

#### **Review Article**

# Nailfold Capillaroscopy a Non-Invasive Tool for Direct Observation of Microvascular Damage in Diabetes Mellitus: Review

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#### Abstract

Capillaroscopy is a non-invasive method for the observation of capillary microvasculature. In recent years, it has gained recognition in the field of diseases that affect microcirculation, especially in rheumatic diseases. However, studies published in the last decade have demonstrated the importance of this innovative technique in non-rheumatic diseases such as diabetes mellitus. The purpose of this review is to describe the technique of capillaroscopy and to emphasize its usefulness in the evaluation of vascular micro architecture in patients with diabetes mellitus and its relation to its complications.

## **INTRODUCTION**

Diabetes Mellitus (DM) is defined as a chronic hyperglycemic state with the development of vascular structure alterations. It is currently considered a chronic disease with a high mortality rate due to its long-term cardiovascular, renal and neurological complications [1,2]. Because of the importance of vascular involvement in diabetes mellitus, direct observation tools such as ophthalmoscopes, magnifying lenses, and among them capillaroscopy [3-6], have been used to evaluate microvasculature. Capillaroscopy is a non-invasive method for the observation of capillary microvasculature [7]; in recent years it has gained recognition in the study of diseases that affect the microcirculation, especially in rheumatic diseases [8,9]. However, studies published have demonstrated the importance of this innovative technique in non-rheumatic diseases such as diabetes mellitus [5,9-11]. These studies conclude that capillaroscopy provides key data for the determination of vascular damage in diabetic patients and thus, allows the evaluation of the progression of the disease [9], making this technique a potential future utility in the microvascular disease evaluation. The purpose of this review is to describe the technique of capillaroscopy and to emphasize its usefulness in the evaluation of vascular micro architecture in patients with diabetes mellitus and the relation to it's complications such as retinopathy, neuropathy and vascular involvement.

#### **Capillaroscopy**

Nailfold capillaroscopy is a simple and useful procedure in the evaluation of the spectrum of sclerodermic diseases, especially those associated with vascular damage presenting alterations of the blood vessels that may have diagnostic and prognostic value.

Indications for capillaroscopy are [11,12]:

- 1. Evaluation of patients with Raynaud's Phenomenon
- 2. Differential diagnosis of collagenopathies
- 3. Primary diagnosis of Scleroderma
- ${\it 4. Diseases that compromise the capillary microarchitecture, like diabetes mellitus}\\$

 $Recommendations\ prior\ to\ a\ videocapilar oscopy\ [13]:$ 

- Nails should not have substances that reduce the visibility of the nail fold such as: nail polish, acrylics, gel, etc.
- Do not have manicure performed for at least of two weeks prior to the study
  - · Avoid onychophagia

A drop of dipping oil should be placed over the nailfold of the four fingers of the hand, the patient should be seated with his hands at the level of the heart and be at an ambient temperature

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of 20-22° C for at least 15-20 minutes before the test [14,15].

The study should be performed on the nail fold of all fingers, except the thumb. Even though the 4 fingers have to be examined, it has been described that the observation of the fourth and fifth fingers allows the obtainment of better images due to the greater transparency of the skin in these fingers [16,17].

When performing the study, the operator should avoid exerting too much pressure on the nail surface as it may interrupt the blood flow and render images difficult to interpret[17,18]. When placing the camera on the nailfold, the first row of capillaries should be located.

#### **Equipment**

Research methods of the capillaries have varied through the years, from the use of stereomicroscopes with magnification of 10-100x for the visualization of the entire nailfold area [15] to new semiautomatic methods for the visualization of the capillaries with an innovative television system called "Capi Shape" [19]. Other optical methods such as ophthalmoscopes and dermatoscopes were also used.

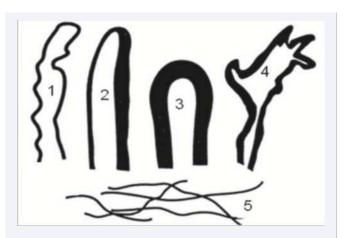
Currently, the gold standard for the observation of capillaries is the video capilaroscopy that consists of a combination of a microscope and a digital camcorder that provides a magnification of 50-100x and allows precise measurements like diameter and length through a software.

#### **Capillaroscopy parameters**

The dermal papillae are located perpendicularly to the cutaneous surface. The capillary arrangement at the nailfold level is located in a parallel or oblique way in relation to the cutaneous plane, in two or three layers, on a usually visible subpapillary venous network or plexus. This plexus is situated below the dermal papillae without following a defined pattern.

The capillary loop consists of an arterial or afferent branch and a venous or efferent branch. The main parameters to be evaluated are: length, diameter, density, venous plexus and morphological abnormalities. These elements should be evaluated in the distal row or near the nailfold. The normal number of capillaries per millimeter is from seven to twelve arranged in an inverted U-shape (Figure 1).

- Capillary diameter: according to Maricq descriptions the normal range is 25-50μm. Ectasias are capillaries with arterial or venous branches that measure >15-20μm [20], and giant capillaries are those that surpass the normal range of 4-10 times the width of the apical loop [21-23], and the determination of a capillary mean that is the result of an average of 3 measurements [16,24]. The capillary diameter consider for evaluation is the total width of the apical loop.
- Cross-linked capillaries: similar to branches that intersect like a number eight and tortuous like capillaries with branches in an undulating, sinuous or twisted arrangement [16-24].



**Figure 1** Capillaroscopic parameters. 1: Perfused capillary (Basal or normal), 2: Ectasia (efferent limb), 3: Dilatated capillary, 4: Ramified capillary, 5: Subpapillary plexus.

- Ramified capillaries: they were described as those capillaries that adopt the shape similar to a tree [16].
- Avascular zones: they were defined as the absence of capillaries in a tract superior to 500 μm [16].
- Haemorrhages: as the hemosiderin deposit, caused by the rupture of one or more capillaries [20].
- Dominant morphology: finding that predominates in more than 20%, whether it's open, tortuous or crosslinked [13,25].
- Visibility of the subpapillar venous plexus: a network of larger vessels with respect to the capillaries. The presence of the parameter was determined according to the Kabasakal et al., by [26]:

0: not visible

- 1: doubtful or limited visibility
- 2: Plexus visible in certain areas
- 3: Fully visible in large areas
- Cuticulitis: inflammation of the insertion of the cuticle at the periungual folds [27].
- Scleroderma Pattern (SD) pattern: is presence of giant capillaries, avascular zones, haemorrhages and ramified capillaries all together [20].

# Diabetes Mellitus and capillaroscopic changes: Pattern description

Nailfold capillaroscopy is a noninvasive method for the observation of the capillary microvasculature. Maldonado et al. demonstrated that the use of capillaroscopy in patients with diabetes allows the identification of capillaroscopic abnormalities, possibly including a characteristic pattern in this group of patients consisting of tortuous, cross-linked capillaries, avascular zones and ectasias [3] (Figure 3). Similarly, Kuriliszyn-Moskal et. al, studied the microvascular changes with capillaroscopy in type I diabetes, and its association with systemic compromise, disease duration impact, and capillary

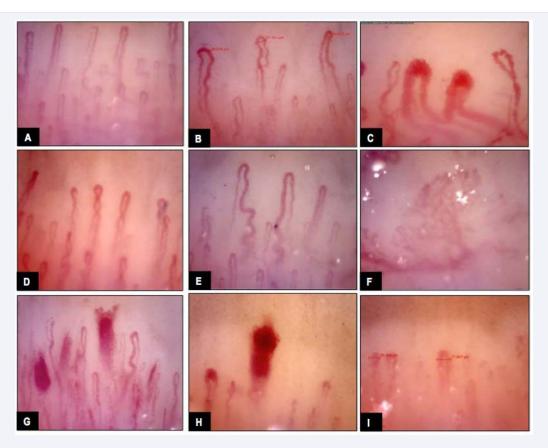


Figure 2 A: Normal pattern "U shaped" capillaries, B: Dilated capillaries, C: Giant capillaries, D: Crosslinked capillaries, E: Tortuous capillaries, F: Ramified capillaries, G: Hemorrhages, H Pattern Scleroderma Pattern: Giant capillary, hemorrhage, neoangiogenesis and avascular zones, I: Avascular zones and dilated capillaries.

architecture changes with metabolic control. They reported that patients with type I diabetes presented important capillary changes such as dilated capillaries, tortuosities and capillary density reduction, when compared to the control group (which presented no capillaroscopic abnormalities). Moderate to severe capillary changes were shown in patients with signs of systemic involvement, and severe capillary changes in patients with poor metabolic control [28]. Meyer et al. also reported morphological capillaroscopic changes in the nailfold on diabetic patients. Findings included an increased capillary diameter, tortuosities, and a capillary density decrease; and were shown to be associated with ischemic vascular reactivity [29].

On the other hand, Barchetta studied the possible relationship of microangiopathic lesions detected in retinal vessels and capillary changes in patients with type I and type II diabetes [30]. It was observed that these patients had a greater capillary diameter, ectasias and nailfold edema, in contrast with healthy subjects. Patients with type I DM had more capillaroscopic alterations than patients with type II DM including: abnormal capillary morphology reduced capillary density, ectasic loops, hemorrhages, abnormal flux and edema/exudates. Also, capillaroscopy was able to identify alterations in almost 50% of patients with DM without retinopathy, demonstrating an early microangiopathic alteration [30].

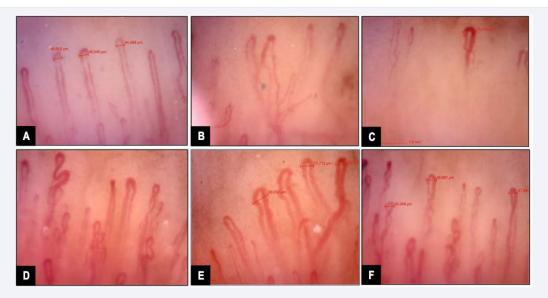
Similar parameters were evaluated by Pazos-Moura and

they found that patients with type I and type II diabetes present capillary tortuosities, as well as an increase in capillary diameter and a capillary density decrease. In the same study, it was shown that patients with type II diabetes had more capillaroscopic alterations than patients with type I diabetes. Thus, an association between capillary findings and metabolic control was established [11].

Furthermore, Romano et al., described the advantages of the use of capillaroscopy in diabetic patients, such as highlighting that this is a non-invasive method of evaluation of the capillary microarchitecture, and also a predictor of extent, severity and disease evolution. This author argued that capillaroscopy is indicated in all pathologies with anatomical and functional abnormalities on the microcirculation, and it is an useful tool for diagnosis and prognosis of diabetic microangiopathy [31].

Studies in a pediatric population and in adolescents with type I diabetes have also being published. Hosking et al. used capillaroscopy to detect microvascular changes and found that the most frequent microvascular alterations found were microhemorrhages and avascular zones. Microhemorrhages were associated with elevated HbA1c levels, and avascular zones with diabetic complications, concluding that capillaroscopy is a method that can detect microvascular damage [32].

Other studies such as the one published by Rajaei et al., showed that capillaroscopic changes in diabetic patients (presence of



**Figure 3 Examples of diabetic capillaroscopic pattern, A:** *Healthy subject pattern, B:* Ramified capillaries, avascular zones with diminished capillary density, C: Giant capillary with extended avascular zones, D: Tortous and dilated capillaries, E: Dilated capillaries, F: Cross linked and tortous capillaries.

ramified and tortuous capillaries) were more frequent in these patients than in the control group [4]. Moreover, Kaminska-Winciorek et al., identified an increase in cross-linked capillaries in patients with diabetes mellitus [33]. Finally, Cicco et al., found a decrease in total capillary density in diabetic patients by 28% [34].

# Complications, evolution of disease and capillaroscopy

 $\label{thm:cause} Vascular\ disease\ is\ the\ most\ common\ morbidity\ and\ mortality\ cause\ in\ diabetic\ patients.$ 

In chronic hyperglicemia, as in diabetes, capillary endotheliais severely altered. This generates microvascular architecture changes [35], which can be evidenced by the use of capillaroscopy.

Several studies have shown that these structural changes progress and are related to prolonged states of hyperglycemia [31,36].

Kuryliszyn et al., found an escalating appearance of ramified capillaries in diabetic patients with a prolonged evolution time (of more than 10 years) [9].

Bollinger et al., showed similar data, in which they described more capillaroscopic alterations in diabetic patients with a disease evolution of over 10 years [15].

Capillary density is an important parameter when evaluating microcirculation because it is a marker of disease severity [19,24,37-40].

Several studies have demonstrated that high capillary density is indicative of microvascular damage. The capillaroscopic alterations observed and analyzed were independent of age, sex and duration of disease. Arboric and tortuous capillaries, avascular zones, cuticulitis and capillary density scores were directly correlated with nephropathy, arteriopathy, central and peripheral vascular disease, hearing loss, neuropathy and ulcers [16,20,40].

These findings overall report the importance on the evaluation of vascular damage in diabetic patients, such as loss of capillary density that is compensated with the appearance of ramifications and capillary dilation.

#### Diabetic retinopathy and capillaroscopy

Retinopathy is a common vascular complication in patients with diabetes mellitus and is caused by capillary degeneration and development of avascular areas which reduced perfusion and leads to tissue hypoxia [41].

The first changes observed in diabetic retinopathy are: microaneurysms, leukocyte adhesion and apoptosis of vascular and neuronal cells. The compensatory mechanism of this progression is the formation of capillary neovascularization [42,43].

In most cases, the appearance of symptoms suggestive of diabetic retinopathy represents advanced and degenerative changes. Direct observation tools, such as funduscopic examination, are currently used to evaluate retinopathy [6,44]. However, these traditional methods do not detect complications until they are established.

A recent study showed an association between microangiopathies seen at the ophtalmoscopy and the presence of ramified capillaries and avascular zones seen at the nailfold level [3]. Chang et al., also found a correlation between diabetic retinopathy and the presence of tortuous, ramified capillaries and capillary dilatation, in addition to confirming that these alterations are increased with the severity of diabetic retinopathy [5].

Kaminska-Winciorek studied the microcirculation in children with type I DM and observed the presence of dilated capillaries and megacapillaries accompanied by a change of coloration in the bottom of the nailbed (intense red) indicating a possible

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angiogenesis, in addition, patients with elevated levels of HbA1c presented greater capillary dilation and decreased capillary number [33]. Hosking found that avascular areas are more frequent in patients with type I DM with complications and that elevated levels of HbA1c were associated with the presence of microhemorrhages [32].

Uyar et al., studied a population of patients diagnosed with diabetes mellitus and evidenced large capillaroscopic changes such as: tortuous capillaries, ramified, increased capillary diameter, compared to the control group. In addition, in patients with diabetic retinopathy, these alterations were increased [45].

These patterns demonstrate that a microvascular component exists in the pathophysiology of diabetic retinopathy and capillaroscopy is a tool that can accurately detect capillaroscopic changes and relate them to systemic vascular complications.

#### Nailfold capillaroscopy of diabetic toes

Diabetic neuropathy is a common complication of the disease; however, capillaroscopy is not frequently used for evaluation of the microvasculature of the feet. Delcourt et al., designed a study protocol for the direct observation of the capillaries in the feet of healthy subjects withvideocapillaroscopy, the same capilaroscopic changes in the feet and hands were evidenced, however, the examination of the capillaries could only be performed in 87 % of the cases [46].

Fragrell et al., used capillaroscopy to evaluate the microangiopathy of patients with diabetes mellitus, they observed an irregular pattern composed of avascular zones and dilated capillaries, these changes were compared with healthy subjects who did not present alterations, however more studies are needed that can support the importance of Use of capillaroscopy in the evaluation of the microvasculature of the feet [47].

#### Healthy population and capillaroscopy

It is important to highlight the fact that a healthy population will present capillaroscopic alterations, but with no capillary damage or clinical expression.

A study carried out by Ríos et al. showed that approximately 86% of the healthy subjects that were studied had capillary findings such as tortuous, cross-linked and ramified capillaries [25]. These results are similar to the study by Hoerth et al. [48], in which it was shown that 85% of the subjects had capillaroscopic findings such as: tortuous, cross-linked and ramified capillaries. Coehlo Andrade studied a more extensive cohort and approximately 81% of the subjects presented capillary findings including ramified and tortuous capillaries [39].

## **CONCLUSION**

Capillaroscopy is a non-invasive tool, reproducible, and trustworthy for a qualitative, quantitative, and precise evaluation of pathologies that affect the peripheral microvasculature. The main limitation remains in the small number of articles focusing on the qualitative findings and relationship with markers of disease progression yet to be established. However, the capillaroscopy is a potential future utility in the microvascular diseases since it has been of great contribution for the evaluation of vascular damage in rheumatic diseases.

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