Diabetic retinopathy: looking beyond the eyes

Rafael Simó^{1,2} · Coen D. A. Stehouwer^{3,4} · Angelo Avogaro⁵

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Abbreviation

CVD Cardiovascular disease

To the Editor: The eye as a tool for identifying systemic diseases has fascinated scientists for centuries. In the era of precision medicine, screening for diabetic retinopathy has emerged as a renewed cost-effective method, not only to prevent sight-threatening disease, but also to identify patients more prone to develop other diabetic complications [1, 2]. In recent years, evidence has accumulated indicating that diabetic retinopathy is not only a herald of microvascular complications, but also of macrovascular complications, such as ischaemic coronary disease and stroke [2, 3]. In addition, the presence of diabetic retinopathy is an independent risk factor for cognitive impairment and dementia and, consequently, is a useful tool to identify candidates for the screening of cognitive status [4].

The current EASD/ADA guideline for treating type 2 diabetes relies on the presence of cardiovascular disease (CVD), but there is no mention of how the presence of

diabetic retinopathy can modulate the current management of the disease [5]. In this comment, several important points related to this commonly forgotten issue will be underlined.

Diabetic retinopathy and CVD

There is epidemiological evidence showing that either diabetic retinopathy or diabetic macular oedema (DMO) independently predict incident coronary heart disease, fatal CVD, heart failure and stroke [2, 3]. In addition, the presence and degree of diabetic retinopathy has recently been found to be an independent and powerful predictor of subclinical CVD [6]. Therefore, screening for CVD should be prioritised in patients with diabetic retinopathy.

Although the underlying molecular mechanisms linking diabetic retinopathy and CVD are still a matter of debate, there are notable similarities in their pathophysiology. In this regard, recent evidence indicates that, in individuals with type 2 diabetes, the vasa vasorum (a network of small blood vessels that supply the walls of large blood vessels) present evolutionary changes similar to those observed in the retina: an initial stage in which endothelial dysfunction and loss of capillaries predominate [7], and more advanced stages in which ischaemia plays a key role, leading to angiogenesis and inflammation in response to the progressive enlargement of the necrotic core within the plaque [8]. This change in plaque phenotype results in a more inflamed and unstable plaque, favouring plaque rupture and a poor outcome of cardiovascular events. Maladaptive vascular reparatory mechanisms may also play a role; a decrease in the number of endothelial colony forming cells (ECFCs) not only predict macroangiopathy but also diabetic retinopathy [9]. Despite these similarities, the vascular beds in the blood vessels in the heart show important differences to those in the retina that could affect the response to treatment approaches. For instance, anti-vascular-endothelial-growth-factor (VEGF) agents are effective for

✉ Rafael Simó
rafael.simo@vhir.org

¹ Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Vall d'Hebron University Hospital, Pg. Vall d'Hebron 119–129, 08035 Barcelona, Spain

² Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain

³ Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands

⁴ Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, the Netherlands

⁵ Section of Diabetes and Metabolic Diseases, Department of Medicine, University of Padova, Padova, Italy

treating proliferative diabetic retinopathy but exert a deleterious effect in coronary arteries by inhibiting the revascularisation after ischaemia [10].

The main structural retinal fingerprints associated with CVD and stroke are displayed in Fig. 1. The presence of hard exudates (a component of non-proliferative diabetic retinopathy) has been particularly associated with CVD and plaque formation [3, 11]. In fact, hard exudates in the retina and plaques in large arteries are the result of leakage of lipids and proteinaceous material through the endothelial barrier, and this may explain why they are related.

In addition, impairment of retinal neurovascular coupling, as assessed by flicker-induced arterial dilatation, is more frequent in patients with coronary artery disease, and it is even more pronounced in patients with heart failure [12]. Notably, the impairment of the neurovascular unit is an early functional abnormality in diabetes that can be detected even before structural changes.

Diabetic retinopathy and cognitive impairment

Individuals with type 2 diabetes have a higher risk of developing cognitive dysfunction and neurodegenerative diseases than age-matched non-diabetic individuals [4]. Since the retina is a brain-derived tissue, it has been suggested that the study of the retina could give valuable information regarding the status of the brain. In fact, retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy, and several pathways

involved in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, have been found to be altered in the retinas from diabetic individuals [13]. Besides neurodegeneration, microvascular abnormalities of the retina in the setting of diabetic retinopathy have been related, not only to a high risk of stroke, but also to cognitive decline and dementia [4, 14]. Overall, these associations may be explained by viewing diabetes as a slowly progressive neuro-microvascular disorder that affects the retina and the brain in parallel and that begins at a very early stage of the disease. The retinal fingerprints that should alert the clinicians of an increased risk of cognitive impairment are shown in Fig. 1.

The value of retinal structural imaging and its functional assessments as predictors of cognitive impairment or dementia is currently evaluated in the RECOGNISED study (ClinicalTrials.gov registration no. NCT04281186). The hypothesis is that individuals with type 2 diabetes in whom neurodegeneration is a predominant event in retinal examinations will be more prone to develop rapid cognitive decline (as is the case in Alzheimer's disease) (Fig. 1). By contrast, in those individuals in whom retinal neurodegeneration is apparently absent, slow cognitive decline will occur and this will be mainly modulated by microvascular impairment.

Scientific and clinical consequences

Several take-home messages emerge from recent evidence linking micro- and macroangiopathy. Perhaps the most

Fig. 1 Main retinal findings associated with CVD, stroke and cognitive impairment. Retinal abnormalities linked to CVD and stroke are within the blue box. Retinal changes related to cognitive impairment comprise both the blue (vascular abnormalities) and the peach box (retinal neurodegeneration). When neurodegeneration is added to vascular impairment, the cognitive decline will be more pronounced. The retinal branching

pattern can be quantified using several global parameters, including fractal dimension, tortuosity and branching angle. Angio-OCT, Optical coherence tomography angiography; NPDR, non-proliferative diabetic retinopathy; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy

important is that diabetic retinopathy and CVD should no longer be considered as entirely separate entities in the setting of diabetes. In fact, diabetic retinopathy should be taken into account as a primary cardiovascular risk factor, at least on the same level as dyslipidaemia and hypertension [3, 6, 15]. The vast majority of studies on CVD in diabetic participants have not considered this important variable in the randomisation process and, therefore, this is a significant drawback that could bias the interpretation of results. Another important point is that the presence of diabetic retinopathy permits us to identify a subset of the diabetic population in which the screening for CVD should be prioritised and risk-factor control optimised.

Additionally, the possibility of identifying patients with type 2 diabetes who have cognitive impairment and prodromal stages of dementia will be crucial in planning treatment, thus allowing for a reduction in the frequency of severe hypoglycaemia and hospital admissions that this subset of the diabetic population presents with.

Finally, it should be noted that although there are fewer data on those with type 1 diabetes than with type 2 diabetes, it is assumed that the retinal findings associated with either CVD outcomes or dementia are generally similar.

Conclusion

In conclusion, the strategy of using retinal assessment, not only to prevent sight-threatening disease in diabetes, but also to identify patients at risk of CVD and dementia, opens up a new era in the management of individuals with diabetes.

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