Neurodegeneration in diabetic retinopathy: Does it really matter?

Simó, R., Stitt, A. W., & Gardner, T. W. (2018). Neurodegeneration in diabetic retinopathy: Does it really matter? Diabetologia, 61(9), 1902-1912. https://doi.org/10.1007/s00125-018-4692-1

Published in:
Diabetologia

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
© 2018 The Authors. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access
This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: http://go.qub.ac.uk/oa-feedback
Neurodegeneration in diabetic retinopathy: does it really matter?

Rafael Simó 1 · Alan W. Stitt 2 · Thomas W. Gardner 3

Received: 4 April 2018 / Accepted: 19 June 2018 © The Author(s) 2018

Abstract

The concept of diabetic retinopathy as a microvascular disease has evolved, in that it is now considered a more complex diabetic complication in which neurodegeneration plays a significant role. In this article we provide a critical overview of the role of microvascular abnormalities and neurodegeneration in the pathogenesis of diabetic retinopathy. A special emphasis is placed on the pathophysiology of the neurovascular unit (NVU), including the contributions of microvascular and neural elements. The potential mechanisms linking retinal neurodegeneration and early microvascular impairment, and the effects of neuroprotective drugs are summarised. Additionally, we discuss how the assessment of retinal neurodegeneration could be an important index of cognitive status, thus helping to identify individuals at risk of dementia, which will impact on current procedures for diabetes management. We conclude that glial, neural and microvascular dysfunction are interdependent and essential for the development of diabetic retinopathy. Despite this intricate relationship, retinal neurodegeneration is a critical endpoint and neuroprotection, itself, can be considered a therapeutic target, independently of its potential impact on microvascular disease. In addition, interventional studies targeting pathogenic pathways that impact the NVU are needed. Findings from these studies will be crucial, not only for increasing our understanding of diabetic retinopathy, but also to help to implement a timely and efficient personalised medicine approach for treating this diabetic complication.

Keywords Diabetic retinopathy · Microvascular impairment · Neurodegeneration · Neuroprotection · Neurovascular unit · Personalised medicine · Review

Introduction

Diabetic retinopathy is the most common complication of diabetes and remains the leading cause of preventable blindness among working-age individuals in most developed countries [1, 2]. Current treatments target late stages of diabetic
The key role of the NVU in retinal physiology

The term ‘neurovascular unit’, was first applied to the blood–brain barrier and refers to the functional coupling and interdependency of neurons, glia and the highly specialised vasculature in the central nervous system (CNS) [18–21]. In the context of the retina, all the component cells of the NVU are in intimate communication and maintain the integrity of the inner blood–retinal barrier (iBRB) whilst dynamically regulating blood flow in response to metabolic demands. The impairment of the NVU is a primary event in the pathogenesis of diabetic retinopathy that can be examined by different methods (Fig. 1).

The components of the NVU are diverse neural cell types (i.e. ganglion cells, amacrine cells, horizontal and bipolar cells), glia (Müller cells and astrocytes), professional immune cells (microglia and perivascular macrophages) and vascular cells (endothelial cells and pericytes) [18–21] (Fig. 2). The intra-retinal vasculature lacks autonomic innervation and, therefore, a dynamic autoregulatory response of the NVU to complex circulatory and neural cues is essential to regulate blood flow through the inner retina [22, 23]. Thus, neuronal and glial-mediated neurovascular coupling is an essential normal homeostatic function of the retinal NVU.

Diabetes results in abnormal retinal blood flow, although the precise nature of this pathophysiology varies according to measurement techniques used and stage of diabetic retinopathy [22, 23]. Nevertheless, there is consistent and robust evidence that normal function of the retinal NVU is impaired in diabetes. For instance, the response to functional hyperaemia, which is critical for supplying oxygen and glucose to the active retinal neurons in the inner and middle retinal layers, becomes impaired as diabetes progresses. This response can be examined by flicker-evoked vasodilation, which is decreased in individuals in the early stages of diabetic retinopathy, even before overt signs of clinical retinopathy are observed [20–25]. These changes clearly demonstrate the relevance of neurovascular coupling or, in other words, interactions between the neurosensory retina and its blood vessels. The progressive dysfunction of neurovascular coupling may be a key causative factor in the development of clinically evident diabetic retinopathy, but longitudinal studies of retinal autoregulatory responses are needed to confirm this.

Is microvascular disease a primary pathogenic event in the development of diabetic retinopathy?

The early stages of diabetic retinopathy include disruption of the iBRB and the thickening of the vascular basement membrane in parallel with the damage and subsequent loss of pericytes and endothelial cells.

Blood–retinal barrier dysfunction in diabetes

The BRB consists of the iBRB and the outer BRB (oBRB). As mentioned previously, the integrity of the iBRB involves complex cell–cell communication between all the components of the NVU [26]. In contrast, the oBRB is formed by retinal
pigment epithelium (RPE). In both the iBRB and the oBRB, the passage of proteins and many other macromolecules into the retina from the bloodstream is controlled by tight junctions and adherens junctions between adjacent cells (i.e. occludin, claudins and zonula occludens-1 [ZO-1]), which effectively block paracellular permeability. The disruption of the BRB, in particular the iBRB, is essential in the pathogenesis of DMO [27]. The main known contributors to the breakdown of the BRB are vascular endothelial growth factor (VEGF), proinflammatory cytokines (e.g. IL-1β, TNF-α, IL-6, monocyte chemotactrant protein-1 [MCP-1]) and components of complement. These are variously secreted from RPE, glia and immune cells. In addition, blood-circulating leukocytes may engage with adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM) and selectins, on the surface of endothelial cells, and the adherence of these cells to the endothelial wall may result in the occlusion of capillaries (leukostasis). Such vascular–immune cell interactions contribute to microvascular damage by releasing cytokines and superoxide via respiratory burst, which alters the integrity of the NVU [28, 29]. In the advanced stages of diabetic retinopathy, in which immune privilege is compromised, circulating immune cells and serum proteins may infiltrate the retina and vitreous, thus participating in chronic inflammation and retinal vascular and neuronal damage [30].

There is robust clinical evidence that the development and progression of retinal microvascular disease is related to glycaemic control and hypertension [6]. However, clinical information on the relationship between glycaemic control and hypertension and retinal neurodegeneration is not available. It is worth mentioning, however, that the major components of the renin–angiotensin system (RAS) have been identified in ocular tissues and they are overexpressed in the retina of individuals with diabetes [31]. In addition, the blockade of RAS in experimental models of diabetes attenuates retinal neurodegeneration [32–34]. Regarding glycaemic control, it should be noted that accumulation of advanced glycation and lipoxidation end-products, and upregulation of the receptor for advanced glycation end-products (RAGE), plays a key role in the hyperglycaemia-induced activation of Müller cells and downstream cytokine production that may contribute to diabetic retinopathy [6].

The text box ‘BRB disruption and diabetic retinopathy’ summarises the main structural factors involved in the disruption of the BRB.

**BRB disruption and diabetic retinopathy**

The disruption of the BRB is one of the most important events in early stages of diabetic retinopathy.

The main factors involved are:

- Dysfunctional basement membrane
- Pericyte loss
- Endothelial damage
- Glial activation → NVU impairment
Basement-membrane thickening in retinal blood vessels

The vascular basement membrane is a key component of the NVU and is essential for both structural integrity and cell–matrix interactions [35]. Thickening of the capillary basement membrane is an early histological change in the retinal blood vessels in diabetic retinopathy. It is a consequence of increased synthesis of vascular basement-membrane components, such as collagen IV and laminin, in combination with reduced degradation by catabolic enzymes. These changes impair cell–cell communications, such as those that occur between endothelial cells and pericytes [6, 35]. Since the protein composition of the thickened basement membrane is modified, the charge selectivity properties of the membrane are also altered and the capacity for cell interactions that promote normal function and survival of the NVU are diminished. In addition, the thickened basement membrane acts less efficiently as a barrier, thus favouring vascular leakage [36].

Pericyte and endothelial cell death in diabetic retina

Pericytes are specialised contractile cells of neural crest, mesodermal and bone marrow origins; they regulate vascular tone and perfusion pressure [37]. Studies in experimental models of diabetic retinopathy have shown that pericyte dropout occurs before endothelial cell loss [38]. The loss of pericytes compromises capillary integrity leading to weakening of the iBRB and vascular leakage. The underlying mechanisms of pericyte loss during diabetic retinopathy remain to be fully elucidated and, although they have intimate physical and paracrine interactions with the vascular endothelium, demise of both pericyte and endothelial cells may occur via independent mechanisms [6, 39].

Endothelial cell injury by exposure to the diabetic milieu is a crucial event in diabetic retinopathy. When endothelial cells die, retinal capillaries become acellular. This so-called vasodegeneration or vasoregression is a central pathogenic response to chronic hyperglycaemia and initiates the progressive ischaemia characteristic of diabetic retinopathy. The importance of vasoregression in the setting of diabetic retinopathy has been comprehensively reviewed by Hammes et al [39, 40] and is conceptually divided into sequential steps: branch selection by flow dichotomy; vessel constriction; occlusion; endothelial retraction/apoptosis/reintegration; and resolution of the remaining empty vascular basement-membrane tube. Blood flow is a critical determinant of endothelial cell damage and sustained, abnormal autoregulatory responses are likely to significantly contribute to vasoregression. This is a highly complex system in which several inter-related signalling pathways are involved following the paracrine exchange of growth-factor signals between cells and differential receptor...
activation. There is accumulating evidence that the balance of wingless-related integration site (Wnt), Notch and angiopoietin–Tie-1 receptor signalling govern vessel formation and regression in the retina [41].

**Imaging early stages of microvascular disease: the role of optical coherence tomography angiography**

Optical coherence tomography angiography (OCTA) provides depth-resolved images of blood flow in the retina with levels of detail far exceeding that obtained with older forms of imaging. Using this approach, the retinal layers can be readily visualised and the distinct capillary plexi readily imaged. OCTA provides the ability to reconstruct and view the retinal vasculature in 3D, as well as to evaluate independently the changes that occur in the superficial, intermediate and deep capillary plexi. OCTA has enabled spatial and temporal visualisation of many of the vascular changes in individuals with diabetes, such as the development of microaneurysms and loss of vascular perfusion (capillary dropout) [42]. It has revealed that such changes happen sooner and are more severe in the deep capillary plexus than in the superficial capillary layer [43]. Indeed, with use of OCTA, these microvascular alterations can be detected in patients with diabetes without clinically detectable diabetic retinopathy on fundus photography (Fig. 3).

**Is neurodegeneration the primary event in the pathogenesis of diabetic retinopathy?**

A growing body of evidence clearly shows that neurodegeneration is an early event in the pathogenesis of diabetic retinopathy that could be linked to the development of microvascular abnormalities [3–6]. Therefore, the study of the underlying mechanisms leading to early disruption of the NVU and later neurodegeneration is essential for the development of new therapeutic strategies.

The hallmarks of diabetes-induced neuroglial degeneration, which include reactive gliosis, diminished retinal neuronal function and neural-cell apoptosis, have been observed to occur before overt microangiopathy in experimental models of diabetic retinopathy and in the retina of diabetic donors [44–46] (Fig. 4). Retinal ganglion cells and amacrine cells are the first neurons in which diabetes-induced apoptosis is detected, but photoreceptors also have an increased apoptotic rate. The structural consequence of this apoptotic death is a reduced thickness of inner retinal layers and the nerve fibre layer, which can be detected by optical coherence tomography (OCT). Multifocal electoretinography (mfERG), the gold standard for assessing retinal functional impairment, has revealed that the functional repercussions of neurodegeneration consist of a delayed P1 implicit time and reduced of traces [47]. These structural and functional alterations have clinical implications in terms of deficiencies in sensory capacity, including decreased hue discrimination, contrast sensitivity, delayed dark adaptation and abnormal visual fields, and thus result in reduced vision-related quality of life [48–50].

At present, it is unknown whether neural-cell apoptosis or reactive gliosis is first in the neurodegenerative process that occurs in the retina in diabetes. However, reactive gliosis (glial activation) may play a role in damage to retinal neurons and may link the neurodegenerative process with microvascular disease. Indeed, the astrocytes and Müller cells of the NVU play a critical homeostatic function by regulating retinal blood flow, and water balance in the neural parenchyma, and by maintaining barrier function [51]. Specifically, Müller cells can undergo reactive gliosis, which is discernible by upregulation of glial fibrillary acidic protein (GFAP). Gliosis is associated with increased expression of VEGF and innate immune-related pathways, resulting in overexpression of pro-inflammatory cytokines and BRB dysfunction.

In addition to macroglial cells, activated microglia, the resident immune cells of the retina and infiltrating monocytes can also mediate diabetes-induced subclinical inflammation. Microglial activation is accompanied by a phenotypic change toward an ameboid shape and presents two opposite roles, triggering either proinflammatory (M1) or anti-inflammatory
(M2) actions [52, 53]. In the early stages of diabetic retinopathy, the M2 response occurs concurrently with the M1 response and ameliorates inflammation and delays the progression of the disease. However, during the progression of diabetic retinopathy, the M1 response is maintained whereas the M2 response declines and the classical proinflammatory signalling pathways are chronically activated [53]. In fact, a shift from pro-survival to pro-neurotoxicity occurs, and transcriptional changes in activated microglia, mediated via the NFκB and extracellular signal-regulated kinase (ERK) signalling pathways, result in the release of various proinflammatory cytokines, chemokines, caspasases and glutamate [54]. These molecular mediators contribute to disruption of the BRB and NVU impairment, and to neuronal death.

**Mechanisms linking retinal neurodegeneration and early microvascular impairment**

The potential mechanisms linking retinal neurodegeneration and early microvascular impairment are summarised in Fig. 5. Apart from glial-mediated vascular damage, the balance between upregulated and downregulated neuroprotective factors in the diabetic retina is very important for the fate of the retinal neurons. In early stages of diabetic retinopathy, downregulation of key factors such as pigment epithelium-derived factor (PEDF), somatostatin, glucagon-like peptide 1 (GLP-1) and other neurotrophic factors is counterbalanced by an upregulation of VEGF and erythropoietin [4, 5]. However, the downregulation of neuroprotective factors may predominate, thus contributing to retinal neurodegeneration. This finding has important therapeutic implications. In this regard, neuroprotective effects have been reported by using insulin [55], PEDF [56, 57], somatostatin [58], GLP-1 [59, 60], dipeptidyl peptidase-IV (DPP-IV) inhibitors [61] and erythropoietin or erythropoietin-linked analogues [62, 63] in various experimental models. The European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR) clinical trial has recently shown that topical administration of somatostatin arrested the progression of neurodysfunction as assessed by mfERG (implicit time) in participants with some degree of neurodysfunction at baseline [64]. As an alternative target, endothelin-1 (ET-1) is upregulated in the retina in diabetes [65] and has dual deleterious action on microvessels and neurons. This is because of its capacity to bind to endothelin

![Fig. 4](image-url)
receptors A (ET\(_A\)) which mainly mediates vasoconstriction and neurodegeneration [66], and B (ET\(_B\)), involved in retinal neurodegeneration [67, 68]. Therefore, the blockade of ET-1 may prevent both microvascular disease and neurodegeneration induced by diabetes.

It should be noted that retinal neurons, themselves, including photoreceptors, may be an important source of oxidative stress that help drive the proinflammatory environment in diabetic retinopathy [69, 70], thus leading to vasoregression. In addition, it has recently been reported that photoreceptor cells release inflammatory products, which directly contribute to increased retinal endothelial permeability in mouse models of diabetes [71]. Furthermore, retinal neuronal cells may secrete molecules, such as semaphorin-3A, that promote BRB dysfunction, and may contribute to macular oedema [72].

When assessed by electroretinogram or other electrophysiological and psychophysical methods, impaired retinal function has been found to occur in individuals with diabetes who do not have detectable microvascular abnormalities [73]. In this regard, neuroretinal dysfunction, as assessed by mfERG, has been reported in individuals with type 1 diabetes without BRB leakage, the latter measured by vitreous fluorometry [74]. In addition, progressive thinning of the inner retina over time (assessed by OCT) occurs in murine experimental models [75], and in humans with type 1 diabetes, without any associated reduction of capillary density [76]. Furthermore, though only performed in a small number of individuals, prospective studies using mfERG have shown that increased implicit time can predict the development of visible vascular abnormalities over a 1 to 3 year period [77, 78]. However, baseline fluorescein angiograms were not performed in these studies, so it is possible that subclinical lesions existed at study entry. These findings raise the possibility, but do not prove, that retinal neurodegeneration may precede the onset of diabetes-induced vascular changes. Robust observational studies or interventional clinical trials that examine the neurovascular relationships are lacking. The recent randomised, placebo-controlled, Phase II–III EUROCONDOR study failed to show any effect of two neuroprotective drugs (brimonidine and somatostatin; administered by eye drops) in preventing or arresting microvascular disease [64]. Nevertheless, it should be noted that the short follow-up of this clinical trial (2 years), the inclusion of a high proportion of patients with no or very mild microvascular disease, and the excellent metabolic control during follow-up (mean HbA\(_1c\), 54.1 mmol/mol [7.1%] in all arms) could explain the negative findings with regards to the effects of neuroprotection on the development or progression of retinal microvascular disease.

**How do we integrate the microvascular and neural components?**

In order to integrate retinal microangiopathy and neuropathy into the definition of eye disease in diabetes, the term ‘diabetic retinal
Glial activation and neuron apoptosis are the two prominent hallmarks of this condition.

The main consequences are:
- NVU impairment and BRB disruption
- Impairment of vision-related quality of life:
  - Decreased hue discrimination
  - Decreased contrast sensitivity
  - Delayed dark adaptation
  - Reduced visual field sensitivity
  - Loss of visual acuity

The assessment of retinal neurodegeneration could help to identify individuals with type 2 diabetes who are at risk of developing Alzheimer’s disease.

Diabetes-induced retinal neurodegeneration

Retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy.

Low-grade inflammation, immune cell activation, extracellular glutamate accumulation and an imbalance of local production of neurotrophic factors are crucial for retinal neurodegeneration development.

Glial activation and neuron apoptosis are the two prominent hallmarks of this condition.

The main consequences are:
- NVU impairment and BRB disruption
- Impairment of vision-related quality of life:
  - Decreased hue discrimination
  - Decreased contrast sensitivity
  - Delayed dark adaptation
  - Reduced visual field sensitivity
  - Loss of visual acuity

The assessment of retinal neurodegeneration could help to identify individuals with type 2 diabetes who are at risk of developing Alzheimer’s disease.
are at risk of developing Alzheimer’s disease. This is an important issue since unrecognised cognitive dysfunction can affect treatment adherence and diabetes self-management, resulting in poor glycaemic control, an increased frequency of severe hypoglycaemic episodes and increased hospital admissions [81]. For these reasons, the early diagnosis of cognitive impairment is not only recommendable in itself, but also permits a more personalised treatment approach for patients with type 2 diabetes. In this regard, it should be noted that the ADA recommends individualised diabetes treatment, taking into account the cognitive capacity of patients [85].

**Where do we go from here?**

Diabetes causes not only classical retinal microangiopathy and DMO, but also neurodegeneration, and these events coalesce with progressive disruption of the retinal NVU. Glial dysfunction plays a crucial role in diabetes-induced neurovascular coupling impairment, thus contributing to the early stages of microvascular disease. However, our knowledge regarding the cellular and molecular mechanisms that link retinal neurodegeneration and microvascular disease remains limited and more research is needed to understand the complex intercellular dynamics within the NVU in health and diabetes. Current evidence suggests that neurodegeneration is an early event in diabetic retinopathy but may or may not be related to the development and progression of microvascular disease. This should be tested further in future long-term clinical trials using highly sensitive new technologies combined with improved stratification of participants.

The consequences of progressive retinal diabetic neurodegeneration, specifically in the absence of clinically appreciable diabetic retinopathy, have been gaining attention [79]. In this regard, it is notable that the loss of neuroretinal thickness (nerve fibre layer, ganglion cell layer and inner plexiform layer) in people with diabetes with no or minimal diabetic retinopathy is around 0.54 μm per year [76]. This mean a loss of 5.4 μm over 10 years and, remarkably, is equivalent to the loss found in severe glaucoma. Since this neuron loss is related to deficient sensory capacity and vision-related quality of life, periodic assessments of neurodegeneration/neurodysfunction in the diabetic population is strongly recommended. In addition, the emergent development of neuroprotective drugs to treat diabetic retinopathy points to screening for retinal neurodysfunction as critical for identifying the subset of patients in whom neuroprotective treatment might be of benefit. Additionally, the assessment of retinal neurodegeneration could be an important index of cognitive status, thus helping to identify individuals at risk of dementia.

In summary, it is now recognised that during diabetes, retinal glial, neural and microvascular dysfunction is interdependent and essential for the development of diabetic retinopathy. Despite this intricate relationship, it should be noted that retinal neurodegeneration is a critical endpoint and neuroprotection, itself, can be considered as a target, independently of its potential impact on microvascular disease. Hence, the decades-old grading schemes of diabetic retinopathy, based solely on non-quantitative assessment of microvascular abnormalities, should be replaced by robust quantitative readouts that are reflective of progressive dysfunction in the retinal NVU. In addition, more interventional studies targeting pathogenic pathways that impact the NVU and that offer both vaso- and neuroprotection are needed. This will be crucial, not only for increasing our understanding of diabetic retinopathy, but also to implement a timely and efficient personalised medicine approach for the treatment of this disease.

**Funding** RS is supported by the following grants: Ministerio de Economía y Competitividad (SAF2016-77784) and the Fundación Marató TV3 (201629-10). AWS is supported by the following grants: Fight for Sight, The Belfast Association for the Blind and The Jules Thorn Trust. TWG is supported by the following grants: R01EY20582, R24DK082841. Research to Prevent Blindness and The Taubman Medical Research Institute.

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.

**Contribution statement** All authors were responsible for drafting the article and revising it critically for important intellectual content. All authors approved the version to be published.

**Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

**References**

1. Yau JW, Rogers SL, Kawasaki R et al (2012) Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 35:556–564
2. Leasher JL, Bourne RR, Flaxman SR et al (2016) Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. Diabetes Care 39:1643–1649
3. Abcouwer SF, Gardner TW (2014) Diabetic retinopathy: loss of neuroretinal adaptation to the diabetic metabolic environment. Ann N Y Acad Sci 1311:174–190
4. Simó R, Hernández C (2014) Neurodegeneration in the diabetic eye: new insights and therapeutic perspectives. Trends Endocrinol Metab 25:23–33
5. Simó R, Hernández C (2015) Novel approaches for treating diabetic retinopathy based on recent pathogenic evidence. Prog Retin Eye Res 48:160–180
6. Stitt AW, Curtis TM, Chen M et al (2016) The progress in understanding and treatment of diabetic retinopathy. Prog Retin Eye Res 51:156–186
7. Solomon SD, Chew E, Duh EJ et al (2017) Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetes Care 40:412–418
49. Wolff BE, Bearse MA Jr, Schneck ME et al (2015) Color vision and neuroretinal function in diabetes. Doc Ophthalmol 130:131–139
50. Trento M, Durando O, Lavecchia S et al (2017) Vision related quality of life in patients with type 2 diabetes in the EUROCONDOR trial. Endocrinology 57:83–88
51. Bringmann A, Wiedeman P (2012) Müller glial cells in retinal disease. Ophthalmologica 227:1–19
52. Coorey NJ, Shen W, Chung SH, Zhu L, Gillies MC (2012) The role of glia in retinal vascular disease. Clin Exp Optom 95:266–281
53. Arroba Al, Valverde AM (2017) Modulation of microglia in the retina: new insights into diabetic retinopathy. Acta Diabetol 54:527–533
54. Altmann C, Schmidt MHH (2018) The role of microglia in diabetic retinopathy: inflammation, microvascular defects and neurodegeneration. Int J Mol Sci 19:110
55. Fort PE, Losiewicz MK, Reiter CE et al (2011) Differential roles of hyperglycemia and hypoinsulinaemia in diabetes induced retinal cell death: evidence for retinal insulin resistance. PLoS One 6:e26498
56. Liu X, Chen HH, Zhang LW (2013) Potential therapeutic effects of pigment epithelium-derived factor in treatment of diabetic retinopathy. Int J Ophthalmol 6:221–227
57. Polato F, Becerra SP (2016) Pigment epithelium-derived factor, a protective factor for photoreceptors in vivo. Adv Exp Med Biol 854:699–706
58. Hernández C, García-Ramírez M, Corraliza L et al (2013) Topical administration of somatostatin prevents retinal neurodegeneration in experimental diabetes. Diabetes 62:2569–2578
59. Hernández C, Bogdanov P, Corraliza L et al (2016) Topical administration of GLP-1 receptor agonists prevents retinal neurodegeneration in experimental diabetes. Diabetes 65:172–187
60. Simó R, Hernández C (2017) GLP-1R as a target for the treatment of diabetic retinopathy: friend or foe? Diabetes 66:1453–1460
61. Hernández C, Bogdanov P, Solá-Adell C et al (2017) Topical administration of DPP-IV inhibitors prevents retinal neurodegeneration in experimental diabetes. Diabetologia 60:2285–2298
62. Sullivan TA, Geisert EE, Templeton JP, Rex TS (2012) Dose-dependent treatment of optic nerve crush by exogenous systemic mutant erythropoietin. Exp Eye Res 96:36–41
63. Busch S, Kannt A, Kolibabka M et al (2014) Systemic treatment with erythropoietin protects the neurovascular unit in a rat model of retinal neurodegeneration. PLoS One 9:e102013
64. Simó R, Bandello F, Egan C et al (2017) Topical administration of somatostatin and brominidine in the early stages of diabetic retinopathy: results of the EUROCONDOR study. Diabetologia 60(Suppl 1):S55 Abstract
65. De Juan JA, Moya FJ, Ripodas A, Bernal R, Fernandez-Cruz A, Fernandez-Durango R (2000) Changes in the density and localisation of endothelin receptors in the early stages of rat diabetic retinopathy and the effect of insulin treatment. Diabetologia 43:773–785
66. Chou JC, Rollins SD, Ye M, Battie D, Fawzi AA (2014) Endothelin receptor-A antagonist attenuates retinal vascular and neuroretinal pathology in diabetic mice. Invest Ophthalmol Vis Sci 55:2516–2525
67. Minton AZ, Phatak NR, Stankowska DL et al (2012) Endothelin B receptors contribute to retinal ganglion cell loss in a rat model of glaucoma. PLoS One 7:e43199
68. Tonari M, Kurimoto T, Horie T, Sugiyama T, Ikeda T, Oku H (2012) Blocking endothelin-B receptors rescues retinal ganglion cells from optic nerve injury through suppression of neuroinflammation. Invest Ophthalmol Vis Sci 53:3490–3500
69. Du Y, Veenstra A, Palczewski K, Kern TS (2013) Photoreceptor cells are major contributors to diabetes-induced oxidative stress and local inflammation in the retina. Proc Natl Acad Sci U S A 110:16586–16591
70. Liu H, Tang J, Duh Y et al (2016) Photoreceptor cells influence retinal vascular degeneration in mouse models of retinal degeneration and diabetes. Invest Ophthalmol Vis Sci 57:4272–4281
71. Tonade D, Liu H, Palczewski K, Kern TS (2017) Photoreceptor cells produce inflammatory products that contribute to retinal vascular permeability in a mouse model of diabetes. Diabetologia 60:2111–2120
72. Cerani A, Tetreault N, Menard C et al (2013) Neuron-derived semaphorin 3A is an early inducer of vascular permeability in diabetic retinopathy via neuropilin-1. Cell Metab 18:505–518
73. Simó R, Hernández C (2012) Neurodegeneration is an early event in diabetic retinopathy: therapeutic implications. Br J Ophthalmol 96:1285–1290
74. Reis A, Mateus C, Melo P, Figueira J, Cunha-Vaz J, Castelo-Branco M (2014) Neuroretinal dysfunction with intact blood-retinal barrier and absent vasculopathy in type 1 diabetes. Diabetes 63:3926–3937
75. Bogdanov P, Corraliza L, Villena JA et al (2014) The db/db mouse: a useful model for the study of diabetic retinal neurodegeneration. PLoS One 9:e97302
76. Sohn EH, van Dijk HW, Jiao C et al (2016) Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. Proc Natl Acad Sci U S A 113:E2635–E2664
77. Harrison WW, Bearse MA Jr, Ng JS et al (2011) Multifocal electroretinograms predict onset of diabetic retinopathy in adult patients with diabetes. Invest Ophthalmol Vis Sci 52:772–777
78. Ng JS, Bearse MA Jr, Schneck ME, Barez S, Adams AJ (2008) Local diabetic retinopathy prediction by multifocal ERG delays over 3 years. Invest Ophthalmol Vis Sci 49:1622–1628
79. Abramoff MD, Fort P, Han IC, Jayasundera KT, Sohn EH, Gardner TW (2018) Approach for clinically useful comprehensive classification of vascular and neural aspects of diabetic retinal disease. Invest Ophthalmol Vis Sci 59:519–527
80. Santos AR, Ribeiro L, Bandello F et al (2017) Functional and structural findings of neurodegeneration in early stages of diabetic retinopathy: cross-sectional analyses of baseline data of the EUROCONDOR project. Diabetes 66:2503–2510
81. Simó R, Ciudin A, Simó-Servat O, Hernández C (2017) Cognitive impairment and dementia: a new emerging complication of type 2 diabetes—the diabetologist’s perspective. Acta Diabetol 54:417–424
82. Sundstrom JM, Hernandez C, Weber S et al (2018) Proteomic analysis of early diabetic retinopathy reveals mediators of neurodegenerative brain diseases. Invest Ophthalmol Vis Sci 59:2264–2274
83. Cheung CY, Ikram MK, Chen C, Wong TY (2017) Imaging retina to study dementia and stroke. Prog Retin Eye Res 57:89–107
84. Ciudin A, Simó-Servat O, Hernández C et al (2017) Retinal microperimetry: a new tool for identifying patients with type 2 diabetes at risk for developing Alzheimer disease. Diabetes 66:3098–3104
85. American Diabetes Association (2013) Clinical practice recommendations. Diabetes Care 36(Suppl 1):S3
86. Carrasco E, Hernández C, de Torres I, Farrés J, Simó R (2008) Lowered cortistatin expression is an early event in the human diabetic retina and is associated with apoptosis and glial activation. Mol Vis 14:1496–1502