Mod Rheumatol (2009) 19:600–605
DOI 10.1007/s10165-009-0221-x

REVIEW ARTICLE

The specificity of capillaroscopic pattern in connective autoimmune diseases. A comparison with microvascular changes in diseases of social importance: arterial hypertension and diabetes mellitus

Sevdalina Nikolova Lambova · Ulf Müller-Ladner

Received: 24 February 2009 / Accepted: 29 July 2009 / Published online: 25 September 2009

Abstract Capillaroscopy is a method with substantial value for diagnosis and differentiation of primary and secondary Raynaud's phenomenon in rheumatic diseases. The most specific finding is in systemic sclerosis—the so-called "scleroderma pattern." which is characterized by the presence of dilated capillaries, hemorrhages, avascular areas, and neoangiogenesis. Similar changes are found in patients with dermatomyositis, overlap syndromes, and others and are termed "scleroderma-like pattern." For the development of these patterns, the most specific finding in the early phase is appearance of dilated capillaries. Capillaroscopic changes in connective autoimmune diseases are specific and differ significantly from those of that can be found in other diseases. Diseases of social importance such as diabetes mellitus and arterial hypertension often present as comorbidity in patients with rheumatic diseases. In diabetes mellitus, the capillaroscopic examination does not show dilated capillaries until the advanced stages of the disease. In the late stages of connective tissue disease, a loss of capillaries is typical. In addition, in diabetes mellitus, the diabetic stiff-hand syndrome and sclerodactyly are common complications, which have to be differentiated from similar signs in rheumatic diseases, and capillaroscopic examination appears to be useful in these situations. In arterial hypertension, a reduced capillary density in different body regions has been observed in patients with established disease as well as in preclinical stages. Analogous phenomenon of reduction in the nail-fold area has also been observed in a group of patients with essential hypertension, none of whom previously received hypertensive drugs.

Keywords Capillaroscopy · Connective autoimmune diseases · Arterial hypertension · Diabetes mellitus

S. N. Lambova (✉)
Clinic of Rheumatology, Medical University,
15A "Vasil Aprilov" Blvd, 4002 Plovdiv, Bulgaria
e-mail: sevdalina_n@abv.bg

U. Müller-Ladner
Department for Internal Medicine and Rheumatology,
Justus-Liebig University Giessen, Department for Rheumatology
and Clinical Immunology, Kerckhoff Clinic, Bad Nauheim,
Germany

Introduction

Nail-fold capillaroscopy is a noninvasive, inexpensive, and easy-to-repeat imaging technique, which is of substantial importance for the evaluation of microcirculation in vivo [1, 2]. The main indication for performing capillaroscopy in rheumatology is the presence of Raynaud's phenomenon (RP). RP is caused by reversible vasospasm of the small arteries and arterioles of the fingers and toes provoked by cold temperatures. RP is currently classified into primary and secondary [1, 3]. Secondary RP is a common symptom in a variety of rheumatic diseases. Here, the nail-fold capillaroscopy plays a key role in differentiating primary and secondary forms of RP, for early diagnosis of systemic sclerosis (SSc), and for other connective tissue diseases (CTD) [1, 4–12]. The current knowledge about this technique suggests also a potential application in a variety of rheumatic diseases, as well as in nonrheumatic diseases such as diabetes mellitus, cardiac syndrome X, arterial hypertension (AH), acromegaly, hyperthyroidism, primary biliary cirrhosis, Crohn's disease, psoriasis, and familial Mediterranean fever [13].

Capillaroscopic pattern in primary and secondary RP in rheumatic diseases

Primary RP

The diagnosis of primary RP is made in patients with no underlying cause for the development of vasospasm. Capillaroscopic examination in primary RP usually reveals capillaries that are normal in number and size. In these patients, the mean capillary diameter, capillary density, and capillary morphology do not differ significantly from those of healthy subjects. The capillary diameter can be slightly enlarged, but it does not have a diagnostic value [4]. Nail-fold capillaroscopy is of crucial importance for differentiating primary and secondary RP in rheumatic diseases. Therefore, in presence of RP the follow-up by nail-fold capillaroscopic analysis is recommended to be performed every 6 months [4, 8, 10, 14].

Secondary RP

Abnormal capillaroscopic findings are characteristic for secondary RP in rheumatic diseases [1, 4, 5, 8, 10].

Systemic sclerosis

RP is one of the most frequent clinical symptoms in SSc: the prevalence is about 90–95% and usually is an initial symptom that precedes other features of the disease by years. RP in SSc is severe and often presents with digital ulcers [15].

The capillaroscopic pattern in SSc is specific and is characterized by the presence of dilated and giant capillaries, hemorrhages, avascular areas, and neoangiogenesis. It has been described for the first time by Maricq et al. (1980) and has been termed "scleroderma type" capillaroscopic pattern [4–10, 16–18]. Maricq et al. found that some of the features of this pattern can also be observed in mixed connective tissue disease (MCTD), undifferentiated connective tissue disease (UCTD), overlap syndromes, and dermatomyositis (DM), and they classified these findings as "scleroderma-like" capillaroscopic pattern [4, 5, 8, 10, 18, 19]. The specific capillaroscopic pattern can be found in a large number of cases with overt SSc: 83–93% [8, 16]. Bergman and co-workers found this type of specific capillaroscopic change in 70.4% of examined patients (19/27) [18], and Nagy and Czirjac [20] found it in 87.5% of patients with diffuse SSc and in 61.6% of cases with limited form of the disease among 102 examined SSc patients.

Systemic lupus erythematosus (SLE)

The prevalence of RP in systemic lupus erythematosus (SLE) is reported to range from 10% to 45% and usually has a benign course without tissue necrosis [14]. Capillaroscopic findings in SLE are less specific in comparison with SSc and other above-mentioned diseases, in which a scleroderma-like capillaroscopic pattern is present [4]. The most frequently described specific changes in SLE are tortuous, meandering capillaries; bizarrely formed loops [21], increased length of capillaries [22, 23], increased diameter [21], and a prominent subpapillary plexus [22, 23]. In some studies, these features have been termed "SLE-type" capillaroscopic pattern [19, 21, 22]. The scleroderma-like pattern is a rare finding in SLE in contrast to other CTD. Its frequency is low, ranging from 2% to 15% [19, 20, 23, 24].

Dermatomyositis and polymyositis (PM)

The prevalence of RP in dermatomyositis (DM) and polymyositis (PM) is >20% [14]. Bergman et al. found a scleroderma-like capillaroscopic pattern in 63.6% of the 11 examined DM patients [1, 19] and Nagy and Czirjac [20] in 26.9% of 26 DM/PM patients.

Mixed connective tissue disease

The frequency of RP in MCTD is about 85% and often appears to be one of the initial symptoms [25]. The high incidence of RP in MCTD supports the essential role of capillaroscopic examination in these cases. In 50–65% of MCTD patients, a scleroderma-like pattern could be found [16, 19, 26].

Undifferentiated connective tissue disease

The term UCTD is used to describe a group of patients with features of connective autoimmune disease but lacking the required characteristics of a well-defined rheumatic disorder. Some of these patients (1/4 to 1/3) later develop particular rheumatic disease (the most frequent), SSc, SLE, RA, and Sjögren's syndrome (SS), but the majority of patients remain in a stable clinical and laboratory condition in the scope of the term UCTD. Nagy and Czirjac [20] found scleroderma-like capillaroscopic pattern in 13.8% of the 65 examined patients with UCTD. Capillaroscopy should be performed in cases with UCTD, and it has been suggested that the method is helpful in selecting the subgroup of patients who are prone to develop SSc or SLE.

Other rheumatic diseases

RP is found in one-third of patients with primary SS [14, 27]. Capillaroscopy is useful for evaluating the microcirculation of SS patients, especially those with secondary RP. In SS patients who present with secondary RP, abnormal capillaroscopic changes have been found, including pericapillary and confluent hemorrhages and a decreased mean capillary density. In some of the cases, a scleroderma-like capillaroscopic pattern has been observed [28, 29]. The prevalence of RP in rheumatoid arthritis (RA) is not well defined. Some authors have argued that such an association is quite rare [14], whereas others include RA among the rheumatic diseases associated with RP [13, 30]. In 31 patients with RA, Redisch [21] found the following capillaroscopic changes: elongated capillary loops, increased tortuousity, and prominent subpapillary plexus. However, a scleroderma-like pattern has not been observed in RA patients [20, 31–33].

Capillaroscopic changes in diseases of social importance: arterial hypertension (AH) and diabetes mellitus

Arterial hypertension

In essential AH patients, rarefaction of capillaries has been found, as has a tendency to vasospasm. It has been reported for different regions such as dorsum of the fingers and the forearm. Similar changes could be observed in conjunctiva vessels [2]. The changes are thought to be structural rather than functional [2, 34–36]. A correlation between mean capillary density in the dorsum of the fingers and values of diastolic blood pressure could be found [34]. Capillary rarefaction has been associated also with borderline essential AH [37]. A reduced capillary count precedes the development of AH and is found in healthy subjects with predisposition to high blood pressure, who are the offspring of AH patients. This suggests that microvascular abnormalities are primary and partly genetically determined [38, 39]. The phenomenon of reduction of capillary density in the nail-fold area has also been observed in patients with essential hypertension who had not previously received hypertensive drugs [35]. It has been therefore hypothesized that the reduced capillary count in hypertensive patients is probably a result of defective angiogenesis. Barker et al. have demonstrated that adults with higher blood pressure are born with lower birth weight. However, hypertensive patients are usually more obese than normotensive controls. The possible explanation of this phenomenon is a faster rate of growth in later life in hypertensive subjects, when more capillaries have to be formed to supply adequate perfusion, potentially leading to microvascular changes and AH [39, 40].

Diabetes mellitus

Microangiopathy is a specific complication for diabetes mellitus, both in the insulin-dependent and the insulin-independent forms. It primarily involves retinal and renal vessels. Microvascular walls (of arterioles, venules, and capillaries) are impaired by biochemical processes, which are based on hyperglycemia: nonenzymatic glycosylation of proteins, altered polyol–inositol metabolism, etc. Glycosylation products also accumulate in structural proteins of the microvasculature. A specific macrophage receptor recognizes proteins to which glycosylation products are bound and stimulates their removal. Different pathologic processes are then activated: increase of endothelial permeability; stimulation of growth factor synthesis by macrophage. As a result, the vessel wall thickens and loses its elasticity. Later, the intensified glycosylation of hemoglobin leads to hypoxia, which is one of the prerequisites for microangiopathy [4].

Additionally, in diabetes mellitus patients, a syndrome of limited joint mobility (diabetic stiff-hand syndrome, diabetic cheiroarthropathy, diabetic waxy skin) can be observed. It is characterized by stiffness of the metacarpophalangeal, interphalangeal, and wrist joints; flexion contractures in long-standing disease with the well known "prayer sign"; as well as with skin thickening with loss of the majority of fine wrinkles, resembling true sclerodactyly. In diabetic stiff-hand syndrome, the joint is not directly involved, and the restricted mobility is due to collagen thickening in periarticular tissue. A nonenzymatic reaction between glucose and proteins is thought to result in formation of advanced glycation end products, which underlie this phenomenon of stiffening. This syndrome could be found as a common complication of both type 1 and type 2 diabetes mellitus, with up to 50% of type 1 diabetic patients and 75% of type 2 being affected. The correlation between development of diabetic stiff-hand syndrome with blood glucose levels and duration of diabetes is not well defined. Autoantibodies and markers of inflammation are not elevated in isolated diabetic stiff-hand syndrome. Of note, an association between this syndrome and the microvascular changes (retinopathy, nephropathy) could be found [41–43]. The skin changes in diabetes mellitus resemble skin changes in SSc and are termed scleroderma-like skin changes. Their presentation consists of thickening and induration, in some instances, waxy appearance of the skin on the dorsum of the fingers (sclerodactyly) and the proximal interphalangeal joints. Skin changes may also involve the metacarpophalangeal joint as well as forearm, arms, and back [41, 43–47].

The scleroderma-like syndrome is described in 8–50% of insulin-dependent diabetes mellitus patients and is the earliest clinically apparent long-term complication of diabetes in children and adolescents. Its frequency appears to be related to disease duration and patient age, whereas the correlation with glycemic control or genetic factors is less clear [48]. Therefore, rheumatologists have to be acquainted with the nail-fold capillaroscopic findings in diabetes mellitus in cases that present the abovementioned complication, that resemble changes in rheumatic diseases, as well as when it presents as concomitant pathology in patients with defined rheumatologic disorder.

In diabetes mellitus type 2, mean capillary density does not differ significantly from healthy individuals of similar age, gender, and body mass index [2]. In diabetes mellitus patients with long-standing disease, capillaroscopy demonstrates slightly dilated and coiled capillaries [4]. Meyer et al. examined the density, diameters, and morphology of nail-fold capillaries in 16 type 1 and 19 type 2 diabetic patients. The capillary density and the arterial limb diameter were similar in diabetic patients compared with the age- and sex-matched control group, whereas capillary diameters of the apical part and the venous limb were enlarged. Tortuous capillaries were more often observed in patients with diabetes mellitus [49].

Similar results were presented by Tibirica et al. [50], who found no difference in mean capillary density at the area of nail fold between 59 patients with diabetes mellitus type 1 and the age- and sex-matched controls. Chang et al. found no significant difference in mean capillary density between patients with diabetes mellitus with and without retinopathy and healthy controls, but increased capillary width and increased tortuosity were more frequently present in diabetic patients. This correlated with the degree of retinopathy, being the most pronounced in cases with proliferative retinopathy. It is known that hyperglycemia induces intensified metabolism, increased oxygen consumption, causes relative tissue hypoxia, and as a result a dilation of blood vessels. In addition, an abnormal interstitial diffusion of fluorescein of nail-fold vessels in diabetes mellitus has been found and is thought to develop prior to capillary dilation [51, 52].

Conclusion

In patients with CTD, the most specific capillaroscopic findings are scleroderma and scleroderma-like pattern. The development of these patterns in the early stage of the disease starts with the appearance of dilated capillaries. Even the detection of a single loop with a diameter >50 μm should be considered as a potential marker of microangiopathy and indicator for future development of CTD disease [5, 8]. These changes in the early phase of CTD are specific and differ significantly from those of diseases of social importance, such as diabetes mellitus and AH. In diabetic patients, the capillaroscopic examination does not show dilated capillaries until the advanced stages of the disease. Difference in mean capillary density compared with healthy individuals has not been found. In the late stages of CTD, loss of capillaries is typical. In AH, capillary rarefaction in different regions of the body has been found in patients with established as well as preclinical stages of the disease in subjects with predisposition to high blood pressure and in borderline AH. This phenomenon has been registered in the nail-fold area in patients with essential hypertension who have not previously received hypertensive drugs. In addition, in diabetes mellitus, diabetic stiff-hand syndrome and sclerodactyly are common complications, which have to be differentiated from similar signs in different rheumatic diseases such as SSc and early arthritis. Here, capillaroscopy can help facilitate the proper diagnosis of the underlying disease. Future studies will disclose the potential of capillaroscopy for the differentiation of rheumatic disease and diseases of social importance and will provide additional information for the daily practitioner.

Acknowledgments Supported by a grant of EULAR (European League Against Rheumatism), 2009.

Conflict of interest statements None.

References

1. Cortes S, Cutolo M. Capillaroscopic patterns in rheumatic diseases. Acta Rheumatol Port. 2007;32:29–36.
2. Shore AC. Capillaroscopy and measurement of capillary pressure. Br J Clin Pharmacol. 2000;50(6):501–13.
3. Ho M, Belch JJF. Raynaud's Phenomenon: state of the Art 1998. Scand J Rheumatol. 1998;27:319–22.
4. Bollinger A, Fagrell B. Clinical capillaroscopy—a guide to its use in clinical research and practice. Toronto: Hogrete & Huber Publishers; 1990. p. 1–158.
5. Cutolo M, Grassi W, Matucci Cerinic M. Raynaud's phenomenon ant the role of capillaroscopy. Arthritis Rheum. 2003;48(11):3023–30.
6. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol. 2000;27(1):155–60.
7. Cutolo M, Pizzorni C, Tuccio M, Burroni A, Craviotto C, Basso M, et al. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. Rheumatol. 2004;43:719–26.
8. Cutolo M, Pizzorni C, Sulli A. Capillaroscopy. Best Pract Res Clin Rheumatol. 2005;19(3):437–52.
9. Cutolo M, Sulli A, Secchi ME, Paolino S, Pizzorni C. Nailfold capillaroscopy is useful for the diagnosis and follow-up of autoimmune rheumatic diseases. A future tool for the analysis of microvascular heart involvement? Rheumatology. 2006;45:43–6.
10. Cutolo M, Sulli A, Secchi ME, Olivieri M, Pizzorni C. The contribution of capillaroscopy to the differential diagnosis of

connective autoimmune diseases. Best Pract Res Clin Rheumatol. 2007;21(6):1093–108.
11. Grassi W, De Anglis R. Capillaroscopy: questions and answers. Clin Rheumatol. 2007;26:2009–16.
12. Herrick AL, Clark S. Quantifying digital vascular disease in patients with primary Raynaud's phenomenon and systemic sclerosis. Ann Rheum Dis. 1998;57:70–8.
13. Gallucci F, Russo R, Buono R, Acampora R, Madrid E, Uomo G. Indications and results of videocapillaroscopy in clinical practice. Adv Med Sci. 2008;53(2):1–9.
14. Block JA, Sequeira W. Raynaud's phenomenon. Semin Lancet. 2001;357:2042–8.
15. Seibold JR, Steen VD. Systemic sclerosis. In: Klippel JH, Dieppe PA, editors. Rheumatology. London: Mosby; 1994. p. 6.8–6.11.
16. Maricq HR, LeRoy EC, D'Angelo WA, Medsger TA Jr, Rodnan GP, Sharp GC, et al. Diagnostic potential of in vivo capillary microscopy in scleroderma and related disorders. Arthritis Rheum. 1980;23(2):183–9.
17. Maricq HR, Harper FE, Khan MM, Tan EM, LeRoy EC. Microvascular abnormalities as possible predictors of disease subsets in Raynaud phenomenon and early connective tissue disease. Clin Exp Rheumatol. 1983;1(3):195–205.
18. Maricq HR. Comparison of quantitative and semiquantitative estimates of nailfold capillary abnormalities in scleroderma spectrum disorders. Microvasc Res. 1986;32(2):271–6.
19. Bergman R, Sharony L, Schapira D, Nahir MA, Balbir-Gurman A. The handheld dermatoscope as a nail-fold capillaroscopic instrument. Arch Dermatol. 2003;139:1027–30.
20. Nagy Z, Czirjac L. Nailfold digital capillaroscopy in 447 patients with connective tissue disease and Raynaud's disease. J Eur Acad Dermatol Venereol. 2004;18(1):62–8.
21. Redisch W. Capillaroscopic observations in rheumatic diseases. Ann Rheum Dis. 1970;29:244–53.
22. Granier F, Priollet P, Housset E. Nailfold capillary microscopy in mixed connective tissue disease. Comparison with systemic sclerosis and systemic lupus erythematosus. Arthritis Rheum. 1986;29(2):189–95.
23. Kabasakal Y, Elvins DM, Ring EF, McHugh NJ. Quantitative nailfold capillaroscopy findings in a population with connective tissue disease and in normal healthy controls. Ann Rheum Dis. 1996;55:507–12.
24. Furtado RNV, Pucinelli ML, Cristo VV, Andrade LE, Sato EI. Scleroderma-like nailfold capillaroscopic abnormalities are associated with anti-U1-RNP antibodies and Raynaud's phenomenon in SLE patients. Lupus. 2002;11(1):35–41.
25. Kirou KA, Crow MK. Raynaud's phenomenon. In: Paget SA, et al., editors. Manual of rheumatology and outpatient orthopedic disorders: diagnosis and therapy. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 82–7.
26. de Holanda Mafaldo Diógenes A, Bonfá E, Fuller R, Correia Caleiro MT. Capillaroscopy is a dynamic process in mixed connective tissue disease. Lupus. 2007;16(4):254–8.
27. Garcia-Carrasco M, Sisó A, Ramos-Casals M, Rosas J, de la Red G, Gil V, et al. Raynaud's phenomenon in primary Sjogren's syndrome. Prevalence and clinical characteristics in a series of 320 patients. J Rheumatol. 2002;29:726–30.
28. Capobianco KG, Xavier RM, Bredemeier M, Restelli VG, Brenol JC. Nailfold capillaroscopic findings in primary Sjögren's syndrome: clinical and serological correlations. Clin Exp Rheumatol. 2005;23(6):789–94.
29. Tektonidou M, Kaskani E, Skopouli FN, Moutsopoulos HM. Microvascular abnormalities in Sjogren's syndrome: nailfold capillaroscopy. Rheumatology. 1999;38:826–30.
30. Le Roy EC, Medsger TA Jr. Raynaud's phenomenon—a proposal for classification. Clin Exp Rheumatol. 1992;10:485–8.
31. Grassi W, Felder M, Thüring-Vollenweider U, Bollinger A. Microvascular dynamics at the nailfold in rheumatoid arthritis. Clin Exp Rheumatol. 1989;7(1):47–53.
32. Grassi W, Blasetti P, Core P, Cervini C. Raynaud's phenomenon in rheumatoid arthritis. Br J Rheumatol. 1994;33:139–41.
33. Lee P, Leung FY, Alderdice C, Armstrong SK. Nailfold capillary microscopy in the connective tissue diseases: a semiquantitative assessment. J Rheumatol. 1983;10(6):930–8.
34. Antonios TFT, Singer RJ, Markandu ND, Mortimer PS, MacGregor GA. Structural skin capillary rarefaction in essential hypertension. Hypertension. 1999;33:998–1001.
35. Gasser P, Bueller FR. Nailfold microcirculation in normotensive and essential hypertensive subjects, as assessed by videocapillaroscopy. J Hypertens. 1992;10(1):83–6.
36. Prasad A, Dunnil GS, Mortimer PS, Mac Gregor GA. Capillary rarefaction in the forearm skin in essential hypertension. J Hypertens. 1995;13(2):265–8.
37. Antonios TFT, Singer RJ, Markandu ND, Mortimer PS, MacGregor GA. Rarefaction of skin capillaries in borderline essential hypertension suggest an early structural abnormality. Hypertension. 1999;34:655–8.
38. Antonios TFT, Rattray FM, Singer RJ, Markandu ND, Mortimer PS, MacGregor GA. Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension. Heart. 2003;89:175–8.
39. Noon JP, Walker BR, Webb DJ, Shore AC, Holton DW, Edwards HV, et al. Impaired microvascular dilatation and capillary rarefaction in young adults with a predisposition to high blood pressure. J Clin Invest. 1997;99:1873–9.
40. Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. Br Med J. 1990;301:259–62.
41. Brown AN, Gilkeson GS. Fibrosing diseases: diabetic stiff hand syndrome, Dupuytren's contracture, palmar and plantar fasciitis, retroperitoneal fibrosis, and Peyronie's disease. In: Koopman WJ, editor. Arthritis and allied conditions. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 2093–108.
42. Rosenbloom AL, Silverstein JH. Connective tissue and joint disease in diabetes mellitus. Endocrinol Metab Clin North Am. 1996;25(2):473–83.
43. Ferringer T, Miller F. Cutaneous manifestations of diabetes mellitus. Dermatol Clin. 2002;20(3):483–92.
44. Yosipovitch G, Loh KC, Hock OB. Medical pearl: Scleroderma-like skin changes in patients with diabetes mellitus. J Am Acad Dermatol. 2003;49(1):109–11.
45. Brik R, Berant M, Vardi P. The scleroderma-like syndrome of insulin-dependent diabetes mellitus. Diabetes Metab Rev. 1991;7(2):120–8.
46. Ikeda Y, Suehiro T, Abe T, Yoshida T, Shiinoki T, Tahara K. Severe diabetic scleredema with extension to the extremities and effective treatment using prostaglandin E1. Intern Med. 1998;37:861–4.
47. Tüzün B, Tüzün Y, Dinççağ N, Minareci O, Oztürk S, Yilmaz MT, et al. Diabetic sclerodactyly. Diabetes Res Clin Pract. 1995;27(2):153–7.
48. Brik R, Berant M, Vardi P. The scleroderma-like syndrome of insulin-dependent diabetes mellitus. Diabetes Metab Rev. 1991;7(2):120–8.
49. Meyer MF, Pfohl M, Schatz H. Assessment of diabetic alterations of microcirculation by means of capillaroscopy and laser-Doppler anemometry. Med Klin (Munich). 2001;96(2):71–7.

50. Tibirica E, Rodrigues E, Cobas RA, Gomes MB. Endothelial function in patients with type I diabetes evaluated by skin capillary recruitment. Microvasc Res. 2007;73:107–12.
51. Chang CH, Tsai RK, Wu WC, Kuo SL, Yu HS. Use of dynamic capillaroscopy for studying cutaneous microcirculation in patients with diabetes mellitus. Microvasc Res. 1997;53(2):121–7.
52. Lefrandt JD, Bosma E, Oomen PHN, Hoeven JH, Roon AM, Smit AJ, et al. Sympathetic mediated vasomotion and skin capillary permeability in diabetic patients with peripheral neuropathy. Diabetologia. 2003;46:40–7.