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MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema

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ABSTRACT

Objective: To assess for the first time the morphology of the lymphatic system in patients with lipedema and lipo-lymphedema of the lower extremities by MR lymphangiography.**Materials and methods:** 26 lower extremities in 13 consecutive patients (5 lipedema, 8 lipo-lymphedema) were examined by MR lymphangiography. 18 mL of gadoteridol and 1 mL of mepivacainhydrochloride 1% were subdivided into 10 portions and injected intracutaneously in the forefoot. MR imaging was performed with a 1.5-T system equipped with high-performance gradients. For MR lymphangiography, a 3D-spoiled gradient-echo sequence was used. For evaluation of the lymphedema a heavily T2-weighted 3D-TSE sequence was performed.**Results:** In all 16 lower extremities (100%) with lipo-lymphedema, high signal intensity areas in the epifascial region could be detected on the 3D-TSE sequence. In the 16 examined lower extremities with lipo-lymphedema, 8 lower legs and 3 upper legs demonstrated enlarged lymphatic vessels up to a diameter of 3 mm. In two lower legs with lipo-lymphedema, an area of dermal back-flow was seen, indicating lymphatic outflow obstruction. In the 10 examined lower extremities with clinically pure lipedema, 4 lower legs and 2 upper legs demonstrated enlarged lymphatic vessels up to a diameter of 2 mm, indicating a subclinical status of lymphedema. In all examined extremities, the inguinal lymph nodes demonstrated a contrast material enhancement in the first image acquisition 15 min after injection.**Conclusion:** MR lymphangiography is a safe and accurate minimal-invasive imaging modality for the evaluation of the lymphatic circulation in patients with lipedema and lipo-lymphedema of the lower extremities. If the extent of lymphatic involvement is unclear at the initial clinical examination or requires a better definition for optimal therapeutic planning, MR lymphangiography is able to identify the anatomic and physiological derangements and to establish an objective baseline.

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Introduction

Lipedema is a syndrome characterized by bilateral, symmetric lower extremity enlargement due to epifascial deposition of fat (Foeldi et al., 2003; Allen and Hines, 1940; Rudkin and Miller, 1994; Harwood et al., 1996). Involvement usually extends from the buttocks to the ankles, whereas the feet are less involved or spared entirely, like riding breeches (Foeldi et al., 2003; Allen and Hines, 1940; Rudkin and Miller, 1994; Harwood et al., 1996). Lipedema is almost exclusively seen in women and was first described by Allen and Hines in 1940, who characterized the condition as “Lipodystrophy” (Allen and Hines, 1940). They reported that the deposition of fat developed commonly after puberty, progressed gradually, and was accentuated by activity and warm temperatures. The syndrome is painful to pressure, non-pitting and usually not discolored or inflamed. The affected areas in

the lower extremities are described as being soft and pliable, in contrast to those seen in the latter stages of lymphedema (Foeldi et al., 2003).

Lipedema must be differentiated from other disorders and is characterized by bilaterally enlarged legs. It is often regarded as an extension of simple obesity or erroneously diagnosed as one of the non-systemic causes of enlarged lower extremities, e.g., lymphedema or mixed lymphovenous disease (Foeldi et al., 2003).

Up to now, magnetic resonance imaging (MRI) and computed tomography (CT) have been used to describe the morphology changes due to the subcutaneous lipomatous hypertrophy (Düewell et al., 1992; Aström et al., 2001; Hadjis et al., 1985; Monnin-Delhom et al., 2002), while conventional lymphography (Rudkin and Miller, 1994; Kinmonth, 1982), indirect lymphography (Partsch et al., 1988), fluorescent microlymphangiography (Amann-Vesti et al., 2001) and lymphoscintigraphy (Weissleder et al., 1995; Bilancini et al., 1995; Bräutigam et al., 1998) have been performed to evaluate the lymphatic pathways and their drainage.

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Magnetic Resonance Lymphangiography (MRL) with intracutaneous injection of an extracellular, paramagnetic contrast agent is a new diagnostic imaging method for the delineation of pathologically modified lymphatic pathways with a high resolution (Lohrmann et al., 2006a,b,c). The technique has proved to be safe and technically feasible in patients suffering from primary and secondary lymphedema. The purpose of this study was to assess for the first time the morphology of the lymphatic system in patients suffering from lipedema and lipo-lymphedema by means of MRL.

Materials and methods

Patients

Between February 2005 and October 2006, 26 lower extremities in 13 patients (mean age 39 years; range 21–71 years; 13 females, 0 male) were examined with MRL. The inclusion criterion was the clinical diagnosis of lipedema, whereas 5 patients (10 lower extremities) suffered from pure lipedema and 8 patients (16 lower extremities) from the mixed form of lipo-lymphedema. Patients with contraindications for MRI, renal insufficiency, or a known gadolinium contrast agent allergy were excluded. This study had been approved by the local ethics committee, and all participants had given their informed consent before being included in the study.



Fig. 1. 40-year-old woman with bilateral lipo-lymphedema of the lower extremities. (A) Coronal heavily T2-weighted 3D-TSE source image demonstrates increased layer of subcutaneous fat at the level of the lower legs (large arrows). Furthermore, subcutaneous regions of lymphedema are detected (small arrows). (B) Axial heavily T2-weighted 3D-TSE source image reveals a severely increased layer of subcutaneous fat up to a diameter of 7.5 cm at the level of both upper legs (large arrows). Additionally, small areas of epifascial lymphedema are seen (small arrows).

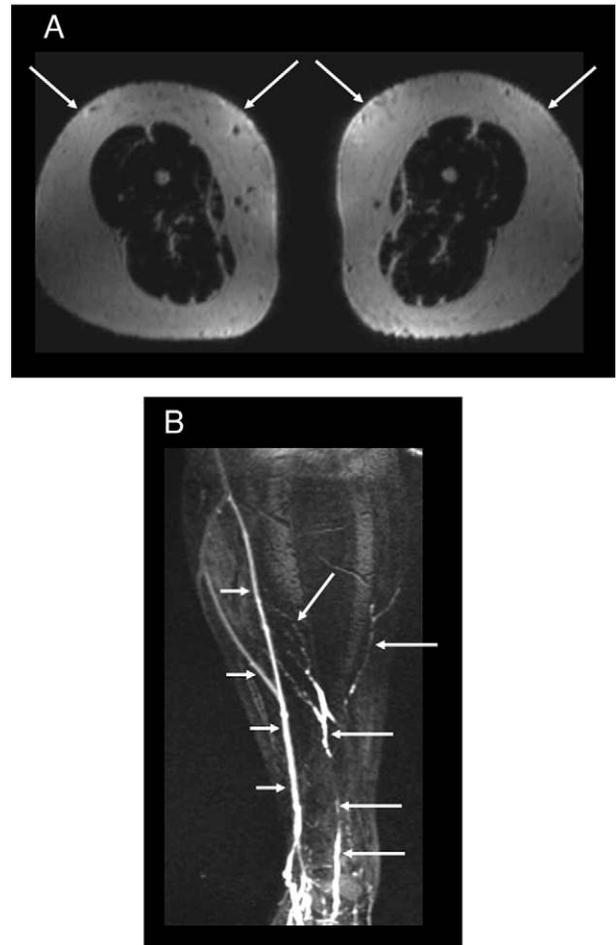


Fig. 2. 26-year-old woman with bilateral lipedema of the lower extremities. (A) Axial heavily T2-weighted 3D-TSE source image reveals a severely increased layer of subcutaneous fat up to a diameter of 7.1 cm at the level of both upper legs (large arrows). No areas of lymphedema are detected. (B) Frontal 3D spoiled gradient-echo MRL MIP-image clearly depicts enlarged lymphatic vessels with their typical beaded appearance up to a diameter of 2 mm at the level of the right lower leg (large arrows), indicating a subclinical status of lipo-lymphedema. This image, obtained 45 min after gadoteridol injection, demonstrates the highest contrast material uptake of the lymphatic vessels at the level of the right lower leg in this patient. Note the concomitantly enhancing vein (small arrow).

Contrast material application

9 mL of Gadoteridol (Prohance[®], Bracco-Byk Gulden, Konstanz, Germany) and 1 mL mepivacainhydrochloride 1% were segmented into 5 portions and injected intracutaneously into the dorsal aspect of each foot in the region of the four interdigital webs; one portion was applied medial to both first proximal phalanges. For the injection of the contrast material we used a thin needle (24 gauge).

MR imaging examinations

MR imaging was performed with a 1.5-T system (Symphony/Avanto; Siemens Medical Systems, Erlangen, Germany). Three stations were examined: first, the lower leg and foot region; second, the upper leg and the knee region; and third, the pelvic region and the proximal upper leg. A phased array body coil was used to image the pelvic region, and a dedicated peripheral surface coil was used to examine the upper and lower leg. To describe the lymphedema, a heavily T2-weighted 3D-TSE sequence (TR/TE: 2000/694; flip angle: 180°; matrix: 256 × 256, bandwidth: 247 Hz/pixel; 6/8 rectangular field of view 480 mm; slices: 96; voxel size: 2.0 × 1.9 × 1.7 mm; acquisition time: 4 min 48 s) was conducted before MRL was performed. For MRL, a 3D

spoiled gradient-echo sequence (Volumetric Interpolated Breath-Hold Examination, VIBE) was used with the following parameters: (TR/TE: 3.58/1.47; flip angle: 35; matrix: 448 × 448, bandwidth: 490 Hz/pixel; 6/8 rectangular field of view with a maximum dimension of 500 mm; slices: 128; voxel size: 1.2 × 1.1 × 1.2 mm; acquisition time: 1 min 40 s). The three stations were first imaged without contrast material and subsequently repeated 15, 25, 35, 45, and 55 min after intracutaneous application of the contrast material for image subtraction.

Since the chosen sequences do have 3D imaging properties, image reconstructions can be made from any desired perspective, alleviating to make the correct diagnosis (Figs. 1–4).

To improve vessel-to-background contrast and to facilitate fast and easy interpretability of data, unenhanced ‘mask’ acquisitions were subtracted from contrast-enhanced datasets.

The enhancement of gadoteritol in the lymphatic pathways, inguinal lymph nodes and veins was assessed by two authors. A diagnosis was reached by consensus.

Results

All patients tolerated the examinations well without complications. In all 16 lower extremities (100%) with clinically lipo-lymphedema high signal intensity areas could be detected on the 3D-TSE sequence (Figs. 1A/B, Table 1). While in six lower extremities (37%) the lymphedema was seen at both the level of the lower leg and the upper leg, the lymphedema was limited to the lower leg in 10 lower extremities (63%). The lymphedema demonstrated an epifascial distribution in all 16 lower extremities (100%). In the 10 examined lower extremities with clinical lipedema no high signal intensity areas indicating lymphedema could be detected on the 3D-TSE sequence (Table 1).

In all 26 examined lower extremities (100%), the MRI-sequences revealed an increased layer of subcutaneous fat at the level of the



Fig. 3. 27-year-old woman with bilateral lipedema of the lower extremities. Inverted frontal 3D spoiled gradient-echo MRL MIP-image reveals slightly enlarged lymphatic vessels with their typical beaded appearance up to a diameter of 1.5 mm at the level of the right lower leg (large arrows), indicating a subclinical status of lipo-lymphedema. This image, obtained 35 min after gadoteritol injection, demonstrates the highest contrast material uptake of the lymphatic vessels at the level of the right lower leg in this patient. Furthermore, a concomitantly enhancing is detected (small arrows).

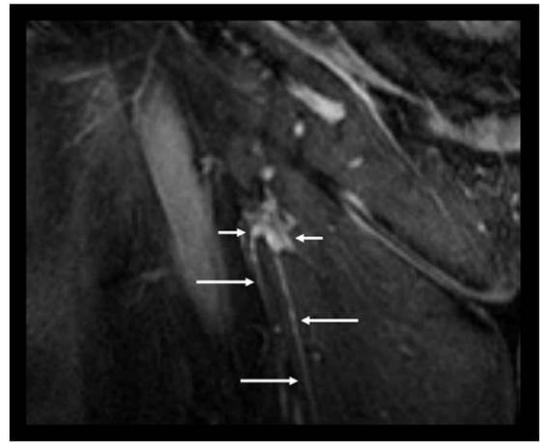


Fig. 4. 44-year-old woman with bilateral lipo-lymphedema of the lower extremities. 3D spoiled gradient-echo MRL source image reveals enhancement of the right inguinal lymph nodes (small arrows) with afferent lymphatic vessels (large arrows) already 15 min after gadoteritol injection, indicating, that her lymphatic outflow is not considerably impaired. Clinically the patient presented with a mild lymphedema component.

lower leg and the upper leg, whereby the maximum mean diameter (measured from the cutis to the epifascial fascia) was 4.4 cm at the level of the lower leg and 7.7 cm at the level of the upper leg (Figs. 1A/B, 2A, Table 1).

In the 16 examined lower extremities with lipo-lymphedema, 8 lower legs and 3 upper legs demonstrated enlarged lymphatic vessels up to a diameter of 3 mm (Table 1). In the remaining extremities with lipo-lymphedema, the diameter of the lymphatic vessels was not enlarged. In two lower legs with lipo-lymphedema an area of dermal back-flow with collateral lymphatic vessels was seen, indicating lymphatic outflow obstruction (Table 1).

In the 10 examined lower extremities with clinically pure lipedema, 4 lower legs and 2 upper legs demonstrated enlarged lymphatic vessels up to a diameter of 2 mm (Figs. 2B, 3). In these extremities, as mentioned above, no lymphedema was detected on the MRI images, indicating thereby a subclinical status. In the remaining extremities with pure lipedema, the diameter of the lymphatic vessels was not enlarged.

In all examined extremities the lymphatic vessels of the upper and lower leg as well the inguinal lymph nodes demonstrated a contrast material enhancement already in the first image acquisition, 15 min after injection (Fig. 4).

In the patients with lipedema, the strongest contrast enhancement of the lymphatic vessels in the lower leg was present after 25 min in 2 lower extremities (20%), after 35 min in 5 lower extremities (50%), and after 45 min in 3 lower extremities (30%) (Table 2). In the patients with lipolymphe-
dema, the strongest contrast enhancement of the

Table 1
Magnetic Resonance Lymphangiography (MRL) findings in 10 lower extremities with lipedema and 16 lower extremities with lipo-lymphedema

MRL findings	Lower extremities with lipedema (n = 10)	Lower extremities with lipo-lymphedema (n = 16)
High signal intensity areas indicating lymphedema	0 (0%)	16 (100%)
Increased layer of subcutaneous fat	10 (100%)	16 (100%)
Enlarged lymphatic vessels lower leg	4 (40%)	8 (50%)
Enlarged lymphatic vessel upper leg	2 (20%)	3 (19%)
Dermal back-flow area with collateral lymphatic vessels	0 (0%)	2 (0%)
Concomitant venous enhancement	10 (100%)	16 (100%)

Table 2
Number of lower/upper legs at the time of highest contrast enhancement after intracutaneous injection of gadoteridol in respect of individual lymphatic vessels (LV) and inguinal lymph node areas (Ing. LN)

	LV, lower leg with lipedema	LV, lower leg with lipo-lymphedema	LV, upper leg with lipedema	LV, upper leg with lipo-lymphedema	Ing. LN areas with lipedema	Ing. LN areas with lipo-lymphedema
15 min	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
25 min	2 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
35 min	5 (50%)	6 (38%)	4 (40%)	2 (13%)	3 (30%)	1 (6%)
45 min	3 (30%)	7 (44%)	4 (40%)	9 (57%)	5 (50%)	8 (50%)
55 min	0 (0%)	3 (18%)	2 (20%)	5 (30%)	2 (20%)	7 (44%)
Total	10 (100%)	16 (100%)	10 (100%)	16 (100%)	10 (100%)	16 (100%)

Number of lower/upper legs at the time of highest contrast enhancement after intracutaneous injection of gadoteridol in respect of individual lymphatic vessels (LV) and inguinal lymph node areas (Ing. LN).

lymphatic vessels in the lower leg was present after 35 min in 6 lower extremities (38%), after 45 min in 7 lower extremities (44%), and after 55 min in 3 lower extremities (18%) (Table 2).

In the patients with lipedema, the highest signal intensities of the lymphatic vessels in the upper leg were present after 35 min in 4 lower extremities (40%), after 45 min in 4 lower extremities (40%), and after 55 min in 2 lower extremities (20%) (Table 2). In the patients with lipo-lymphedema, the highest signal intensities of the lymphatic vessels in the upper leg were present after 35 min in 2 lower extremities (13%), after 45 min in 9 lower extremities (57%), and after 55 min in 5 lower extremities (30%) (Table 2).

In the patients with lipedema the inguinal lymph node groups demonstrated the highest signal intensities in 3 lower extremities after 35 min (30%), in 5 lower extremities after 45 min (50%) and in 2 lower extremities after 55 min (20%) (Table 2). In the patients with lipo-lymphedema the inguinal lymph node groups demonstrated the highest signal intensities in one lower extremity after 35 min (6%), in 8 lower extremities after 45 min (50%) and in 7 lower extremities after 55 min (44%) (Table 2).

As demonstrated in prior studies (Lohrmann et al., 2006a,b,c), accompanying venous enhancement was detected in the lower and upper leg of all 26 lower extremities (100%) (Figs. 2B, 3, Table 1). Source images and 3D maximum intensity projection-images at different angles of view provided, however, a detailed outlining of the lymphatic vessels, and allowed differentiation from veins based on their beaded appearance.

Discussion

The etiology and pathogenesis of lipedema are yet not fully understood. The syndrome predominantly affects women, and, according to an epidemiologic study performed by Foeldi et al., (2003), is at present in about 11% of the female population. Lipedema frequently manifests itself around menarche, menopause or during pregnancy. In seldom cases, lipedema affects the male population; the syndrome is accompanied by reduced levels of sexual hormones and disturbances of liver function (Foeldi et al., 2003). In the early stages of lipedema, the skin appears regular, but if progression occurs typical signs of "cellulite" can be observed. In the later stages of the syndrome, predominantly in untreated patients, epifascial nodules are palpable due to sclerosis of the subcutaneous connective tissue. In severely affected patients, immobility may result from elephantiasic swelling of the legs. The color of the skin is unapparent, unless lipedema is accompanied by "erythrocyanosis crurum puellarum" (Foeldi et al., 2003).

In lipedematous regions, patients are very sensitive to pressure, and even mild traumata can cause severe tenderness. Patients with lipedema are, additionally prone to mental disorders, strongly impairing their quality of life (Foeldi et al., 2003).

An early histological finding in lipedema is microangiopathy in the region of the adipose tissue, leading to increased fragility of the blood capillaries and therefore higher permeability to the plasma proteins.

Clinical features are edema due to an accumulation of high protein fluid in the pericellular space, as well as the tendency in developing hematomas in the subcutaneous tissue (Foeldi et al., 2003). Pericellular fluid accumulation dilates the prelymphatic drainage system, resulting in a massively decreased transport rate of the interstitial fluid towards the initial lymphatic vessels. Therefore, the most important complication of lipedema is the development of lipo-lymphedema.

It has been proven that the lymph capillaries of the skin show pathological changes, e.g., Amann-Vesti et al. (2001) demonstrated by means of fluorescence microlymphography that multiple microlymphatic aneurysms of lymphatic capillaries are a consistent finding in the affected skin areas of patients with lipedema. Compared to fluorescence microlymphography, the presented MR lymphangiography protocol is able to evaluate small lymphatic vessels in millimetre dimensions. The lymphatic capillaries in humans, due to their low diameter in micrometer dimensions, are although unachievable by MRL.

Weissleder et al. demonstrated that early stages of lymphostasis in patients with lipedema can be detected with lymphoscintigraphy. They pointed out, that a normal lymphoscintigraphy examination almost certainly excludes a lymphatic component and mentioned, that lymphoscintigraphy is able to differentiate lipedema versus lipolympheidema (Weissleder et al., 1995). The results of the presented study indicate, that these conclusions can also be made by MRL. In actual fact, all lower extremities with clinically lipo-lymphedema demonstrated high signal intensity on the MRL images, evidencing a lymphedema component. In the 10 examined lower extremities with clinical pure lipedema no lymphedema could be revealed at MRL. Regarding the evaluation of early stage lymphostasis, MRL detected enlarged lymphatic vessels up to a diameter of 2 mm in 2 patients with clinically pure lipedema, indicating a subclinical status. This is of mandatory importance, since pure lipedema is fairly resistant to compression therapy and a diagnosis of a mixed form of lipedema improves the prognosis of successful limb-compressing treatment (Aström et al., 2001). Furthermore Weissleder et al. concluded, that indirect lymphography should only be used to rule out morphological abnormalities of lymphatic vessels, if the lymphoscintigraphic study had shown a pathological outflow (Weissleder et al., 1995).

The major advantage of MRL in contrast to lymphoscintigraphy and indirect lymphography is the possibility to receive all this information in one for the patient minimal-invasive examination. Small lymphatic vessels are precisely visualize and delineate in subsequently repeated image acquisitions 15, 25, 35, 45, and 55 min after intracutaneous application of the contrast material. Thereby, it is not only possible to demonstrate preferential ways of lymphatic drainage obtaining functional information as demonstrated by lymphoscintigraphy, but also to receive exact morphological informations by describing the number, appearance and anatomic course of the lymphatic vessels.

In a further lymphoscintigraphy study performed by Bräutigam et al. (1998), all patients with pure lipedema showed normal lymph transport rates in both the epifascial and subfascial compartments. In the presented MRL study all examined extremities (patients with

lipedema and lipo-lymphedema) demonstrated a contrast material enhancement of the inguinal lymph nodes already in the first image acquisition 15 min after injection, indicating no considerable impairment of the lymphatic outflow. The enhanced lymphatic vessels in the lower/upper leg and inguinal lymph nodes of the patients with lipedema and lipo-lymphedema demonstrated the highest contrast material uptake in the later acquisitions 35, 45 and 55 min after injection. Compared to the patients with pure lipedema, more patients with lipo-lymphedema showed the highest contrast material uptake in the lymphatic vessels at the level lower/upper leg in the image acquisitions 45 and 55 min after injection, probably indicating the lymphedema component with altogether slower lymphatic outflow. Clinically the 5 patients with lipo-lymphedema presented with a mild lymphedema component.

Harwood et al. conducted photoplethysmography and quantitative lymphoscintigraphy to investigate the role of the venous and lymphatic systems in the pathogenesis of lipedema (Harwood et al., 1996). They concluded that lipedema is a distinct syndrome rather than a direct consequence of any primary insufficiency of the venous or lymphatic system. In addition, they established that lymphoscintigraphy has some benefits for the differential diagnosis of lymphedema, but is not conclusive in diagnosing lipedema.

According to prior MRL studies, accompanying enhancement of veins was seen in all extremities in the presented MRL study (Lohrmann et al., 2006a,b,c). Nevertheless, baseline- and 3D MIP images at different angles of view were able to exactly delineate the lymphatic vessels, and allowed differentiation from veins based on their beaded appearance in all examined extremities. In comparison to the study by Harwood et al. was a detailed analysis of the venous system due to the interstitially applied contrast material not reasonable.

Partsch et al. (1988) described in a study that instead of typical encircled, round depots, indirect lymphography reveals flamed-shaped contrast medium depots in lipedema patients, from which in some female patients lymphatic outflow takes place into regular lymphatic collectors. These flamed-shaped depots probably represent distended prelymphatic spaces, contrast material filled by the injection pressure in the presence of low tissue resistance. The pattern contrast material spread corresponds, in all probability, to the connective tissue fibers, which criss-cross around the lobules of fat and serves as low “resistance pathways”. Partsch et al. showed that collectors fail to opacify in other women, because the injection pressure leads only to a distension of the prelymphatic spaces. Partsch et al. therefore concluded that the morphology demonstrated by indirect lymphography corresponds to the etiologic concept of lipedema by Foeldi et al. (2003). In the presented MRL study the authors could not reveal flamed-shaped contrast medium depots at the area of the contrast media injection sites. In all extremities (lipedema and lipo-lymphedema) the round contrast media depots in the forefoot were resolved at the latest in the 55-min post-injection images. In comparison to Partsch et al., lymphatic vessels were observed to originate from the contrast media depots in the examined women.

According to Foeldi et al., conventional lymphangiography is obsolete in patients with lipedema or lipo-lymphedema, since it can cause or worsen lymphedema. Earlier, Kinmonth (1982) noticed a corkscrew-like aspect of the lymphatics in patients with lipedema when performing conventional lymphographies. In a study by Rudkin and Miller (1994), 2 patients with lipedema had a lymphography, which in both instances revealed a moderate dilatation of the lymphatics and some tortuosity consistent with incompetent valves. The number of lymphatic collectors was, however, inconspicuous. In the presented study the number of lymphatic vessels at the level of the lower and upper leg was also inconspicuous. According to Kinmonth, a corkscrew-like aspect of the lymphatics was not detected on MRL, whereby enlarged lymphatic vessels were revealed up to a diameter of 3 mm in patients with lipo-lymphedema and up to 2 mm in patients with lipedema.

Regarding cross-sectional imaging, only a few studies have been performed examining patients with lipedema (Düewell et al., 1992; Aström et al., 2001; Hadjis et al., 1985; Monnin-Delhom et al., 2002). Düewell et al. (1992) assessed the use of MRI in differentiating lymphedema, phlebedema and lipedema of the legs. They concluded that this differentiation is possible with MRI and that lipedema is characterized by an increased layer of subcutaneous fat with no changes in signal intensity between T2- and T1-weighted imaging or after intravenous administration of contrast material. They confirmed thereby the assumption, that lipedema represents lipomatous hypertrophy and that the subcutaneous tissue does not contain excess fluid. In another study Aström et al. (2001) demonstrated that MRI has an important role in evaluating mixed forms of lipedema, such as lipo-lymphedema and lipo-phlebo-lymphedema. Hadjis et al. (1985) performed CT scans in three patients and found enlargement of the subcutaneous regions of the legs with no specific imaging pattern. All patients demonstrated normal skin thickness and subfascial compartment.

In contrast to the conventional cross-sectional imaging examinations, it was not only possible by MRL to exactly demonstrate and delineate the epifascial fat compartment and the distribution of the lymphedema, but also evaluate the lymphatic system in a morphological and functional way. Utilizing both examination parts of the MRL, important information is obtained about the lymphatic system, e.g., to detect mixed forms of lipedema, like lipolymphe-*de*ma, in order to optimize therapy with complex decongestive therapy.

In conclusion, MRL is an excellent, minimal-invasive imaging modality with a high resolution to identify the anatomic and physiological derangements and to establish an objective baseline in patients with lipedema and lipo-lymphedema. Due to the minimal invasiveness and lack of radiation, diagnostic follow-up MRL's can be performed routinely and with no risk for the patient.

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