# Prediabetes and Microcirculation

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Prediabetes is a significant metabolic status since there is high potential for future progression of diabetes mellitus (DM). People with prediabetes are at increased risk of cardiovascular disease (CVD) and mortality. Endothelial and microvascular dysfunction is considered a key step towards the development and progression of CVD. The term microcirculation refers to the circulation in vessels with diameter <150 μm, including the small arteries and veins, as well as the capillaries. The main function of microcirculation is to ensure the provision of nutrients and oxygen to tissues. It also regulates hydrostatic pressure at the level of capillaries and blood flow, and consequently, it helps in the regulation of blood pressure through the increase of peripheral resistance.

prediabetes skin retinopathy

## 1. Prediabetes and the Retina

The retina offers an easy window to study the human microcirculation. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM) and remains the main cause of blindness inworking-age population. One third of patients with DM show signs of retinopathy and one third of them develops severe damage, which could potentially lead to blindness [1]. In the meta-analysis by Yau et al., concerning the global prevalence of DR, it was demonstrated that 35% of patients with DM will develop some type of retinopathy (proliferative in 7% of the cases) [2]. Similarly, the Wisconsin study highlighted that the 10-year incidence of DR was 74% for all patients with DM who participated [3].

In addition to the devastating effects on patients' vision, the presence of DR is an independent risk factor for the development of cardiovascular disease (CVD). Even mild retinopathy has been associated with a high risk for stroke, coronary heart disease and heart failure, as diabetic retinopathy is indicative of the presence of TOD in patients with DM [4][5]. However, in the Gutenberg study involving 5000 participants with prediabetes, no association between retinopathy and cardiovascular risk factors was detected [6].

Pathogenetic mechanisms that are implicated in DR have not yet been clarified. They are categorised as biochemical and vascular. The main biochemical factor is the vascular endothelial growth factor (VEGF). In diabetic retinopathy, retinal hypoxia induces over-expression of VEGF, which acts as a mitogenic agent of endothelial capillary cells. As a result, the permeability of the blood-retinal barrier increases and, finally, causes macular oedema. VEGF is also responsible for neovascularization, as it induces the proliferation of capillary endothelial cells of retina [7].

Abnormalities of the mean diameters of the retinal arterioles and venules, i.e., narrowing and widening, have emerged as novel vascular biomarkers indicative of individual cardiovascular risk and future onset of cardiovascular diseases, including hypertension [8]. A decade ago, researcher's group showed that subtle alterations of the retinal microvascular diameters (**Figure 1**A) may even identify divergent hypertension phenotypes [9] with subsequent studies documenting the presence of altered retinal microvascular diameters in other high risk populations [10]. In contrast, there is still limited evidence regarding retinal vessel alterations in patients with prediabetes. There are few studies confirming the existence of retinopathy in prediabetic patients [11], with venular dilation being the main finding [12][13]. A recent cohort study showed that decreased macular thickness and retinal arterial stenosis were the main findings in the prediabetic group compared to the normoglycemic group [14].

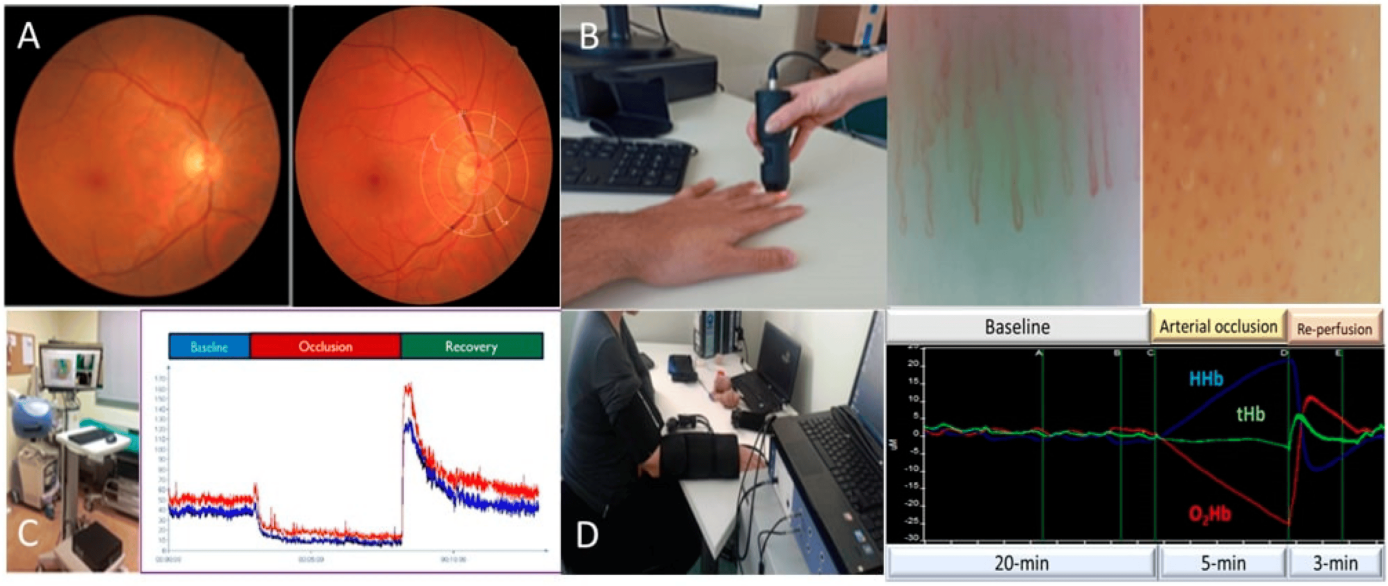


**Figure 1.** Indices of microvascular assessment. (**A**) Non-mydriatic digital fundus photography and imaging of retinal vessels. (**B**) Nailfold video capillaroscopy (NVC), examination and a representative image obtained during NVC. (**C**) Recording of skin microvascular reactivity during arterial occlusion and re-perfusion using Laser Speckle Contrast Analysis. (**D**) Near infrared spectroscopy—representative data of skeletal muscle oxygenation during arterial occlusion and after re-perfusion. HHb: Deoxygenated haemoglobin, tHb: Total haemoglobin, $O_2$Hb: Oxygenated haemoglobin.

However, studies investigating the relationship between the diameter of the retinal vessels and the risk of developing prediabetes and DM in the future have shown conflicting results. More specifically, in the Rotterdam study, a positive correlation in univariate analysis identified between decreased arteriovenous ratio (AVR) and the risk of IFG [OR:1.29 (1.13–1.46)], which however disappeared after adjusting for confounding factors [OR:1.14 (0.98–1.32)]. In this research, the risk of IFG and DM with AVR was thought to be due to the venular dilatation rather than the arteriolar narrowing [15]. Similarly, in the “Blue Mountains” study, a correlation between the retinal venular dilation and the development of IFG was found, mainly in middle-aged people, while the diameter of arteries did not show a significant correlation [16]. In contrast, the AusDiab study showed that only the retinal arteriolar narrowing was associated with a higher risk of developing DM [17]. Similar results were observed in both

the ARIC sub-study and the Wisconsin study [18][19]. In the latter, the risk of developing DM was three times higher in individuals with retinal artery stenosis and co-existed hypertension, compared to the normotensive participants without arteriolar narrowing [OR:3.41 (1.66–6.98)] [18].

Some very recent studies documented retinal vascular changes using optical coherence tomography angiography (OCTA) in prediabetic individuals compared to control individuals. The OCTA is a non-invasive fundus angiography imaging technique for assessing retinal vascular disease. Xu et al. showed that some parameters of the OCTA, more specifically, the size of focal avascular zone and the macular vessel diameter, were larger in the prediabetic patients compared to the control group. Moreover, the vessel area density in superficial macular area decreased in prediabetes [20]. In accordance with this research, Ratra et al. found that the decreased vessel diameter was positively correlated with HbA1c [21]. Another study from Ratra's group, focusing on prediabetic individuals, found no difference in focal avascular zone parameters, even though the central foveal thickness significantly decreased in prediabetes compared to the control [22]. Similarly, Arias et al. found no alteration in focal avascular zone area, but pointed out that perfusion density and vascular length density decreased in prediabetic people compared to the control [23]. On the other hand, Peng et al. identified some neuroretinal changes regarding the thickness of macula and the peripapillary retinal nerve fiber layer using both OCT and fundus fluorescein angiography, even though microvascular alterations were not detected in prediabetic individuals [24].

Another novel method for assessing retinal vascular dysfunction is the flickering light stimulus. In healthy individuals, the flickering light stimulus normally causes an increase of the retinal blood flow and blood vessel diameter, whereas in diseases, such as DM retinal vasodilation, they decrease. Lott et al. examined retinal vascular dilation responses to flicker in a study including a prediabetic, a diabetic and a control group, finding similar attenuated vasodilator responses in prediabetic and diabetic patients compared to the control group. These findings remained unchanged even after the adjustment for age, blood pressure and body mass index (BMI) [25].

## 2. Prediabetes and Albuminuria

Measurement of urine albumin excretion is a simple assessment tool of renal microvascular function. Albuminuria is defined as the urine albumin-to-creatinine ratio (ACR) ≥ 30mg/g [26]. Although the older terms, microalbuminuria (MAU) defined by ACR 30–299mg/g and macroalbuminuria (ACR ≥ 300mg/g), should be avoided according to the ADA guidelines, many studies still apply these terms [27]. In the same way, the normal ranges of 2.5−25 mg/mmol for males and 3.5−35 mg/mmol for females are still used [28]. MAU is a well-documented risk factor for cardiovascular morbidity and mortality. Patients with MAU are at high risk for acute coronary heart disease, stroke and peripheral arterial disease [28][29].

There are few data confirming the occurrence of MAU in prediabetes. The AusDiab study, including more than 10.000 participants, showed that the prevalence of MAU in IGT is 9.9%, in IFG 8.3%, and more than double in patients with diabetes (both type 1 and 2) [30]. It is worth mentioning that 30% of individuals with newly diagnosed DM already had some degree of kidney damage. This fact suggests that the effects of hyperglycaemia on the kidney may occur in the early stages, even before glucose levels reach diabetic ranges. A meta-analysis of nine

cohort studies, including over 180,000 participants, showed that prediabetes was linked to an increased risk of renal dysfunction after adjustment for established risk factors [RR:1.11 95%CI (1.02–1.21)] [31].

There is further evidence that the presence of MAU in prediabetes could be an early indicator for the development of DM. A 10-year cohort study conducted in participants with MAU without DM showed that people with MAU were more likely to develop DM, even after adjustment for the presence of prediabetes [32]. Similarly, a Chinese cohort study showed that MAU was associated with increased risk of diabetes after a three-year follow-up in populations with normal glucose tolerance and impaired glucose regulation. Nevertheless, MAU did not remain a significant predictor of DM after adjustment for hypertension [33]. Moreover, Bahar et al. showed that people with prediabetes and albuminuria had a four-fold higher risk of developing DM compared to those with prediabetes without albuminuria [34]. In contrast, a study conducted in the United States did not find an independent predictive role of microalbuminuria for developing DM in obese patients with pre-diabetes [Hazard ratio, HR:0.98 (0.91–1.06)] [35].

It remains unclear whether other risk factors such as hypertension are also involved in the presence of MAU in prediabetes. A prospective, population-based, cohort study conducted in Netherlands with over than 6000 obese (BMI ≥ 27) participants showed that the prediabetes and newly diagnosed DM were associated with increased MAU [OR:1.6 (0.9–2.7) and OR:2.8 (1.5–5.4) respectively]. Moreover, FPG [OR:1.21 (1.04–1.42)] and HbA1c [OR:1.36 (1.00–1.86)] were positively associated with MAU. On the other hand, after adjustment for confounding risk factors (age, BMI, hypertension, smoking), the association between MAU and prediabetes did not remain statistically significant [36]. Similar studies found a positive correlation between microalbuminuria and the occurrence of prediabetes [37][38], whereas Kim et al. showed that this correlation is rather influenced by coexistence of hypertension in these individuals [OR:0.77 (0.55–1.09)] [39].

In conclusion, most data advocate that there is a positive association between prediabetes and some degree of renal dysfunction, in terms of kidney microvascular dysfunction. Thus, it might be possible that screening for microalbuminuria in individuals with prediabetes may lead to early detection and interventions resulting in fewer new cases of renal dysfunction.

## 3. Prediabetes and Skin—Muscle Microcirculation

The most widespread method of estimating skin microcirculation is nailfold capillaroscopy (**Figure 1**B). It is a non-invasive method that allows the imaging of capillaries by a stereomicroscope, usually applied to the fingernail bed. Capillaroscopy has been mainly used in rheumatic diseases, such as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis [40][41][42]. In recent years, scientific interest has turned to the study of dermal microcirculation disorders which are involved in the pathophysiology of CVD. Although functional impairment can be detected by means of nailfold video capillaroscopy, assessment of morphological abnormalities is more frequently applied both in research and in clinical practice. Structural alterations of skin microcirculation have been consistently observed in patients with hypertension, with a decrease in the number of capillaries per field of vision being the main finding [43][44]. This finding has been demonstrated in other high cardiovascular risk populations, such as those with rheumatoid arthritis [45].

Studies on skin microcirculation showed that qualitative morphological changes in capillaries (tortuosity, absence of vessels, capillary dilation, irregular shape) were more commonly present in patients with type 2 DM than in individuals without type 2 DM history [46][47]. Furthermore, studies in patients with type 2 DM have shown that capillary abnormalities positively correlated with the occurrence of other microvascular complications of the disease [48][49][50]. Similarly, in the study of Kuryliszyn-Moskal et al., qualitative changes in capillaries were more common in patients with type 1 DM than in healthy control patients and positively correlated with indicators of endothelial dysfunction [51].

To date, there is no study investigating dermal capillaroscopy in patients with prediabetes. However, there are data from small studies in healthy populations, identifying capillary changes of the skin in potentially precursor forms of DM, such as individuals with insulin resistance and increased glucose. More specifically, a study by Irving et al. in young healthy men studying changes in skin microcirculation based on blood pressure levels and insulin resistance, showed that individuals with higher FPG concentrations had decreased capillary density and increased flow rate [52]. Another study in a healthy population showed that individuals with greater insulin sensitivity had higher capillary density in the examined limb after removal of the occlusive cause [53].

Laser Speckle Analysis (LASCA) is a non-invasive method for assessing skin microvascular function (**Figure 1**C). LASCA represents an evolution of the older laser doppler flowmetry techniques, but providing better spatial resolution. It enables assessment of microvascular perfusion in a larger tissue area and with higher reproducibility. The method is based on the speckle phenomenon to create dynamic two-dimensional maps of skin microvascular perfusion and visualize blood flow in real time with high spatial and temporal resolution. Microvascular responsiveness can be assessed using various stimuli, such as iontophoresis with acetylcholine or post-ischemic forearm skin reactive hyperaemia, which is the most commonly used. The first studies included mainly patients with rheumatic diseases [54][55][56][57][58]; nevertheless, in recent years, it has been applied in patients with CVDs [59][60].

Regarding patients with DM, Matheus et al. showed that microvascular reactivity of patients with type 1 DM was significantly affected compared to healthy individuals based on the response of the skin vessels' microcirculation in various stimuli (iontophoresis with acetylcholine, ischemia) [61]. It has also been used for the estimation of the extent of skin lesions in foot ulcers of people with type 2 DM [62].

More evidence is available regarding the use of near infrared spectroscopy (NIRS) in patients with DM. The NIRS method (**Figure 1**D) estimates tissue oxygenation and provides information about indicators of tissues' local oxygen consumption, as well as their blood flow. This technique is non-invasive, easy to use and with good reproducibility, emerging as a valuable tool for assessing microvascular function and dysfunction. Recently, Dipla et al. showed that women with gestational DM, exhibited a blunted muscle oxygenation and microvascular reactivity compared with women with uncomplicated pregnancies. These changes also showed a positive correlation with aortic stiffness (as estimated by pulse wave velocity) and 24-h blood pressure measurements [63]. Furthermore, a recent study of Townsend et al. using NIRS, showed that insulin resistance, which is considered to be a predisposing factor of DM, is associated to reduced microcirculatory response to induced ischemia based on tissue oxygenation parameters [64]. Soares et al. studied vascular responsiveness after an oral glucose challenge using

NIRS combined with a vascular occlusion test in a small group of healthy individuals. They found that there were differential responses regarding the oxygen saturation, which corresponds to vascular adjustment to hyperglycaemia [65]. As far as we know, there is no data in the literature regarding the use of the NIRS method in prediabetes

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