interobserver agreement for the ultrasound diagnosis of lymphoedema.

Statistical analysis

Given the number of patients and the non-normal distribution, tests comparing average dermal thickness between different groups were nonparametric tests (Wilcoxon test) using Epi Info® software (http://www.cdc.gov/epiinfo/). $P < 0{\cdot}05$ was considered significant. Sensitivity, specificity and the positive likelihood ratio of ultrasound to diagnose lymphoedema from lipoedema were calculated. The interobserver agreement was expressed as a raw concordance rate and kappa coefficient.

Ethics

High-resolution ultrasonography is routinely used in our department to diagnose lipoedema and lymphoedema. It is a noninvasive, painless procedure that does not expose the patient to any particular risk. The study followed the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Results

Subjects

The study included 32 consecutive patients: 16 patients with lymphoedema (22 lower limbs affected), eight patients with lipoedema (16 legs) and eight control subjects.

Dermal thickness

The average measurements of dermal thickness in patients and control groups are given in Table 1. There was a significant difference in dermal thickness between patients with lymphoedema and lipoedema at all sites (thigh $P = 0{\cdot}0027$, lower leg and ankle $P < 0{\cdot}001$), and patients with lymphoedema and controls (thigh $P = 0{\cdot}0016$, leg and ankle $P < 0{\cdot}001$). No significant difference in dermal thickness was found between patients with lipoedema and controls at the thigh or ankle ($P = 0{\cdot}94$ and $P = 0{\cdot}29$, respectively), and the difference for the lower leg reached the limit of significance ($P = 0{\cdot}0497$).

Table 1 Average dermal thickness in patients with lymphoedema, lipoedema and in controls

	Average dermal thickness, mm (SD)		
	Patients with lymphoedema (n = 22 legs)	Patients with lipoedema (n = 16 legs)	Controls (n = 16 legs)
Thigh	2·15 (0·62)	1·51 (0·31)	1·46 (0·21)
Lower leg	2·73 (0·65)	1·59 (0·27)	1·41 (0·26)
Ankle	3·04 (0·70)	1·53 (0·29)	1·40 (0·20)

Echogenicity of the dermis

Dermal hypoechogenicity was shown in at least at one of the three sites in 100% of patients with lymphoedema (22 legs), 12·5% of patients with lipoedema (16 legs) and 6·25% of controls (16 legs) (Table 2). Hypoechogenicity affected the entire dermis in all cases of lymphoedema except in one patient where it prevailed in the upper dermis (Fig. 1). In contrast, in cases of lipoedema (Fig. 2) and in controls, when hypoechogenicity was seen, it was only at the ankle and prevailed in the upper dermis.

Dermohypodermal junction

The dermohypodermal junction was not clearly delimited (Fig. 1e) in at least one of the three sites in 68% (15/22) of cases of lymphoedema. In contrast, the dermohypodermal junction was well delimited in controls and in patients with lipoedema. The crenulated feature (Fig. 1f) was observed in at least in one site in 50% (eight of 16) of cases of lipoedema and 9% (two of 22) of cases of lymphoedema and not in any other cases.

High-resolution ultrasonographic diagnosis

The expert diagnosed all lower limbs with lymphoedema through analysis of ultrasound images alone; the sensitivity was 100% [95% confidence interval (CI) 87–100] and the specificity 87·5% (95% CI 62–98). The positive likelihood ratio was 8 (95% CI 2·2–29·2). It was not possible to distinguish patients with lipoedema from controls, but none of them was diagnosed as lymphoedema (Table 3). Exact

Table 2 Dermal hypoechogenicity in patients with lymphoedema and lipoedema and in controls

	Dermal hypoechogenicity, n (%)		
	Patients with lymphoedema (n = 22 legs)	Patients with lipoedema (n = 16 legs)	Controls (n = 16 legs)
Thigh	13 (59)	0	0
Lower leg	19 (86)	0	0
Ankle	21 (95)	2 (12·5)	1 (6·25)
At least one of the three sites	22 (100)	2 (12·5)	1 (6·25)

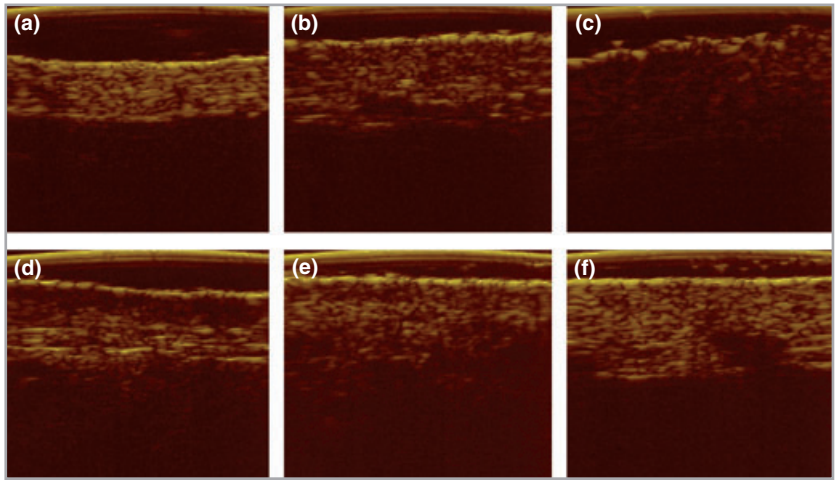

Fig 1. High-resolution ultrasound imaging. (a) Normal appearance of dermis; (b, c) hypoechogenicity and thickening of dermis; (d) upper dermal hypoechogenicity; (e) unclear lower junction between dermis and hypodermis; (f) crenulated junction between dermis and hypodermis and normal dermal echogenicity.

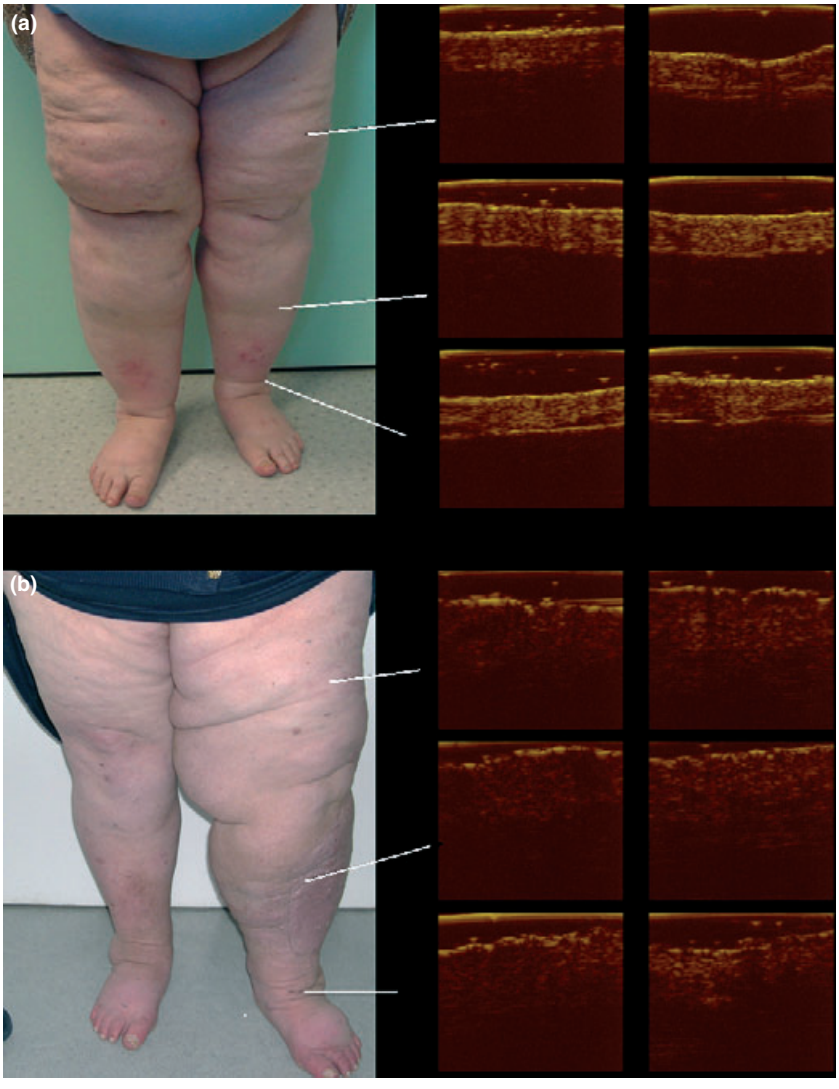

Fig 2. Clinical and ultrasound views. (a) Lipoedema: normal echogenicity and thickness of dermis. (b) Lymphoedema: decreased echogenicity and increased thickness of dermis.

Table 3 Frequency of ultrasound imaging abnormalities in patients with lymphoedema or lipoedema and in controls

	Patients with lymphoedema	Patients with lipoedema	Controls
Ultrasound image			
Abnormal	22	2	1
Normal	0	14	15
Total	22	16	16

interobserver agreement was excellent for the ultrasound diagnosis of lymphoedema (0·98, 95% CI 90·1–100) and for the diagnosis of normal skin or lipoedema (1·00 and 0·94, respectively). The kappa coefficient was also excellent (0·98).

Discussion

We showed in this blind study that high-resolution cutaneous ultrasonography can be used to separate lipoedema from lymphoedema. This is to our knowledge the first study comparing these two conditions with this imaging tool and demonstrating that ultrasound imaging can be a valuable diagnostic test. In patients with lipoedema, dermal thickness and echogenicity were normal, while dermal thickness was increased and echogenicity decreased in patients with lymphoedema.

Other imaging tests, in particular high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), have been proposed to differentiate lymphoedema and lipoedema.[19–21] Compared with these tests, high-resolution cutaneous ultrasonography has the advantage of being readily available, of low cost and with no ionizing radiation. Moreover, the examination can be performed in very overweight subjects, unlike CT or MRI, a common problem for obese patients with lipoedema, and the resolution of high-frequency ultrasound is better than CT and MRI.[16] Because differential diagnosis using these devices is mainly made with hypodermal analysis, which shows the honeycomb pattern in lymphoedema compared with the homogeneous increase in subcutaneous fat in lipoedema, rather than dermal analysis, these imaging devices could also be used in combination with high-resolution ultrasonography.

The gold standard for the diagnosis of lymphoedema is often an abnormality on lymphoscintigraphy.[22] Lymphoscintigraphy is an ionizing examination which is only available in some centres. In addition, lymphoscintigraphy studies have shown that there may be slowness of the lymphatic system, revealing a functional disorder in patients with lipoedema.[23,24] We therefore believe that lymphoscintigraphy is not totally reliable for differentiating these two diseases. Moreover, we were unable to find any blind study comparing lymphoscintigraphy for lipoedema and lymphoedema. One previous study showed that it was impossible to differentiate lymphoedema from lipoedema with an ultrasound device operating at 7·5 MHz.[21] However, traditional ultrasound devices are not accurate enough to explore the skin.[14] High-resolution cutaneous ultrasonography at 20 MHz is able to analyse dermal changes and therefore to identify and quantify dermal oedema. Indeed, certain previous studies have shown that dermal echogenicity is inversely proportional to its concentration in water.[17] Dermal oedema results therefore in a loss of echogenicity of the skin in high-resolution cutaneous ultrasonography.[15–18,25] The hypoechogenic aspect of the dermis observed in lymphoedema is in accordance with the only study concerning this condition with high-resolution ultrasonography.[15] It confirms the particular appearance of oedema in lymphoedema as global and homogeneous dermal hypoechogenicity that is related to the pathophysiology of lymphoedema and that contrasts with the elective superficial dermis localization described in venous insufficiency.[15,25] Lymphatic dysfunction results in accumulation of protein-rich exudative interstitial fluid in the skin and subcutaneous tissue which remains trapped by the protein it contains at the point where it was formed. It is therefore different from mobile transudate oedema of venous insufficiency that accumulates in the superficial dermis, which is less dense and more vascularized than the deeper dermis. A surgical procedure involving lymphaticovenous anastomosis may explain the single case of lymphoedema in our study where there was oedema of the superficial dermis.

Unlike previous studies, analysis of echogenicity and diagnosis was carried out directly on images by a dermatologist blind to the clinical examination. This method is more subjective than objective measurement of skin density or skin thickness and may be observer dependent, but it is as close as possible to the real-time clinical use of ultrasound imaging. We demonstrated in this study that the measurement of dermal thickness was a simple and valid way to quantify dermal oedema. Unclear lower dermis limits were observed and this has never been reported before in lymphoedema. This may be attributed to the subcutaneous, i.e. hypodermal, oedema that is frequently described in lymphoedema.[26,27] Thickness and dermal hypoechogenicity increased from the thigh to the ankle in lymphoedema of the lower limbs, which confirms the clinical evidence that the distal portion of the lower limb is more affected than the proximal in congenital lymphoedema.

Our study described for the first time the imaging features of lipoedema with high-resolution ultrasonography. It confirms that lipoedema is due to an increase in hypodermal tissue with no true dermal oedema. Indeed, lipoedema showed dermal echogenicity that was similar to that of normal skin. This normal dermal echogenicity was very different from the ultrasound image of lymphoedema described above. On the other hand, the crenulated feature of the dermohypodermal junction, which was seen in half of the patients with lipoedema, may help in the diagnosis of true lipoedema and to differentiate it from obesity with no lipoedema.

Obtaining a reliable diagnosis through high-resolution cutaneous ultrasonography should provide guidance for therapy and avoid unnecessary costs and morbidity.

What's already known about this topic?

- Lipoedema is frequently mistaken for lymphoedema leading to unnecessary investigations and inefficient treatments.

What does this study add?

- High-resolution ultrasound examination makes it possible to differentiate lymphoedema from lipoedema. This may be valuable for improving the treatment of both conditions.

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