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A proposal for early and personalized treatment of diabetic retinopathy based on clinical pathophysiology and molecular phenotyping

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ABSTRACT

This paper presents a new approach to the prevention and treatment of early stage diabetic retinopathy before vision is severely impaired. This approach includes two major steps. The first step is to understand the mechanisms of vision impairment and classify diabetic retinopathy on the basis of pathophysiologic adaptations, rather than on the presence of advanced pathologic lesions, as defined by current clinical practice conventions. The second step is to develop patient-specific molecular diagnoses of diabetic retinopathy so that patients can be treated based on their individual characteristics, a process analogous to the individualized diagnosis and treatment of cancer patients. This step is illustrated by proteomic analysis of vitreous fluid that reveals evidence of neuroretinal degeneration and inflammation, as well as vascular proliferation. Together, these steps may lead to improved means to preserve vision in the ever-increasing number of patients with diabetes worldwide.

1. Clinical Characterization of diabetic retinopathy

1.1. Introduction

Professor Eva Kohner exemplifies a tradition of doing the right thing for patients with diabetes. She exemplified this approach whether in the context of clinical research trials such as the United Kingdom Prospective Diabetes Study, and in her discussions of individual patients. In addition, Professor Kohner has always supported the development of young investigators, so this lecture is presented jointly by a senior (TWG) and a younger investigator (JMS). Fig. 1 shows Professor Kohner surrounded by a large group of male colleagues at the 1968 Airlie House Symposium. The Airlie House Classification of diabetic retinopathy (Goldberg & Fine, 1969) was born at this symposium and became the forerunner of the Early Treatment Diabetic Retinopathy Study classification (Anonymous, 1991; Diabetic retinopathy study, 1981) that has formed the basis for the important diagnostic and therapeutic trials over the last 50 years. While this classification scheme has been extremely helpful, it was designed in an era when the essential questions were about the benefit of pituitary ablation for proliferative diabetic retinopathy, and when the benefits and risks of panretinal laser therapy for proliferative diabetic retinopathy were still debated, a decade before the Diabetic Retinopathy Study results were published. Therefore, the context was the need for a structure by which to address severe blinding retinopathy. The success of that classification now brings us to the 21st century when there is the opportunity and the need for better intervention of early stage disease before patients are at risk for losing vision. The first section of this presentation focuses on the clinical characterization of diabetic retinopathy and the quantification of structural and functional changes in diabetic retinopathy. This work and the associated concepts are the product of many investigators, notably Drs. David Antonetti, Steven Abcouwer, Patrice Fort and Gregory Jackson, who are investigating distinct aspects of the neurovascular unit and its alterations in diabetes.

2. Classification of diabetic retinopathy—past and future

Current clinical teaching is that diabetes impairs vision because of visible features such as tractional retinal detachment, non-clearing vitreous hemorrhage, neovascular glaucoma, macular

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Fig. 1. Attendees at the 1968 Airlie House Symposium with Professor Eva Kohner front and center (Goldberg, Fine, & Program, 1969).

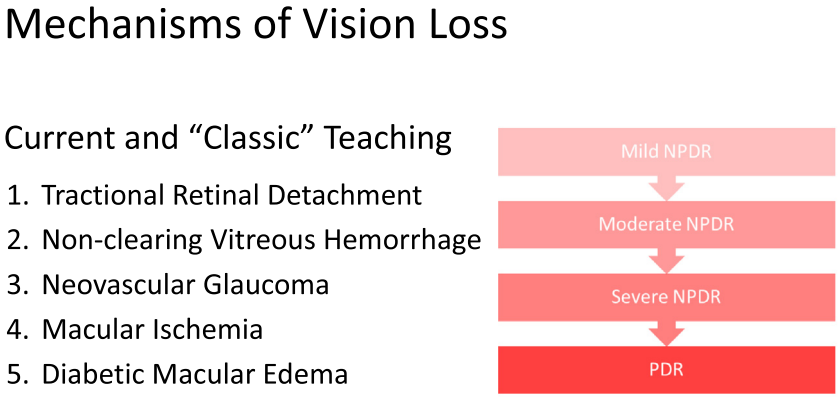

Fig. 2. Classification of mechanisms of vision loss in diabetic retinopathy. The clinical features of diabetic retinopathy that are associated with vision loss (left) do not coincide directly with the severity scale (right).

ischemia and/or diabetic macular edema. However, as shown in Fig. 2, these events do not strictly correlate with the clinical classification of retinopathy as mild, moderate or severe, non-proliferative retinopathy or proliferative retinopathy. People with mild retinopathy and macular edema can have reduced vision and patients with advanced proliferative retinopathy can have nearly normal vision, when vision is defined as visual acuity.

An alternative approach to this classification based on pathologic lesions is to consider the evolution of events in a continuum of pathophysiologic events from the onset of diabetes to clinical manifestations (Gardner & Davila, 2017). Fig. 3 illustrates a concept with at least 3 stages. In the first, multiple adaptive responses occur within weeks to months of the onset of diabetes. These responses, as measured primarily in animal models, include reduced electrical activity, reduced biosynthetic activity such as protein and lipid synthesis, autophagy and apoptosis (Barber et al., 1998; Fort et al., 2014; Fox et al., 2006; Tikhonenko et al., 2010). Likewise, patients with clinically intact retinas exhibit impaired autoregulation in which there are defective vascular responses to breathing 100% oxygen or to flickering light (Lott et al., 2012, 2015; Pemp et al., 2009). In this first stage vision is intact and we consider that there is no diabetic retinopathy because adaptive responses compensate for the metabolic insults. However, after approximately 5–10 years, a second stage can develop in which adaptive changes begin to decompensate and there are early clinical signs such as retinal hemorrhages, microaneurysms, macular edema, vascular non-perfusion and gliosis. At this point, subtle aspects of vision, such as visual field and contrast sensitivity, are impaired and this may be considered an early form of decompensation when non-proliferative retinopathy develops. A third stage occurs after additional time and suboptimal diabetes control, a state of aberrant repair may develop with neovascularization, gliosis, fibrosis, retinal neovascularization and frank loss of vision. This pathophysiologic stage is consistent with proliferative diabetic retinopathy. The current regulatory strategies for treating retinopathy are limited to the stages of adaptive decompensated and aberrant repair and have not yet been developed for patients that have mild retinopathy and good vision. However, a recent workshop sponsored jointly by the National Eye Institute and Food and Drug Administration strongly emphasized the need

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