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MICROLYMPHATIC ANEURYSMS IN PATIENTS WITH LIPEDEMA

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ABSTRACT

"Lipedema," a special form of obesity syndrome, represents swelling of the legs due to an increase of subcutaneous adipose tissue. In 12 patients with lipedema of the legs and in 12 healthy subjects (controls), fluorescence microlymphography was performed to visualize the lymphatic capillary network at the dorsum of the foot, at the medial ankle, and at the thigh. Microaneurysm of a lymphatic capillary was defined as a segment exceeding at least twice the minimal individual diameter of the lymphatic vessel.

In patients with lipedema, the propagation of the fluorescent dye into the superficial lymphatic network of the skin was not different from the control group ($p>0.05$). In all 8 patients with lipedema of the thigh, microaneurysms were found at this site (7.9 ± 4.7 aneurysms per depicted network) and in 10 of the 11 patients with excessive fat involvement of the lower leg, multiple microlymphatic aneurysms were found at the ankle region. Two obese patients showed lymphatic microaneurysms in the unaffected thigh and in only 4 patients were microaneurysms found at the foot. None of the healthy controls exhibited microlymphatic aneurysms at the foot and ankle, but in one control subject a single microaneurysm was detected in the thigh.

Multiple microlymphatic aneurysms of lymphatic capillaries are a consistent finding in the affected skin regions of patients with lipedema. Its significance remains to be elucidated although its occurrence appears to be unique to these patients.

Lipedema is a special form of obesity syndrome that is characterized by symmetrical swelling of the legs without involving the feet (1-3). The typical increase in size of the subcutaneous adipose tissue layer is best documented by magnetic resonance imaging (4).

The initial lymphatics of human skin may be visualized by fluorescence microlymphography (5). After a subepidermal injection of macromolecular dextran 150,00,0 the superficial lymphatic capillaries (microlymphatics) fill and form a discrete network in the skin of the foot, ankle (5,6), and forearm (7). This minimally invasive technique has been used to study disorders such as primary and secondary lymphedema (5,8,9), chronic venous incompetence (10), scleroderma (11) and psoriasis (12). Whereas impeded flow of lymph into deeper lymphatic capillaries is associated with enhanced fluorescent dye extension into the superficial lymphatic network (5), lymphatic microangiopathy occurs with obliteration of lymphatic capillaries as seen in chronic venous insufficiency (10) and in scleroderma (11). Aplasia or hyperplasia of microlymphatics is more typical of congenital lymphedema (8,13). The technique to visualize lymphatic capillaries has also been used to directly measure microlymphatic pressure (14,15) and lymph flow velocity (16).

The etiology and pathogenesis of lipedema are still poorly understood. Lymphatic drainage from the subepidermal compartment is usually normal or only marginally impaired (17,18) in these patients, and the contrast medium injected during

indirect lymphography has a flame-shaped appearance (19). Because the possible role of morphological changes of the superficial skin microlymphatic network has not been examined, we studied 12 female patients with lipedema and 12 age-matched healthy control subjects by fluorescence microlymphography at different levels of the leg.

CLINICAL STUDIES

Twelve female patients with typical lipedema of the lower limbs (mean age 43.7 years, range 21-76 years) and 12 healthy women (mean age of 34.6 years, range 24-56 years) with no signs of phlebedema or lymphedema were studied. Lipedema involved only the calves in 4 patients and in 7 patients calves and thighs. In one patient lipedema was limited to the thighs. Lipedema was diagnosed by clinical means (1,2). In 5 patients magnetic resonance imaging was performed showing the typical finding of homogeneously enlarged subcutaneous fat tissue (4). Clinical examination and conventional Doppler ultrasound excluded other common causes of leg swelling such as chronic venous insufficiency and lymphedema. Patients with elevated levels of blood creatinine or hypoalbuminemia were excluded.

Fluorescence Microlymphography and Diameter Measurements

The technique of fluorescence microlymphography has been described previously in detail (5,6). In brief, 0.01 ml of 25% fluorescein isothiocyanate (FITC)-labeled dextran 150,000 (Sigma Chemical) was injected subepidermally at the dorsum of the foot, at the medial ankle, and at the ventral thigh 15cm above the patella. From the original dye depot the lymphatic capillaries of the skin were filled by the fluorescent tracer and visualized by fluorescence video microscopy at a final magnification of 24x on the television screen (plan objective 1/0.04). Lymphatic capillary diameters were measured at a final magnification of 165 times (plan objective 6.3/0.20). Microvessel filling was recorded on videotape for 15 minutes. The distance between the depot border and the most distant meshes depicted were measured 10 minutes after injection at each site. The morphology of microvessels was evaluated off-line by replay of the television recordings. The lymphatic capillary diameters were determined on single frames of the television video recording by drawing the capillary contours on transparent paper. Care was taken to measure the caliber not at the intersections of meshes, but on free segments of the microvessels. The individual capillary diameter in each healthy control was calculated as the mean of 3 measurements on different capillary segments. Aneurysms were diagnosed when a segment exceeded at least twice the minimal diameter of the same or adjacent microvessel. At each of the 3 sites of examination (foot, ankle, thigh) the total number of aneurysms visualized in the depicted network were counted.

Statistics

Statistical analysis was performed on a personal computer (Compaq Deskpro 4000 p II) using a statistics program (Stat View II) and the data were expressed as means ± SD. The lymphatic network extension, the lymphatic capillary diameter and the number of lymphatic microaneurysms in control subjects were compared with patients with lipedema using a paired t-test.

Informed consent was obtained from each participant and the Ethical Committee of the University Hospital Zürich approved the protocol.

RESULTS

Capillary Diameter and Network Extension

The mean diameters of the lymphatic capillaries at the thigh, at the medial ankle,

TABLE 1
Lymphatic Capillary Diameter (µm) and Network Extension (mm) in Healthy Subjects (Controls) Compared with Patients with Lipedema (Mean ± SD)*

Site	Controls (n=12) capillary diameter (µm)	Controls (n=12) network extension (µm)	Lipedema (n=12) capillary diameter (µm)	Lipedema (n=12) network extension (µm)
Thigh	50.0 ± 5.6	3.8 ± 0.8	53.3 ± 19.5	6.7 ± 3.5
Medial Ankle	49.0 ± 5.1	5.6 ± 1.1	48.7 ± 22.1	5.8 ± 4.7
Dorsum of the foot	46.6 ± 21.1	5.2 ± 1.3	51.1 ± 4.6	5.7 ± 2.0

*No statistical difference between the controls and the patients at all 3 sites ($p>0.05$)

and at the dorsum of the foot in healthy subjects and patients with lipedema are shown in *Table 1*. There was no statistical difference in diameter between the different sites and the values in patients and in controls were in the same range.

There was also no statistically significant difference in the mean maximum extension of the depicted microlymphatic network between the three different locations in both groups and no difference was found in patients compared with controls *(Table 1)*.

Morphology of the Microlymphatic Network

In healthy subjects and in lipedema patients fluorescence microlymphography revealed an intact superficial network with only a few meshes depicted at each site of examination *(Fig. 1)*. Network configuration was almost identical at the thigh, at the medial ankle and at the foot dorsum. An exception was one lipedema patient with disease duration of more than 10 years. In this patient the microlymphatic network was interrupted by multiple obliterations and the maximal dye spread into the superficial network was enhanced (14mm).

The mesh segments of the initial lymphatics involved showed saccular or fusiform microaneurysms with a diameter more than twice the minimal diameter measured in the same patient *(Fig. 2)*. In some meshes diffuse microvessel widening was observed. The walls of the lymphatic capillaries were not smooth like those in control subjects but irregular in shape. More or less long segments with normal diameter were intersected between enlarged segments or detected in other parts of the network. The maximal diameter of a single microaneurysm observed in lipedema patients reached 240 µm (125-240 µm). The segments of the initial lymphatics adjacent to microaneurysms were often of normal shape and not enlarged. Among the 12 healthy controls, no microaneurysms were seen at any of the three sites in 11. In one subject a single enlarged microvessel was detected at the thigh. In those skin regions of the lipedema patients exhibiting typical clinical alterations, however, multiple microlymphatic aneurysms were common. In all 8 patients, where the thigh was affected by lipedema, microaneurysms were visualized (7.9± 4.7 microaneurysms per depicted network). In 10 of the 11 patients with lipedema involving the lower leg, microlymphatic aneurysms were detected at the ankle region. Two patients showed microaneurysms in the unaffected thigh and only 4 patients at the foot *(Table 2)*.

The number of microaneurysms in the

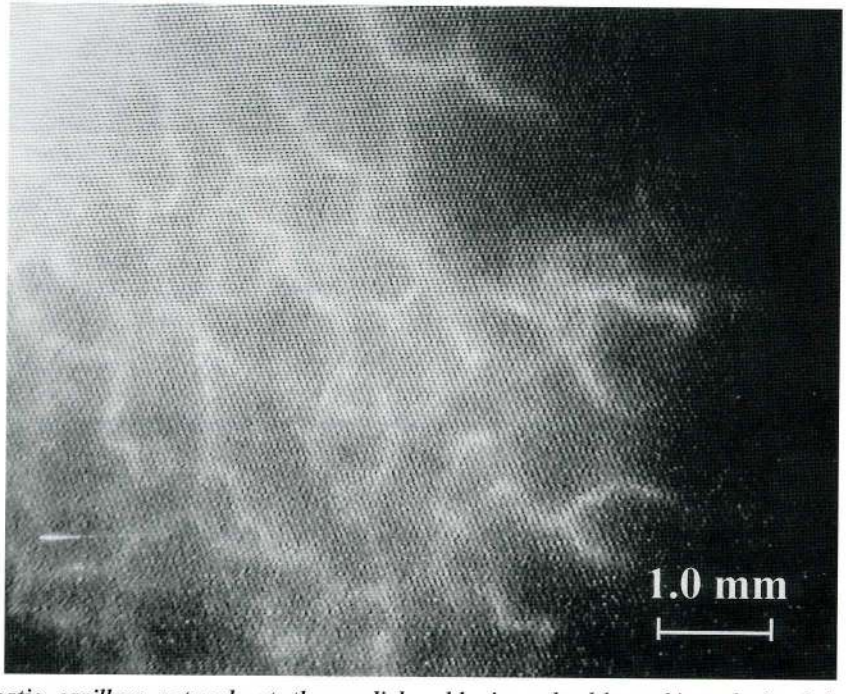

Fig. 1. Lymphatic capillary network at the medial ankle in a healthy subject depicted by fluorescence microlymphography.

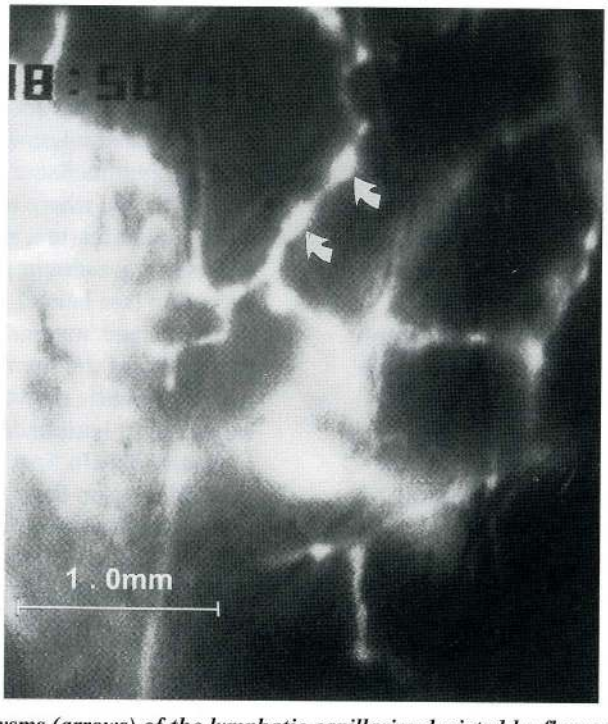

Fig. 2. Several microaneurysms (arrows) of the lymphatic capillaries depicted by fluorescence microlymphography in a patient with lipedema.

TABLE 2
Prevalence (Mean Number and Range in Parenthesis) of Microaneurysms in Lymphatic Capillaries in Patients with Lipedema

Lipedema Site	Thigh	Medial ankle	Dorsum of the foot
Thigh and Lower Leg (n=7)	7.9 (2-14)	7.0 (0-16)	1.0 (0.3)
Lower leg (n=4)	0.5 (0-1)	5.3 (2-8)	0.3 (0-1)
Thigh (n=1)	6	0	0

diseased skin region of lipedema patients was compared with the number of microaneurysms in the identical region of the control subjects. The mean number of microaneurysms at the affected thigh in 8 patients was 7.6 (2-14) and 0.08 (0-1) in controls. This difference was statistically significant ($p<0.05$). Between the non-affected foot and the affected thigh the difference of microaneurysms found in lipedema patients was statistically significant ($p<0.05$).

DISCUSSION

The present study documents that formation of multiple microlymphatic aneurysms is common to the diseased skin region of lipedema. The diameters of the initial lymphatics adjacent to the microaneurysms or in other unaffected lymph vessel segments were within the normal range (56.3±9 µm, range 45-73 µm) as described previously (6,8).

Histological studies in patients with lipedema revealed dilatation of subdermal blood capillaries, fibrosis of the arterioles, fibrosis and dilatations of the venules and hypertrophy and hyperplasia of the adipocytes (20,21). Our *in vivo* findings obtained in initial lymphatics conform to these histological observations.

The pathophysiological role of lymphatic microaneurysms in lipedema as described remains to be established. The damaged walls of the dilated lymphatic segments might be more permeable to macromolecules than normal initial lymphatics and induce lipedema or contribute to its formation. On the other hand, the unknown process causing lipedema may induce lymph vessel microaneurysms as a secondary phenomenon.

Thus far, no other disorder with relatively large numbers of lymphatic microaneurysms has been described. The salient feature of lymphatic microangiopathy in severe chronic venous incompetence is obliteration of microvessels (10). As in primary lymphedema, uncomplicated by erysipelas (6), where microaneurysms are not a prominent feature, microlymphatic occlusions are absent in lipedema with one exception (see below). The main difference between lipedema and lymphedema is that the spread of the fluorescent dye into the microlymphatic network is significantly enhanced in lymphedema (6) but unremarkable in lipedema *(Table 1)*. The probable reason for this difference is impeded lymphatic drainage from hypoplastic deep collectors in primary lymphedema (22,23) or obstruction of the deep collectors in secondary lymphedema (9), compared with a normal or only slightly impaired lymph transport in lipedema (17-19).

Transitions between lipedema and lipolymphedema have been described (23).

The only lipedema patient in our study who exhibited lymphatic microvascular obliterations and increased fluorescent dye spread, suggesting reduced lymphatic transport capacity into the deep lymphatic vessels, probably suffered from lipolymphedema.

Whether multiple microlymphatic aneurysms is specific for lipedema has not been established, but in a variety of other disorders (e.g., scleroderma, venous insufficiency), lymphatic microaneurysms have not been detected (8,10-13). The significance of the lymphatic microaneurysm and its relation, if any, to the pathogenesis of lipedema remains to be elucidated.

REFERENCES

1. Allen, E, EA Hines: Lipedema of the legs: A syndrome characterized by fat legs and orthostatic edema. Proc. Staff Mayo Clin. 15 (1940), 184-187.
2. Rudkin, GH, TA Miller: Lipedema: A clinical entity distinct from lymphedema. Plast. Reconstr. Surg. 94 (1994), 841-847.
3. Harwood, CA, RH Bull, J Evans, et al: Lymphatic and venous function in lipoedema. Br. J. Dermatol. 134 (1996), 1-6.
4. Duewell, S, KD Hagspiel, J Zuber, et al: Swollen lower extremity: Role of MR imaging. Radiology 184 (1992), 227-231.
5. Bollinger, A, K Jäger, F Sgier, et al: Fluorescence microlymphography. Circulation 64 (1981), 1195-1200.
6. Bollinger, A, B Fagrell: Clinical Capillaroscopy, A Guide to its Use in Clinical Research and Practice. Hogrefe and Huber, Toronto, Lewiston NY, Bem, Göttingen, Stuttgart, 1990.
7. Stanton, AW, P Kadoo, PS Mortimer, et al: Quantification of the initial lymphatic network in normal human forearm skin using fluorescence microlymphography and stereological methods. Microvasc. Res. 54 (1997), 156-163.
8. Pfister, G, B Sässeli, U Hoffinann, et al: Diameters of lymphatic capillaries in patients with different forms of primary lymphedema. Lymphology 23 (1990), 140-144.
9. Mellor, RH, AWB Stanton, P Azarbod, et al: Enhanced cutaneous lymphatic network in the forearms of women with postmastectomy oedema. J. Vasc. Res. 37 (2000), 501-512.
10. Bollinger, A, G Isenring, UK Franzeck: Lymphatic microangiopathy: A complication of severe chronic venous incompetence (CVI). Lymphology 15 (1982), 60-65.
11. Leu, AJ, SB Gretener, S Enderlin, et al: Lymphatic microangiopathy of the skin in systemic sclerosis. Rheumatology 38 (1999), 221-227.
12. Cliff, S, AJ Bedlow, AWB Stanton, et al: An *in vivo* study of the microlymphatics in psoriasis using fluorescence microlymphography. Br. J. Dermatol. 140 (1999), 61-66.
13. Bollinger, A, G Isenring, UK Franzeck, et al: Aplasia of lymphatic capillaries in hereditary and congenital lymphedema. Lymphology 16 (1983), 27-30.
14. Spiegel, M, B Vesti, A Shore, et al: Pressure of lymphatic capillaries in human skin. Am. J. Physiol. 262 (1992), H1208-H1210.
15. Zaugg-Vesti, B, J Dörffler-Melly, M Spiegel, et al: Lymphatic pressure in patients with primary lymphedema. Microvasc. Res. 46 (1993), 128-134.
16. Leu, AJ, DA Berk, F Yuan, et al: Flow velocity in the superficial lymphatic network of the mouse tail. Am. J. Physiol. 267 (1994), H1507-H1513.
17. Bräutigam, P, E Földi, I Schaiper, et al: Analysis of lymphatic drainage in various forms of leg edema using compartment lymphoscintigraphy. Lymphology 31(1998), 43-55.
18. Bilancini, S, M Lucchi, S Tucci, et al: Functional lymphatic alterations in patients suffering from lipedema. Angiology 46 (1995), 333-339.
19. Partsch, H, Ch Stöberl, A Urbanek, et al: Clinical use of indirect lymphography in different forms of leg edema. Lymphology 21 (1988), 152-160.
20. Curri, SB, JF Merlen: Troubles microvasculaires du tissu adipeux. J. Mal. Vasc. 11(1986), 303-309.
21. Merlen, JF, SB Curri, AM Sarteel: Cellulitis, a conjunctive microvascular disease. Phlebologie 32 (1979), 279-282.
22. Kinmonth, JB: *The Lymphatics, Surgery, Lymphography and Diseases of the Chyle and Lymph Systems*. E. Arnold, (Ed.), London, 1982.
23. Földi, M, S Kubik (Eds): *Lehrbuch der Lymphologie*. Gustav Fischer, Stuttgart, 1989.

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