Lymphatic disturbances in lipoedema

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Summary
Aim: In pathophysiology of lipoedema, almost exclusively seen in women, lymphatic insufficiency might play a significant role. However, little is known about the pathophysiology of these abnormal localized depositions of body fat. We studied the involvement of the lymphatic system in lipoedema of the type Allen-Hines as well as of Typus Rusticanus Moncorps. **Patients, methods:** The standard (epifascial pathway) and a modified method (subcutaneous pathway) of lymphoscintigraphy was carried out with 28 patients suffering from lipoedema. Uptake percentages normalized to the injected dose were used as functional quantitative parameters. Visual assessment of both studies were done and scored. Patients with oedema of the legs because of venous insufficiency (Widmer stage II) served as a control group. **Results:** All patients of the control group and all patients with lipoedema of Typus Rusticanus Moncorps showed a normal standard lymphoscintigraphic study by visual scoring as well as by quantitative outcome. Lymph transport from the subcutaneous fat tissue was significant higher ($p < 0.012$) in the group of patients with lipoedema diagnosed as type Allen-Hines than in Typus Rusticanus Moncorps. **Conclusion:** Epifascial lymph drainage in patients with lipoedema is not significantly disturbed. However, subcutaneous lymphatic drainage significantly differed in patients with lipoedema of type Rusticanus Moncorps in comparison with type Allen-Hines hinting at a differing lymphatic pathophysiology.

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Schlüsselwörter
Lipödem, Allen-Hines, Typus Rusticanus-Moncorps, Lymphszintigrafie

Zusammenfassung
Ziel: Die lymphatische Insuffizienz könnte bei dem fast ausschließlich bei Frauen auftretenden Lipödem pathophysiologisch eine bedeutende Rolle spielen. Über die Pathophysiologie dieser abnorm lokalisierten Körperfettablagerungen ist wenig bekannt. Untersucht wurde die Beteiligung des Lymphsystems bei Lipödem vom Typ Allen-Hines sowie bei Typus Rusticanus-Moncorps. **Patienten, Methoden:** Bei 28 Patienten mit Lipödem wurden die Standard-Lymphszintigraphie (epifaszial) und eine modifizierte Lymphszintigraphie (subkutan) durchgeführt. Die prozentualen Uptakes in Relation zur injizierten Dosis dienten als funktionale quantitative Parameter. Beide Studien wurden visuell bewertet. Patienten mit Ödemen der Beine infolge Veneninsuffizienz (Stadium II nach Widmer) dienten als Kontrollgruppe. **Ergebnisse:** Die Standard-Lymphszintigraphie zeigte bei allen Patienten der Kontrollgruppe sowie allen Patienten mit Lipödem vom Typ Rusticanus-Moncorps einen normalen Befund hinsichtlich der visuellen Bewertung und des quantitativen Wertes. Der Lymphtransport aus dem subkutanen Fettgewebe war im Patientenkollektiv mit Lipödem vom Typ Allen-Hines signifikant höher ($p < 0{,}012$) als beim Typus Rusticanus-Moncorps. **Schlussfolgerungen:** Die epifasziale Lymphdrainage bei Patienten mit Lipödem ist nicht signifikant gestört. Die subkutane Lymphdrainage bei Patienten mit Lipödem vom Typ Rusticanus-Moncorps unterschied sich jedoch deutlich von der bei Patienten mit Lipödem vom Typ Allen-Hines, was auf eine unterschiedliche lymphatische Pathophysiologie hindeutet.

Lymphatische Abflussstörungen bei Lipödem

Mots clés
Lipoedème, Allen-Hines, type Rusticanus Moncorps, lymphoscintigraphie

Résumé
Objectif: L'insuffisance lymphatique peut jouer un rôle important dans la physiopathologie du lipoedème, affection observée quasi exclusivement chez la femme. Toutefois, on sait peu de chose de la physiopathologie de ces dépôts de graisses corporelles localisés anormaux. Nous avons étudié l'implication du système lymphatique dans le lipoedème de type Allen-Hines et Rusticanus Moncorps. **Patients, méthodes:** On a réalisé une lymphoscintigraphie sur 28 patients souffrant de lipoedème selon la méthode standard (voie épifasciale) et une méthode modifiée (voie sous-cutanée). Les pourcentages de captation normalisés par rapport à la dose injectée ont été utilisés comme paramètres quantitatifs fonctionnels. Une évaluation visuelle et une cotation ont été effectuées pour ces deux explorations fonctionnelles. Des patients ayant un œdème des membres inférieurs dû à une insuffisance veineuse (stade II selon Widmer) ont servi de groupe témoin. **Résultats:** Tous les patients du groupe témoin et tous les patients atteints de lipoedème du type Rusticanus Moncorps avaient une étude lymphoscintigraphique standard normale par évaluation visuelle ainsi que par les résultats quantitatifs. Le transport lymphatique à partir du tissu graisseux sous-cutané était significativement plus élevé ($p < 0{,}012$) dans le groupe de patients atteints d'un lipoedème diagnostiqué comme appartenant au type Allen-Hines plutôt qu'au type Rusticanus Moncorps. **Conclusion:** Chez les patients atteints de lipoedème, le drainage lymphatique des fascias superficiels n'est pas perturbé significativement. Cependant, le drainage lymphatique des fascias sous-cutanés différait chez les patients atteints de lipoedème de type Rusticanus Moncorps par rapport au type Allen-Hines, laissant supposer une physiopathologie lymphatique différente.

Troubles lymphatiques dans les lipoedèmes

Lipoedema is a clinical entity firstly described in 1940 by Allen and Hines (1, 32). It occurs almost exclusively in women and starts between puberty and menopause with a progressive, nearly symmetrical enlargement of the legs and buttocks (Fig. 1) or sometimes the arms. The enlargement is often accompanied by aching distress, burning sensations in the plantar surface of the feet and easy bruisibility. In contrast with lymphoedema the feet and lower ankles are not involved and apparently enlargement stops abruptly at the ankle joint. These so-called "Egyptian column" legs are characteristic and are due

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Fig. 1 Legs of a woman (28 years old) with lipoedema type Allen-Hines (note: no edema of the feet)

to consistent fat pad tissue between the Achilles tendon and medial malleolus (2, 20). Moncorps et al. (18) drew the attention to a syndrome consisting of local fat deposits around ankles, wrists and hips (Matronenspeck), erythrocyanosis puellarum crurum and perniosis follicularis, which occurs in young women. These women showed menstrual cycle disturbances and were prone to develop striae distensae. Patients with this constitution were often called "Typus Rusticanus", because these girls showed the rosy rural appearance of farmer's daughters.

In the early stages of lipoedema, computerised tomography (11, 28), magnetic resonance imaging (8, 31) and biopsy (10) have demonstrated that oedema is minimal and limb swelling is due entirely to lipomatous hypertrophy and hyperplasia. Despite this distinct clinical picture, the condition is frequently underdiagnosed (17) and frequently mistaken for oedema, lymphoedema or obesity. In a review (20) of 250 patients with lymphoedema, nine patients were found to have clinical characteristics typical for lipoedema.

Phlebography (10, 23), photoplethysmography (12) and arteriography (23) did not show any consistent abnormality, suggesting that vascular pathology is not likely to be involved in the pathogenesis of lipoedema. The precise mechanism responsible for fat and (lymph)oedema formation has not yet been established. Our study was intended to evaluate if the lymphatic system of patients with lipoedema, either of type Allen-Hines or – Typus Rusticanus Moncorps – Is involved in the disease process.

Patients and methods

Twenty-eight untreated women with lipoedema of which twenty-two were of type Allen-Hines (mean age 39 years, range 46 years) and six of them were of Typus Rusticanus Moncorps (mean age 32 years, range 22 years) were included in our study. The diagnosis of lipoedema of the legs was established by clinical history and physical examination. Seven patients (mean age 45 years, range 26 years) with venous insufficiency of the legs (Widmer stage II) served as control group. Venous insufficiency was proven or excluded in all patients by photophletysmography and Doppler sonography.

All patients firstly underwent a standardised lymphoscintigraphic protocol. The patients were placed in supine position. Prior to injection, the injection side was cleaned with a 70% alcohol solution to prevent infection. Subsequently, 0.5 mCi (18 MBq) ^{99m}Tc-nanocoll (Sorin Biomedica S p.A., Vercelli, Italy) in 0.2 ml was injected subcutaneously, using a 26 G needle, in the first web space of both feet. The radiopharmaceutical preparation was checked for free ^{99m}Tc-pertechnetate by thin layer chromatography and the labelling yield was always >95%. Care was taken of the time between preparation and injection (always >30 min).

All images were obtained from anterior. A static image of 12 s of the injection sides (depots) were acquired immediately after injection with a large field-of-view camera: two-headed Siemens Camera equipped with Low Energy High Resolution (LEHR)-collimators. The energy setting was at the 140 keV photopeak (window 15%) for ^{99m}Tc. A matrix size of 128 × 128 was used. The counts collected during this 12 s were normalised to 100%. After sitting in the waiting room during half an hour, three static images of 3 min were taken of the lower legs and feet (without the depots), the knees, femora and the pelvis. The uptake in the inguinal regions was measured at 45 min post injection (p. i.). Now the patient was instructed to walk for one hour. After this walk three static images of 5 min were obtained from the same area as mentioned above. Two static images of 1 min were taken of depots, inguinal regions and the liver. Regions of interest were selected to obtain quantitative data. The uptake percentages in the inguinal regions were calculated at 45 min and 2 h p. i. The activity in the depots and liver was calculated at 2 h p. i. For each area the activity was corrected for physical decay and background activity and was expressed as a percentage of the activity found at time zero.

Normal uptake values for the inguinal regions were at 2 h p. i. set to >10% which is in accordance with literature data (12, 29, 30). The percentage in the depot and in the liver was calculated at 2 h p. i. For the depots a decrease of >20% (at 2 h p. i.) was considered as reference value. A few days later (within a week) the same procedure was repeated with the only exception that the injections were now given in the subcutaneous fat tissue (1-2 cm deep) 15 cm above the malleolus medialis in both legs (liposcintigraphy).

Visual assessment of the lymph- and lipo-scintigraphies were done double blinded by two experienced observers (Fig. 2). Visual interpretation include abnormalities as dermal backflow, the presence of large collateral lymph channels, crossover filling, extravasation into lymphatic fistula and lymphangiectasias. A semi-quantitative analysis was performed using a Transport-Index (TI) as described in literature (7, 16). Briefly transport kinetics, distribution pattern, time in minutes for appearance of regional lymph nodes and vessels were scored in a grading system (range: 0-9). TI <10 was considered as normal.

Lymph transport was estimated from the ratio of inguinal radioactivity after 2 h / 45 min p. i.

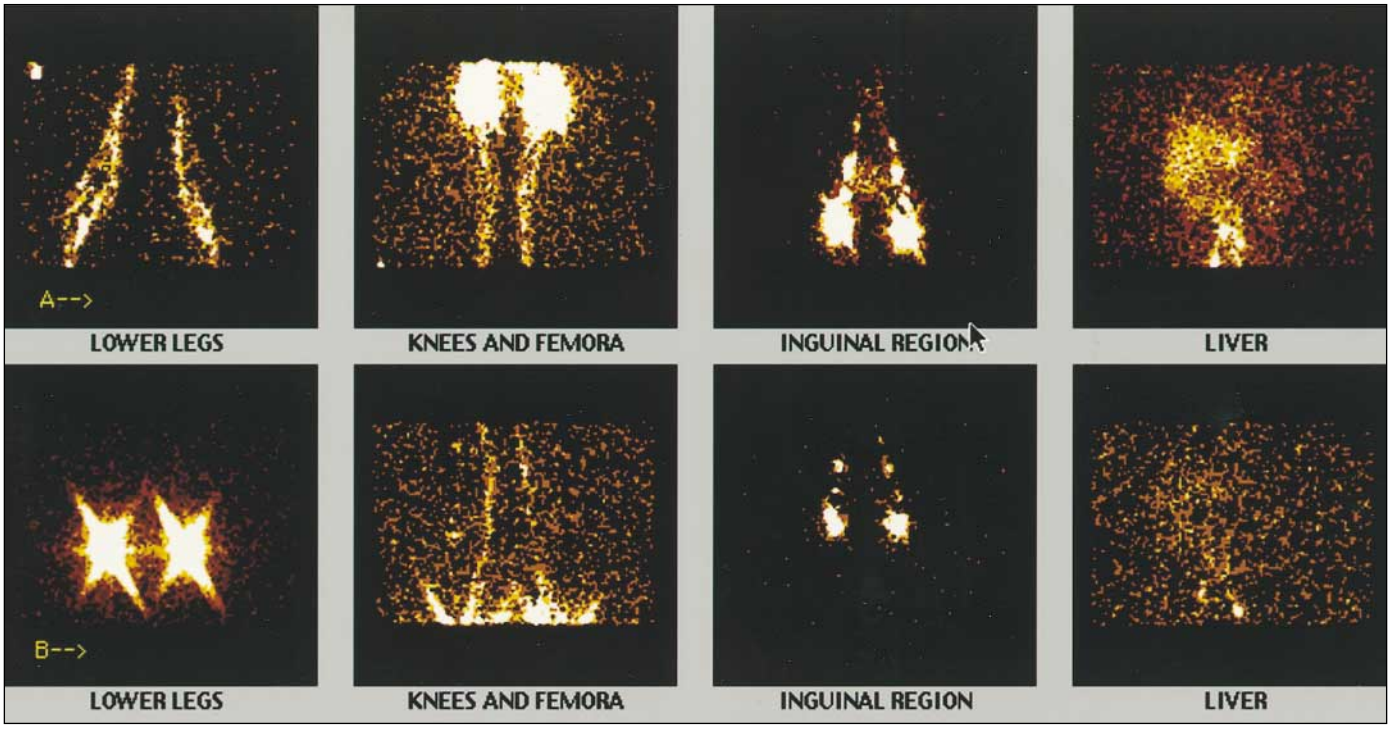

Fig. 2 Standard (A) and modified lymphoscintigraphic (B) study

Distributions are described by the median and the range. Differences in lymphoscintigraphic parameters between groups were analyzed using the Mann-Whithney test and a two-sided significance level of 0.05. Interobserver agreement as well as the correlation between age and the lymphoscintigraphic parameters were determined with Spearman rank correlation coefficient.

Results

Lymphoscintigraphic studies were adequate and radioactivity in the liver was always calculated <0.9% of the injected radioactivity. The interobserver agreement was very good for the standard lymphoscintigraphic study (rho = 0.95) and somewhat less for the liposcintigraphic studies (rho = 0.88).

All control patients and all patients with lipoedema of Typus Rusticanus Moncorps had a normal standard lymphoscintigraphic study by visual scoring and by quantitative evaluation as well. Two patients of type Allen-Hines showed an abnormal lymphoscintigraphic study. However, group comparison (lipoedema versus controls) showed no significant differences. The statistical results of the patients enrolled in this study are summarised in Table 1. The differences in the median values among the ratio of lymph transport between patients with Allen-Hines and Typus Rusticanus Moncorps were higher than expected by chance (p <0.012). Lymph transport from the subcutaneous fat tissue was higher in the group of patients with Allen-Hines and was better correlated with age (-0.794).

Tab. 1 Uptake percentage (median, range in parenthesis) in the inguinal region and depot in the three patient groups; reference values after 2 h: <80% (depot), >10% (lymph; inguinal region); p-values comparing Allen Hines with Rusticanus patients: p = 0.05 (†); p = 0.01 (††)

	Allen Hines n = 22	Rusticanus Moncorps n = 6	control n = 7
depot lymph after 2 h	66 (51-97)	74 (54-87)	61 (60-83)
lymph after 45 min	2.8 (0.2-12)	2.1 (1.1-5.5)	2.1 (0.1-2.1)
lymph after 2 h	18 (0.4-39)	12 (6.2-26)	18 (6-39)
ratio: 2 h / 45 min	5.3 (1.8-16)	5.1 (2.7-15)	7.7 (2.4-64)
lymph score	1.5 (0-17)	1 (0-4.0)	1.0 (0-4.5)
depot lipo	99 (91-100)	96 (87-98)	97 (86-100)
lipo after 45 min	0.1 (0.1-1.0)	0.2 (0.1-0.3)	0.1 (0.1-0.6)
lipo after 2 hrs	1.5 (0.1-6.4)	3.1 (1.0-8.4)†	2.6 (0.2-5.1
ratio: 2 h / 45 min	5.0 (1.0-24)	20 (10-42) ††	16 (2-51)
lipo score	15 (6.5-45)	11 (7.5-22)	9 (3-35)

Discussion

Lymphoscintigraphy is a safe, effective and non-invasive technique to determine the functional status of peripheral lymphatic vessels. The method proved as reliable in patients with swollen legs to distinguish lymphoedema from oedema of other origins with a sensitivity as high as 92-97% and a specificity of nearly 100% (7, 9, 16, 24, 25, 27, 29).

An overview of lymphoscintigraphic studies involving patients with lipoedema revealed abnormalities ranging from normal (4, 5, 27, 30), not regularly present (2, 26) to abnormal lymphatic function in more than 50% of the legs (12, 15). Our results showed no significant lymphatic disturbances in patients with lipoedema as measured with dynamic lymphoscintigraphy.

Lymphangiographic studies (15, 20, 23, 30) showed no abnormalities, too. However, sometimes characteristic patterns for lipoedema with tortuous vessels with small diameters were observed (30). It has been hypothesised (23) that lipoedema is possibly conditioned by a slight mechanical obstruction of the small lymphatic vessels by the increase in pressure exerted by the growing fat tissue. The increased deposition of subcutaneous fat causes resistance to the passage of fluid into the tissue from the blood and so lymphostasis will arise in a normal lymphatic vessel system. A disturbance of the lymphatic system of the septa of the panniculus was suggested (13).

Histological studies (23, 30) in lipoedema patients showed dilatation of hypodermal capillaries, fibrosis of arterioles, fibrosis and dilations of venules, accompanied by hypertrophy and hyperplasia of the fatty cells. Investigations by fluorescence microlymphography proved that lymphatic microvessels are also involved in the disease process (3). Thus, lymph vessels in the subcutaneous fat tissue might be involved in the pathophysiology of lipoedema. The lymphatic clearance in lipoedema could be diminished or show an abnormal pattern. The latter was demonstrated with direct lymphangiography, in which contrast giving substances injected directly in the subcutaneous fat tissue gave rise to a characteristic flame like pattern (19, 21).

Our study is of interest, since in analogy of the above mentioned lymphangiographic study we also injected a depot of a contrast giving agent directly in the subcutaneous fat tissue. Our depot consisted of radiolabeled nanocolloidal particles. Their clearance in the subcutaneous lymphatics was quantitatively determined. We observed a significant difference in clearance between patients diagnosed as type Allen Hines and those with Typus Rusticanus Moncorps. Actually, these two types are considered as subdivisions of lipoedema (22). Jagtman et al. (14) considered lipoedema a subdivision of the idiopathic musculo-fascial pump insufficiency group of Arnold.

The importance of studying the subcutaneous lymphatics with special regard to pathophysiology was also demonstrated by Bräutigam et al. (6). This team investigated the subfascial lymphatic system by an intramuscular injection of radiocolloids into the dorsolateral sole of the foot. They demonstrated that the subfascial lymphatic pathway was compromised in post thrombotic syndromes, whereas the epifascial lymphatic pathway was intact. Brauer (4) recently investigated the subfascial lymph drainage by injecting the radiopharmaceutical agents directly subcutaneously supramalleolair anterolateral in patients with lipoedema, but did not get additional information by this technique.

Conclusion

We could not reveal any direct relationship between lymph vessel pathology and fat formation. However, we demonstrated in the study presented here that lymphatic transport from the subcutaneous fat tissue varies in lipoedema patients. In all our patients with lipoedema, clinically diagnosed of type Allen-Hines, the subcutaneous lymphatic transport was higher than in Typus Rusticanus Moncorps and showed a good correlation with the patient's age and concomitantly with the duration of disease.

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