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Original Contribution

Non-contrast MR Lymphography of lipedema of the lower extremities

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ABSTRACT

Aim: To assess imaging findings and characteristics of the lymphatic system in patients affected by lipedema and lipolymphedema of the lower extremities on Non-Contrast MR Lymphography (NCMRL).

Materials and methods: 44 lower extremities in 11 consecutive female patients affected by lipedema, and 11 patients with lipolymphedema were examined by NCMRL. MR imaging was performed on 1.5-T system MR equipment. The examination consisted of one 3D short-tau inversion recovery (STIR) and one heavily T2-weighted 3D-Turbo Spin Echo (TSE) sequence.

Results: All patients showed symmetrical enlargement of the lower extremities with increased subcutaneous fat tissue. The fat tissue was homogeneous, without any signs of edema in pure lipedema patients. In all the extremities with lipolymphedema, high signal intensity areas in the epifascial region could be detected on the 3D-TSE sequence ($p < .001$) with evidence of mild epifascial fluid collections ($p < .001$). No sign of honeycomb pattern fat appearance was observed. The appearance of the iliac lymphatic trunks was normal in both lipedema and lipolymphedema patients. Dilated peripheral lymphatics were observed in 2 patients affected by lipedema, indicating a subclinical status of lymphedema, and in 10 patients with lipolymphedema ($p = .001$). Signs of vascular stasis were observed in both groups, without statistically significant difference ($p = .665$).

Conclusion: NCMRL is a non-invasive imaging technique that is suitable for the evaluation of patients affected by lipedema and lipolymphedema, helping in the differential diagnosis.

1. Introduction

Lipedema is a chronic impairment of lipid metabolism. It almost exclusively affects women presenting during hormonal changes related to puberty, pregnancy or menopause, and is characterized by swelling of the extremities due to alterations of fat distribution and storage, and hyperplasia of single fat cells [1].

Lipedema occurs primarily in the lower limbs, typically sparing the feet and trunk, and is rarely accompanied by edema of the upper extremities. The enlargement is symmetrical and located between the pelvic crest and the ankle [2–4]. Patients typically show disproportionality between a normal upper body and symmetrically enlarged lower limbs, and this is often associated with an elevated body mass index (BMI) levels. A key aspect of lipedema fat is the non-responsiveness to physical activity or diet restrictions, and the loss of non-lipedema fat can result in an increased size disproportion between the trunk and the persisting enlarged lower extremities [3]. Typical clinical complaints include pain upon pressure, easy bruising of the affected areas, feeling of tension [1]. Despite its description in 1940 by Allen and Hines [5,6] the pathogenesis is still unknown and seems to involve different mechanisms including genetic predisposition, hormonal changes, microangiopathy, or lymphangiopathy [2].

Lipedema seems to be a distinct clinical entity, rather than a direct consequence of any primary venous or lymphatic impairment [7]. It is characterized not only by enlarged adipocytes but also by a thickening of the interstitium with increased interstitial fluid [8]. Therefore, in the first phase, the edema is likely secondary to overwhelming the lymphatic transport capacity, rather than an altered function of the lymphatic system. The deposition of protein-rich fluid is associated to tissue fibrosis and further impairs lymphatic drainage. As lipedema progresses, the lymphatics start to stretch and dilate, with development of "microaneurysms" that tend to leak: these microaneurysms, and the increased interstitial fluid, favor the stage of the disorder called "lipolymphedema" [9,10].

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Table 1
Magnetic Resonance acquisition protocol.

	T2 TSE SPACE FAT SAT	T2 STIR
Sequence	3D	3D
Orientation	Coronal	coronal
FOV (mm × mm)	460 × 504	460 × 504
Matrix (pixel × pixel)	378 × 384	315 × 384
Voxel size (mm × mm × mm)	1,1 × 1,1 × 1,0	1,1 × 1,1 × 1,0
TR (msec)	2500	3000
TE (msec)	802	254
TI (msec)	–	160
Flip angle	140°	–
Scan time (minutes: seconds)	05:05	04:48

FOV = field of view
TR = repetition time
TE = echo time
TI = inversion time
SPACE = single slab 3D TSE sequence with slab selective, variable excitation pulse, which enables acquisition of high-resolution 3D datasets.
STIR = short-tau inversion recovery
The T2 TSE fat-saturated sequence enhances the fluid-filled structures with background tissue signal suppression. The T2 STIR is used for morphological assessment, to analyze the signal of the muscle compartment and subcutaneous fat tissue, and to assess the diameter of the limbs.

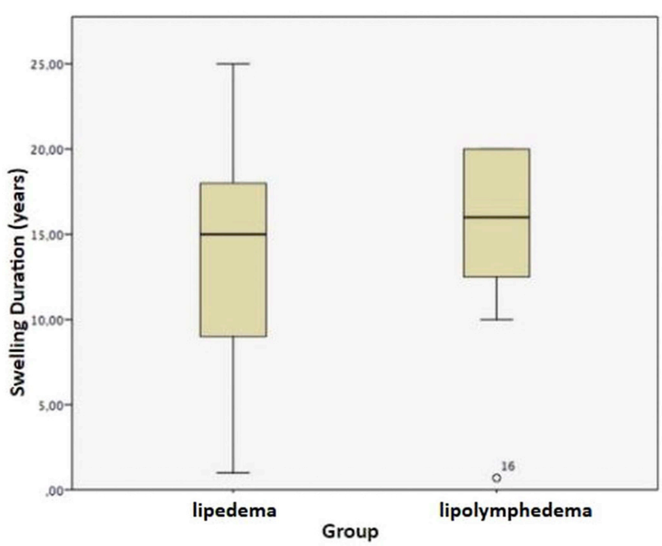

Fig. 1. The bar graph shows no statistically significant difference in limb swelling duration between lipedema and lipolymphedema patients, $p = .62$.

The recruitment of inflammatory cells within the interstitium may contribute to the signaling pathways involved in the stimulation of adipocyte hypertrophy [11].

Lipedema is often underdiagnosed or erroneously diagnosed as simple obesity, lymphedema, or mixed lymphovenous disease. However, the need to properly identify this disease as a unique entity has major implications for the appropriate therapeutic approach.

There is no consensus about the best imaging technique to assess lipedema. The use of lymphoscintigraphy has no role in the routine clinical diagnosis and is reserved for limited cases for the study of associated abnormalities of lymphatic drainage, and it is limited by radiation exposure, invasiveness, high costs, poor temporal and spatial resolution and limited anatomical detail [12].

Ultrasound [13] and Magnetic Resonance Imaging (MRI) [14–16] have recently been used to study lipedema with promising results. Contrast-Enhanced Magnetic Resonance Lymphography (CEMRL) with gadolinium [17] has been successfully used to assess the morphology of the lymphatic system in patients affected by lipedema and lipolymphedema [18]. However, CEMRL is limited as the intracutaneous injection of gadolinium is still off-label and can cause patients' discomfort and local reactions. Moreover, the recent evidence of gadolinium deposition after contrast-enhanced MR imaging has pushed towards the development of a new MR Lymphography technique, which does not require the administration of any contrast medium, the Non-

Fig. 2. Symmetric increase of the subcutaneous fat.
NCMRL of a 36-year-old female, who developed lower limb enlargement after the pregnancy, about 5 years before, affected by pure lipolymphedema.
The image is obtained by composing the STIR acquisitions of the different lower limb stations and demonstrates the bilateral symmetric increased representation of the subcutaneous fat. The enlargement characteristically begins at the level of the iliac crests and ends caudally at the ankles. The honeycomb pattern is absent. Minimal epifascial fluid collection is visible (white arrows). The muscle compartment is normal for morphology and signal intensity.

Table 2
The maximum thickness of the subcutaneous fat calculated at four different stations for patients affected by lipedema and lipolymphedema. No statistically significant difference was observed between the two groups of patients for all stations.

Stations	Stations definition	Maximum thickness of the subcutaneous fat		Statistical difference at Pearson's X2 test	95% Confidence interval
		Patients with lipedema	Patients with lipolymphedema		
Station 1	10 cm below the femoral head	67 ± 9.6 mm	67 ± 9.6 mm	p = 1	−8.56335- 8.56335
Station 2	10 cm cranial to the medial tibial plate	37.7 ± 9.6 mm	37.4 ± 9.3 mm	p = .87	−8.71300- 8.16754
Station 3	10 cm below the medial tibial plate	22 ± 3.8 mm	22 ± 3.7 mm	p = .85	−3.39756- 3.39756
Station 4	7 cm cranial to the peroneal malleolus	20.1 ± 4.8 mm	19.8 ± 4.6 mm	p = .86	−4.56990-3.84263

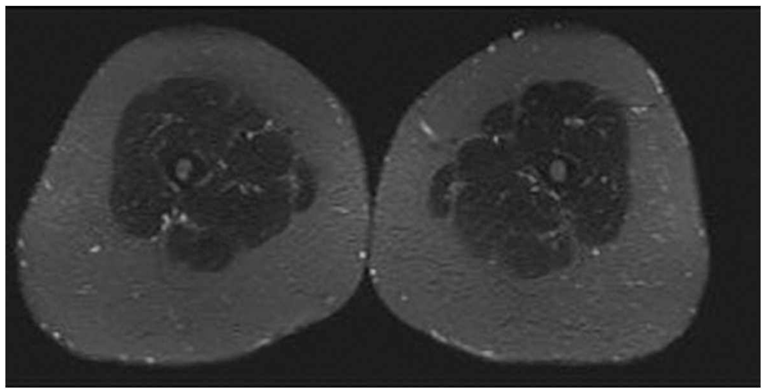

Fig. 3. Increased fat tissue thickness in lipedema.
STIR reconstructed axial image representing the increased fat representation in a patient affected by lipedema. The subcutaneous fat thickness is markedly increased, in a symmetric way between the two limbs, with homogenous signal intensity.

Contrast MR Lymphography (NCMRL). This technique is based on heavily T2-weighted turbo-spin-echo sequences (TSE) in order to highlight the signal of static or slow-moving fluid-filled structures as lymphatic vessels, with background tissues suppression [19–22].

Our aim was to assess imaging findings and characteristics of the lymphatic system in patients affected by lipedema and lipolymphedema of the lower extremities by NCMRL.

2. Material and methods

This study has been approved by the local ethical committee and follows local and international laws and guidelines (Helsinki Declaration). All participants gave their informed consent.

Two radiologists, with 3 and 3 years of experience in NCMRL, in consensus retrospectively reviewed images of patients presented to our Radiology Department with a clinical diagnosis of lipedema and mixed form of lipolymphedema. Agreement was reached by consensus.

Patients with a history of cancer, lymph node dissection, or radiation treatments were excluded from the study. All patients underwent NCMRL between September 2018 and January 2020. Diagnosis of lipedema was performed by two Plastic Surgeons in consensus, based on physical examination and patients' history, according to the criteria first described by Wold et al. [6]. These criteria are as follows: female sex; visual inspection demonstrating extensive deposition of subcutaneous fat tissue, with adiposity granular to palpation, between the iliac crest and the malleoli, with bilateral and symmetrical distribution and minimal involvement of the feet; minimum pitting edema; the presence of pain, tenderness on pressure, and easy bruising; the persistence of the enlargement despite elevation of the extremities or weight loss [6]. The diagnosis of lipolymphedema was based on previous diagnosis of lipedema, with the appearance of the following modifications: skin changes such as thickening and hardening, progressive onset of swelling ankles and back of the feet, and evidence of pitting edema in the lower legs and feet, not previously identified.

NCMRLs were performed on 1.5-T MR equipment (MAGNETOM Avanto^{fit}; Siemens Medical Systems, Erlangen, Germany), with a peripheral angiography coil and 8-channel phased-array body coil placed on the lower abdomen. No preparation was required for this exam. The examination was obtained in 3 steps to cover all the following anatomical stations: (1): foot, ankle, calf; (2): knee, lower and middle thigh; (3): proximal thigh, inguinal and pelvic region [19,20].

The study included two 3D sequences, a T2 TSE and a short-tau inversion recovery (STIR) sequence, with acquisition parameters listed in Table 1.

MRI datasets were then post-processed; Maximum Intensity Projection (MIP) reconstructions and rotational MIP reformations were obtained.

The radiologists analyzed: (1) the symmetry/asymmetry of the extremities enlargement, defined as the comparison between left and right limbs; (2) the maximum thickness of the subcutaneous fat, from the epifascial surface to the dermis, calculated in four stations; (3) the presence of signs of lymphatic stasis, identified as fluid infiltration of the subcutaneous fat, honeycomb pattern (corresponding to enlarged fat pockets surrounded by thick septa), epifascial fluid collection (visible as high signal intensity areas consistent with fluid accumulation located in the epifascial compartment) [20]; (4) any abnormalities in the muscular compartment, consisting of signal alteration of the muscles and increased or reduced muscular trophism; (5) the characteristics of iliac lymphatic trunks, assessed according to a previously published classification for lymphatic vessels on NCMRL: aplasic if no lymphatic trunks were demonstrated; hypoplasic, when fewer than 3 lymphatic trunks were visible; normal, when 3 to 6 lymphatic trunks were present; or hyperplasic, when > 6 lymphatic trunks were detected [20]; (6) the presence of dilated distal lymphatic vessels (lymphatic vessels in the

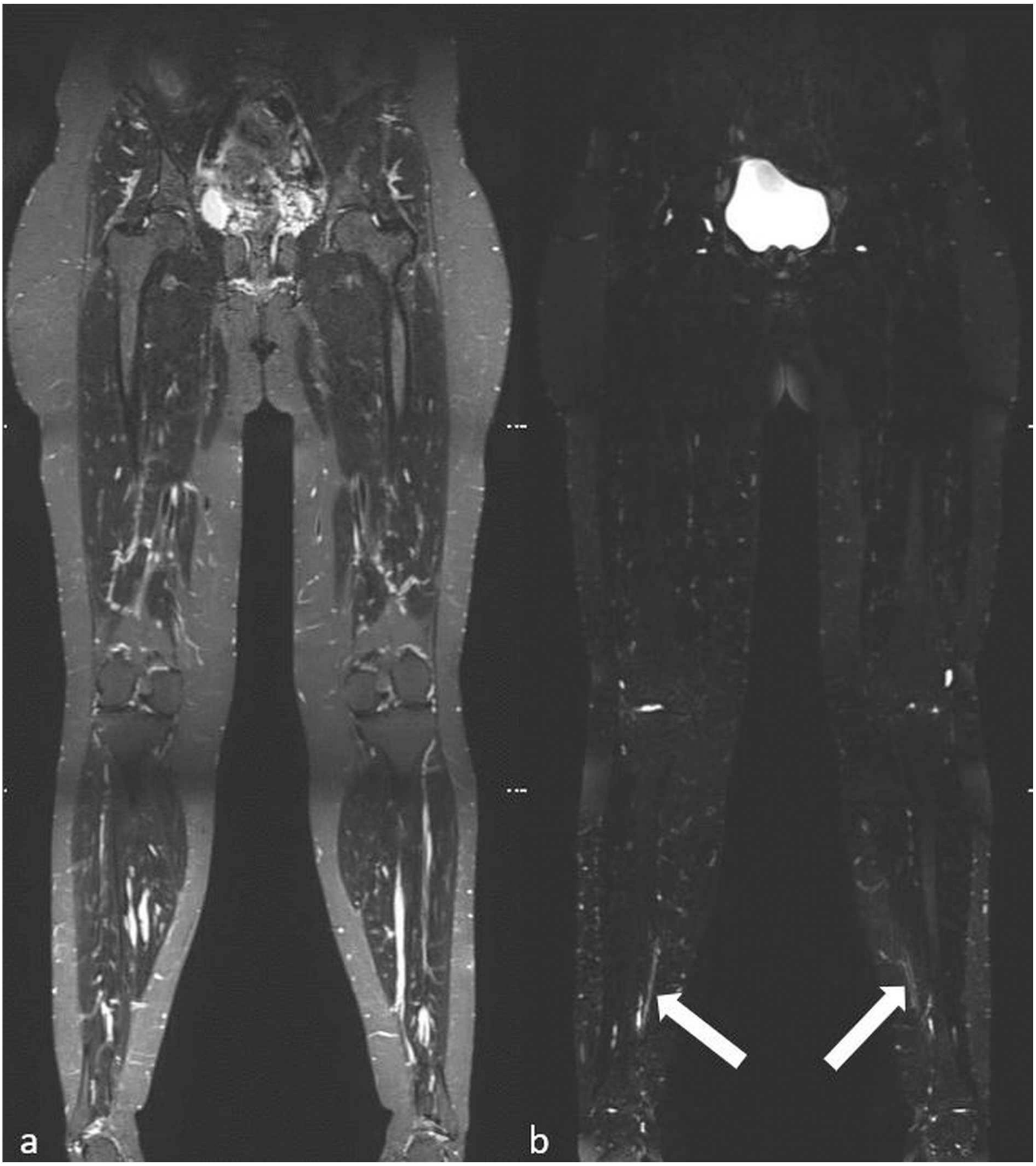

Fig. 4. Minimal epifascial fluid in lipolymphedema.
NCMRL of a 41-year-old female, diagnosed as lipolymphedema. (a) image is obtained from the composing function of STIR images acquired for the different lower limb segments, whereas (b) is obtained from the composing of the heavily T2 TSE weighted acquisitions. The increased representation of the subcutaneous fat tissue is well-evident in both images; enlargement is symmetrical between the right and left sides. No areas of honeycomb pattern are visible. In (b), a minimal epifascial fluid is bilaterally present (white arrows). Thin linear hyperintensities related to vascular structures are bilaterally recognizable in the adipose tissue. Minimum knees joint effusion is bilaterally recognizable.

legs with caliber > 3 mm); (7) signs of vascular stasis, identified as dilated vessels in the subcutaneous fat, creating a reticular pattern.

Values were checked with one-sample Kolmogorov–Smirnov test for normality. The significance of the association between the group variable (lipedema or lipolymphedema) and each radiological feature as a categorical variable was evaluated through Pearson X2 test. The two-sided *t*-test was used to test the difference between the means in parametric distributions. $p < .05$ was regarded as statistically significant. Statistical analysis was performed using SPSS 20 (IBM, Chicago, IL).

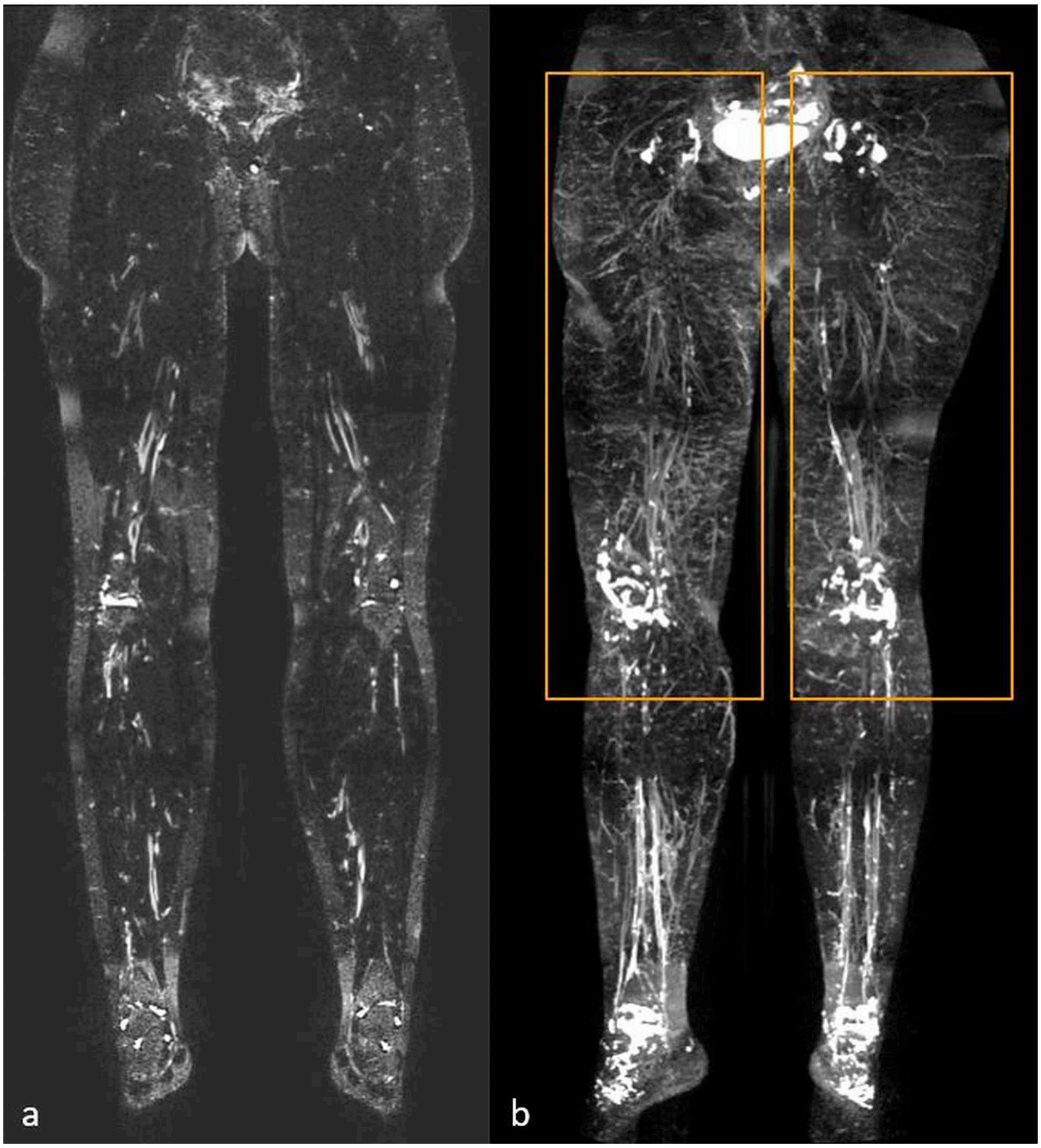

Fig. 5. Example of a case of lipedema.
The composing of T2 TSE acquisitions (a) and MIP reconstructions (b) of a 28-year old female patient shows bilateral enlargement of the lower limb due to mild increased symmetrical representation of the subcutaneous thickness. No honeycomb pattern is visible. The fat shows a hypertrophic appearance with hyperintense thin stripes with a horizontal course (orange rectangles). No sign of epifascial fluid infiltration is present. Hyperintense structures with vertical course referable to vascular structures are bilaterally evident. Ankle and knee joint effusions are bilaterally recognizable.

3. Results

We included forty-four lower limbs of twenty-two Caucasian female patients (mean age: 36.3 ± 10 years; age range: 21–64 years). Eleven patients had a clinical diagnosis of lipedema (8 of stage 1 and 3 of stage 2) and eleven patients of lipolymphedema. The group with lipedema had a mean age of 33.2 ± 7 years, and the one with lipolymphedema of 39 ± 12 years ($p = .082$); mean BMI was 31.2 ± 1.1 for lipedema patients and 31.4 ± 1.2 for lipolymphedema patients ($p = .797$).

Mean swelling duration was 13.3 ± 7.4 years for lipedema patients, and 14.7 ± 5.9 years for lipolymphedema patients. The normal distribution of the data was confirmed using the Kolmogorov–Smirnov test; no statistically significant difference of limb swelling duration was observed between the two groups, $p = .62$ (Fig. 1).

In all patients of both groups the lower extremities, the enlargement was symmetric between the left and the right extremities, with extension from the pelvic crest to the ankle.

In all the lower extremities (100%), MRI demonstrated diffusely increased thickness of subcutaneous fat (Fig. 2).

The maximum thickness of the subcutaneous fat for the four different stations is listed in Table 2.

We did not observe any statistically significant differences of the subcutaneous fat maximum thickness: $p = 1$, 95% for station 1, $p = .87$, for station 2, $p = .85$, for station 3, $p = .86$, for station 4.

Subcutaneous fat was thickened in all patients with lipedema (Fig. 3), without signs of epifascial fluid infiltration; in patients with lipolymphedema, the fat did not show honeycomb pattern, but with minimal signs of edema, more evident at the lower third of the legs,

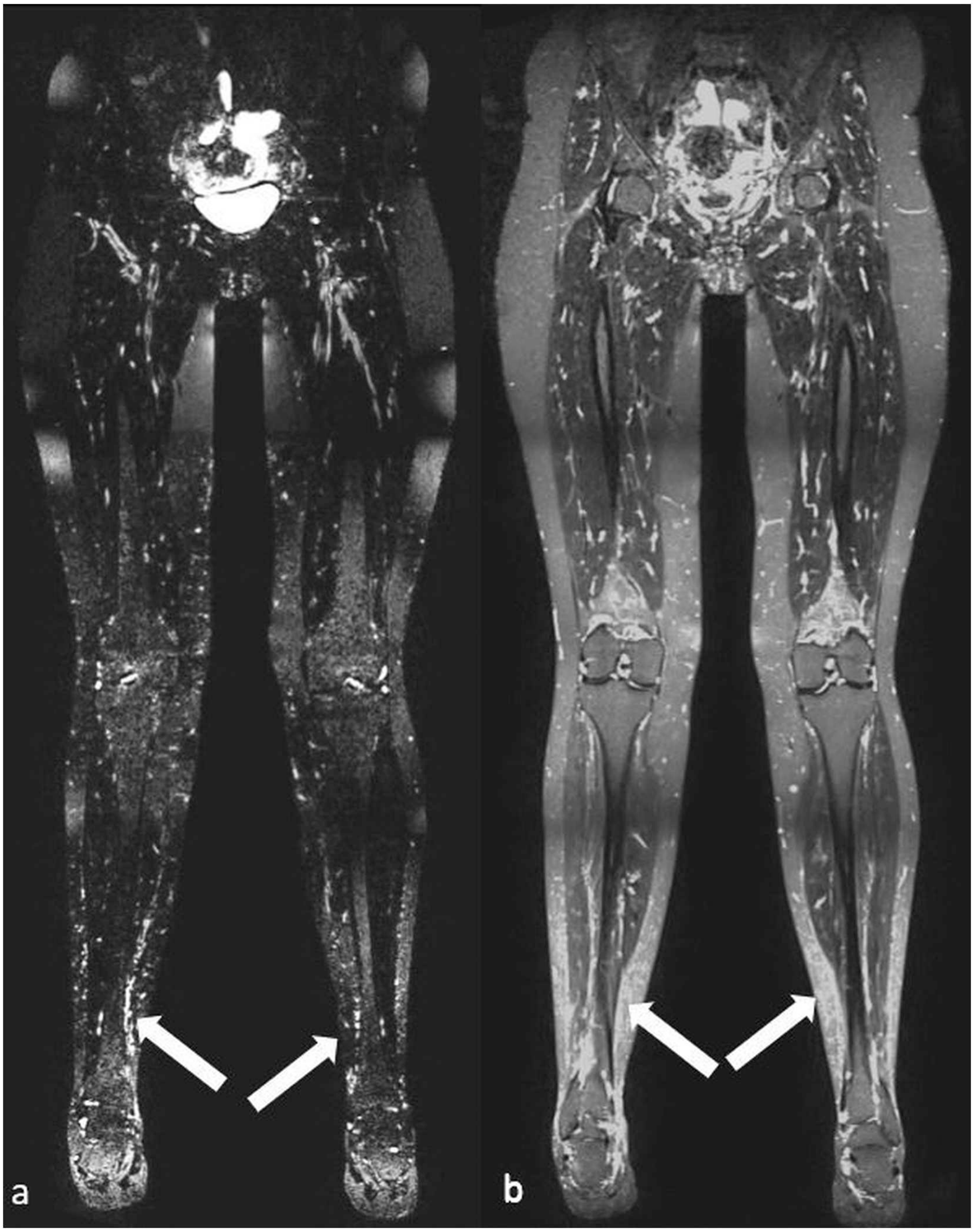

Fig. 6. Example of a case of lipo-lymphedema in a 35-year-old female patient.
Composing of 3D T2 TSE acquisitions (a), STIR acquisitions (b). A mild bilateral symmetrical enlargement of the subcutaneous fat is present; no honeycomb pattern areas are present, but mild signs of epifascial fluid infiltration are visible (white arrows), at both lower legs, more evident on the right side.

with statistically significant difference in comparison to lipedema patients ($p < .001$).

None of the limbs showed the honeycomb pattern that is typical of lymphedema. Extremities affected by lipedema did not show any epifascial fluid collection but a minimal amount (< 3 mm) (Fig. 4) was observed in patients with lipolymphedema, with statistically significant difference in comparison to lipedema patients ($p < .001$).

The different imaging appearances of lipedema and lipolymphedema are displayed in Figs. 5 and 6, respectively.

No signal abnormalities of the muscular compartment were observed in both groups. Mild reduction in muscular trophism of the proximal third of the thigh was observed in 4 patients with lipedema and in 5 lipolymphedema patients, ($p = .665$) (Fig. 7).

MRI findings in the two groups are listed in Table 3. Iliac lymphatics showed normal appearance in all cases (Fig. 8); dilated distal lymphatic vessels were observed in both groups (Fig. 9), with higher rate in the lipolymphedema group and statistically significant difference ($p = .001$).

Signs of vascular stasis (Figs. 10, 11) were found in both groups without statistically significant difference ($p = .665$).

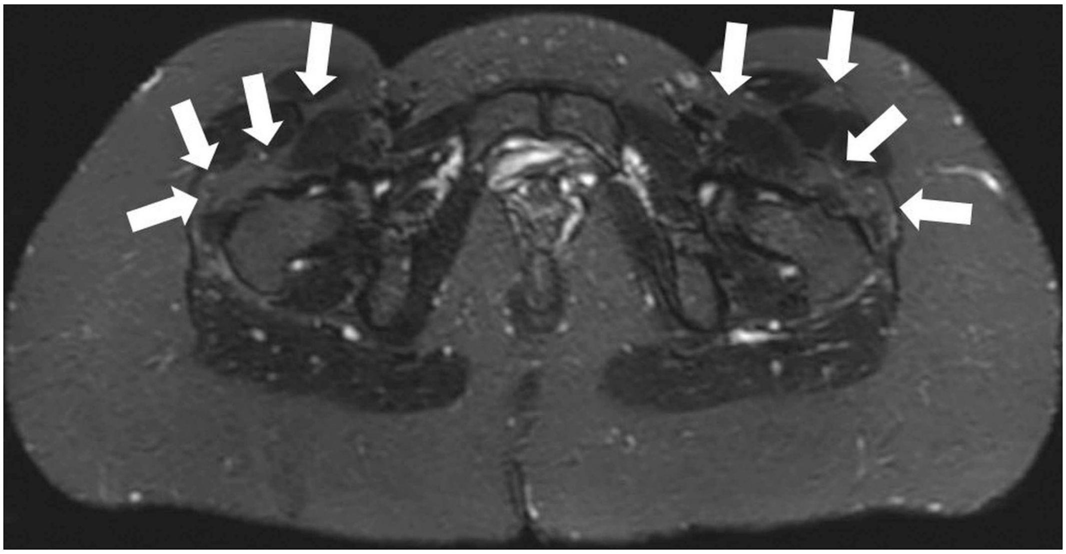

Fig. 7. Reconstructed axial STIR image of a 34-year old patient with lipedema shows a bilateral reduced trophism of the muscles at the root of both thighs: the fat representation among the muscles (white arrows) is increased in relation to the patient' age.

Table 3
Imaging findings in patients with lipedema and lipolymphedema.

NCMRL findings	Patients with lipedema	Patients with lipolymphedema	Statistical differences at Pearson's X2 test
Symmetric involvement of lower limbs	11 (100%)	11 (100%)	
Enlarged subcutaneous fat	11 (100%)	11 (100%)	
Honeycomb pattern	0 (0%)	0 (0%)	
Fluid infiltration of the subcutaneous fat	2 (18.2%)	11 (100%)	$p < .001$
Epifascial fluid collection	0 (0%)	11 (10%)	$p < .001$
Reduction in muscular trophism	4 (36.3%)	5 (45.4%)	$p = .6$
Normal appearance of the main lymphatic truncks	11 (100%)	11 (100%)	
Dilated distal lymphatic vessels	2 (18.2%)	10 (90.9%)	$p = .001$
Signs of vascular stasis	4 (36.3%)	5 (45.4%)	$p = .6$

4. Discussion

The etiology and pathogenesis of lipedema are still not clear. Lipedema, also called *adiposis dolorosa*, is an uncommon chronic condition, characterized by disproportionate adipocyte hypertrophy and localized painful fat tissue, and almost exclusively occur in women [1], consisting in symmetrical enlargement of the limbs, more frequently lower extremities, sparing the feet, hands, and trunk. Later stages of this disorder are characterized by column leg appearance, with masses of nodular fat, easy bruising, and pain [2]. Lipedema is often associated with a family cluster and becomes manifest at hormonal changes, such as around menarche, menopause, or during pregnancy [3]. Men with lipedema have been rarely described in the literature, usually in association with conditions including higher estrogen and lower testosterone levels, as in the case of liver disease. Patients are often misdiagnosed with obesity and lymphedema. The exact impact of the lipedema on the alteration of the lymphatic circulation remains unclear, without conclusive results from previous studies [7,9,23], however, a recent study that assessed with lymphoscintigraphy the lymphatic function in patients affected by lipedema [24] demonstrated the impairment of lymphatic transport in these patients, including an altered transport index, collateral pathways, and dermal backflow and that these alterations worsen with the degree of lipedema.

Regarding the appearance of lymphatics, on lymphographic studies a moderate dilatation and tortuosity of the lymphatics consistent with incompetent valves, or a corkscrew-like aspect were noticed [24,25]: we observed the same finding in our patients affected by lipolymphedema and in 2 patients with lipedema.

The presence of peripheral enlarged in lymphatic vessels that we highlighted in these patients had already been described by Kinmonth [25], with the observation of lymphatic vessels up to a diameter of 3 mm in patients with lipolymphedema and up to 2 mm in lipedema.

A less invasive alternative to lymphoscintigraphy to assess lymphatics appearance and to distinguish lymphedema from lipedema is represented by CEMRL. In line with our results, a study on patients with lipedema and lipolymphedema [18] has previously demonstrated that all lower extremities with clinical lipolymphedema showed high signal intensity with epifascial distribution on MRI that was not recognizable in patients with clinically pure lipedema. The authors also showed peripheral dilated lymphatics both in patients with lipolymphedema and in some patients with clinically pure lipedema, indicating a lipolymphedema subclinical status, as we observed in our patients. This is particularly important in the management of these patients, as pure lipedema is resistant to compression treatments whereas lipolymphedema can benefit from this therapy [25].

The spatial resolution of CEMRL is far higher than lymphoscintigraphy and contrast enhancement of lymphatics is optimal near the contrast media site. However, even if less invasive than lymphoscintigraphy, CEMRL has also some limitations, as it involves the subcutaneous injection of contrast medium, causing patients discomfort and concern regarding gadolinium deposition, as well as long acquisition times.

Some studies are available on cross-sectional imaging, magnetic resonance imaging (MRI) [14,15], and computed tomography (CT) in patients with lipedema, with MRI showing higher sensitivity [25–28]. On MRI lipedema is characterized by an increased layer of subcutaneous fat with no changes in signal intensity between T2- and T1-weighted imaging [16], without subcutaneous tissue fluid, as observed

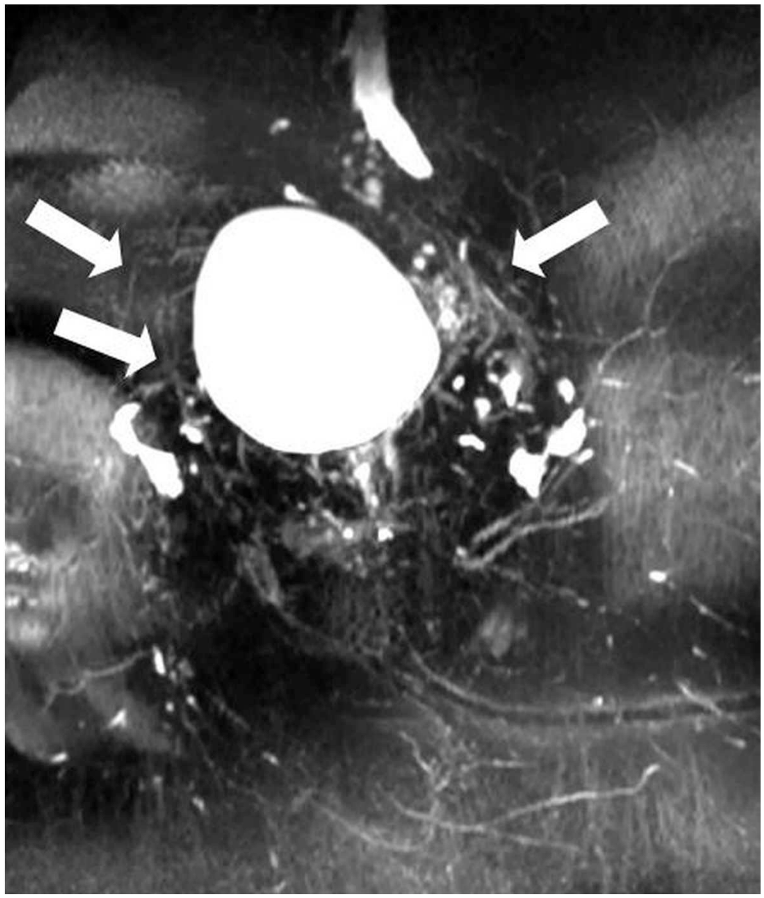

Fig. 8. Iliac lymphatics.
Oblique MIP reconstruction of heavily T2 TSE weighted sequence of the pelvis in a patient affected by lipolymphedema. Bilateral evidence of linear fluid-filled structures referable to lymphatic vessels, with normal appearance (white arrows). The fluid-filled bladder is recognizable in the middle of the figure.

in our study, whereas in lymphedema MRI can show dermal and subcutaneous tissue thickening, and a honeycomb appearance due to fluid within the adipose tissue [28]. In our study, patients with lipolymphedema showed enlargement of the subcutaneous fat tissue, with mild signs of edema and minimal epifascial fluid, without honeycomb appearance, that is typical for lymphedema.

Two studies on a 3 T MRI machine demonstrated significantly elevated sodium in the skin and subcutaneous fat, and higher fat/water volume in patients with lipedema, in comparison to the control subjects; the authors hypothesized that the accumulation of tissue sodium and fat, was suggestive of a reduced vascular clearance or increased deposition and inflammation in the pathophysiology of lipedema, suggesting the role of tissue sodium as objective imaging biomarkers for the differential diagnosis between lipedema and obesity [14,15].

Ultrasound showed promising results in the differentiation between lipedema and lymphedema [13]: in a study including 12 patients with lipedema and 10 with lymphedema, lymphedema appeared to be associated with increased skin thickness and dermal hypoechogenicity, mainly represented in the distal lower extremity, whereas, lipedema was characterized by an increased thickness and hypoechogenicity of the subcutaneous fat in the whole limb.

In some of our patients we observed an interesting finding, not previously described by other studies: the signs of vascular stasis, visible as a reticular pattern of subcutaneous dilated venous vessels, recognizable in both patients affected by lipolymphedema and lipedema. Even if lipedema is considered a distinct entity, not primarily related to lymphatics or vascular dysfunction, we can suppose that the enlargement of the fat cells influenced and impaired not only the lymphatic circulation but also the vascular circulation, conditioning stasis and vessels dilatation.

The differentiation of lymphatics from veins is based on beaded-appearance of lymphatic vessels on MRI, as previously described [17,18].

NCMRL, as a single examination, can provide useful information on lipedema. This examination shows the enlargement of the limbs, its extension, and symmetry, making objective measurements available for the follow-up, and the appearance of the subcutaneous fat, to help the differential diagnosis of lipedema or lipolymphedema. This technique is also able to highlight the characteristics of peripheral and iliac lymphatics, and signs of vascular stasis. All these data are given in a non-invasive way, without exposure to ionizing radiation or contrast medium injection.

These are preliminary results. The main limitations of this study are represented by the lack of a comparative imaging modality, and the limited number of patients, however similar to a previous study on lipedema [14].

Another limitation is intrinsic to this relatively new imaging technique and is the suboptimal spatial resolution, which may be improved with advances in MRI systems.

Studies with wider case series are needed to further validate the role of this relatively new technique in this disorder, and of its accuracy, in comparison to consolidated imaging techniques.

In conclusion, NCMRL is a non-invasive technique that can provide useful information in patients with lipedema and lipolymphedema to aid in their differential diagnosis and assessment of the appearance of the lymphatics. It can be also used to obtain objective measurements of the enlarged limbs to monitor the efficacy of the treatments. More studies are needed to determine its role in the management of these patients.

Fig. 9. Dilated peripheral lymphatic vessel in lipolymphedema.
Heavily T2 TSE weighted sequence in a patient affected by lipolymphedema. A dilated lymphatic vessel with a corkscrew-like aspect is well evident in the lateral aspect of the right thigh.

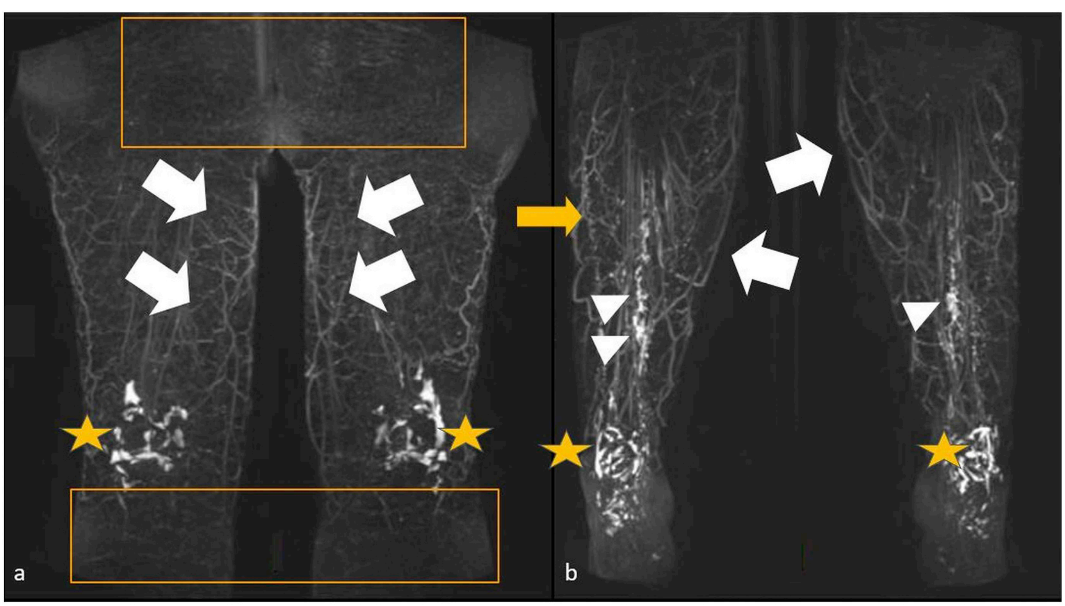

Fig. 10. Signs of vascular stasis.
MIP reconstructions of the thigh (a) and leg (b) of the heavily T2 TSE weighted lymphangiographic sequence in a 34-year-old patient with lipolymphedema. Mild epifascial fluid components are visible (white arrowheads); peripheral lymphatic dilatation is present (yellow arrow), and signs of vascular stasis are bilaterally recognizable as dilated veins creating a reticular pattern (white arrows). Hypertrophic appearance of the subcutaneous fat, with hyperintense thin stripes (orange rectangle). Bilateral evidence of knee and ankle joint effusions (yellow stars).

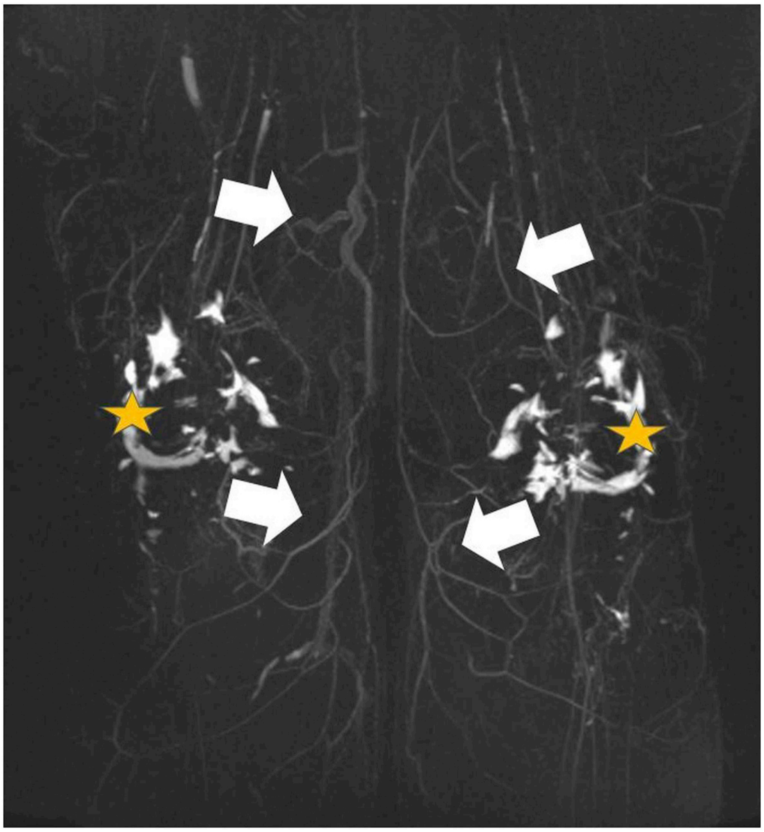

Fig. 11. MIP reconstructions of the heavily T2 TSE weighted lymphangiographic sequence in a 32-year-old patient with lipedema. Signs of stasis, with dilated veins, are bilaterally recognizable (white arrows). Bilateral evidence of knee joint effusion (yellow stars). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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