Dr. P. Sivasubramaniam Oration – 2019

The evolution in the treatment of diabetic retinopathy

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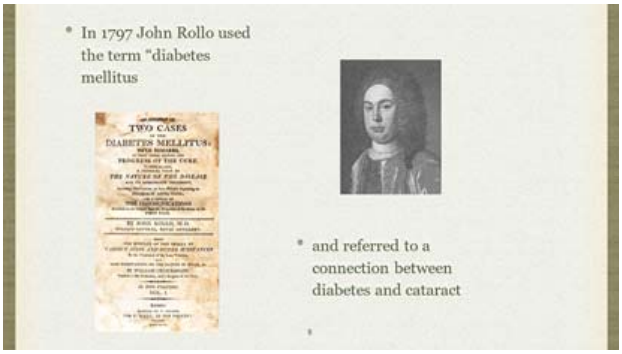
The history of diabetes reaches back to ancient times. The first recorded reports are from Egypt and are believed to be about 3500 years old. The first clinical description of diabetes recorded, is in the Ebers Papyrus dating around the time of 1530 BC[1]. It was subsequently believed to be a disease of the kidneys and lot of attention was paid to patients' urine, which as Characa, a doctor living in India during the period 800-200BC, noticed – "attracted ants and flies". Hippocrates described diabetes as disease with polyuria which led to emaciation. The word "diabetes" originates from the Greek word for "syphon" or "the flow of water through the body" and was first used by Aretaeus of Cappadocia (50 AD)[1]. He was also first to present to a full clinical description of a patient with diabetes. The term "diabetes mellitus" was first used by John Rollo in 1797, to differentiate it from diabetes insipidus[1].



Although diabetes was a well-known disease from the 2nd century AD onwards, the first description of the involvement of the eye was in 1846 when the French Ophthalmologist and Professor of Hygiene, in Paris, Appolinaire Bouchardat reported the development of visual loss in the absence of cataract in diabetics[2]. He also made a very astute observation that the visual loss was partly reversible with better control of diabetes through specific diets. The first clinical descriptions of diabetic retinopathy was by Eduard Jager[1]. He constructed an ophthalmoscope integrating the principles of Helmholtz. Using this instrument, Jager was able to observe the changes in the macula in diabetes which he published in 1855. Jager had inexhaustible patience and exemplary precision in both in ophthalmoscopy and in illustrating his findings. He meticulously incorporated even the smallest details into his pictures. He used the newly developed direct ophthalmoscope in order to produce one of the first atlases containing 21 colour plates of fundus paintings, which were drawn after 20-40 clinical sessions per patient. He described 'roundish or oval, yellowish spots, and 'full or partial thickness extravasations through the retina in the macular region' of a diabetic patient. However, his findings were met with skepticism, and Von Graefe who was a very influential ophthalmologist at that time dismissed his findings, emphasizing that there was no proof of a cause-effect relationship between diabetes and retinal complications, which of course was correct. Even in 1858 Von Graefe's skepticism was adopted by many of his colleagues, with the exception of Desmarres.

It took another 11 years for Henry Noyes to publish an article in the USA supporting the link between diabetes mellitus and maculopathy and his observations were confirmed again in 1872 by Edward Nettleship in London, who presented his classic paper "On oedema or cystic disease of the retina and presented the first histopathological proof of a cystoid degeneration of the macula in diabetic patients. Five years later, Nettleship published another article with Sir Steven Mackenize which described in detail the abnormal retinal changes induced by diabetes. Concomitantly in 1876, Wilhelem Manz published his seminal paper on retinitis proliferans containing several drawings of

[1]*Consultant Ophthalmologist.*

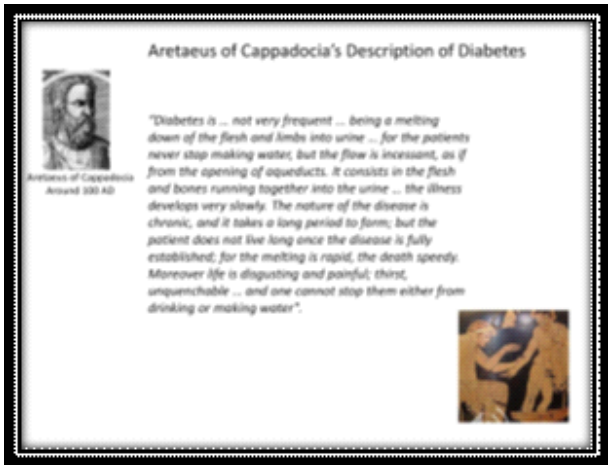
'fibrovascular degeneration of the optic disc and vitreoretinal adhesions in the retina'. In 1890, Julius Hirschberg classified diabetic retinopathy into four types (retinitis centralis punctuate, haemorrhagic form, retinal infarction and haemorrhagic glaucoma), thus describing the full natural history of diabetic retinopathy. The descriptive term, diabetic retinitis, implying that it was inflammatory in nature continued to be used for several years until it was dropped when other theories were expounded, and I will allude to this later in my talk.

Even at the beginning of the 20th century there was still the unresolved debate as to whether macular changes where directly related to diabetes or whether they were caused by atherosclerosis and hypertension. Arthur James Ballantyne from Glasgow, suggested that diabetic retinopathy represents a unique form of vasculopathy and his work showed for the first time the role of capillary wall alternations in the development of diabetic retinopathy, as well as the presence of deep waxy exudates in the outer plexiform layer and thus establishing the disease of diabetic retinopathy[2].

Dr. Arthur James Ballantyne of University of Glasgow

However, there was no treatment for diabetic retinopathy and it was not a priority in anyway, as the life expectancy for newly diagnosed diabetic was dismal at the turn of the century, where a 50 year old if diagnosed of diabetes was expected to live only 8 years and if diagnosis was made in a 10 year old then it was only 1. 4 years.

So at the end of the 19th century, life for a diabetic patient was not significantly different from Aretaeus of Cappadocia's description in 100 AD.

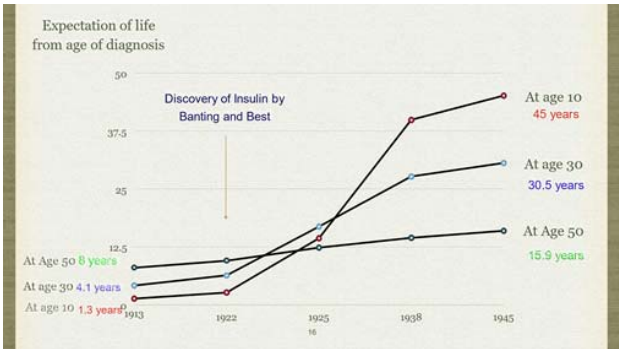


However at the beginning of the 20th century, it was well known that excision of a pancreas produced diabetes, which could be reversed by transplanting the gland or cross circulation where blood from a healthy dog was perfused through another dog without a pancreas, causing a prompt fall in blood glucose. Several scientists came very close to producing an effective pancreatic extract to Rx diabetes but success was achieved only in 1922.

Insulin was discovered in Toronto. To quote from Michael Bliss in his book "the Discovery of Insulin". This involved more than a bit of serendipity. In retrospect, it is obvious that many of those who tried came very close: conversely, so many had failed that only someone very inexperienced would be optimistic enough even to try. That someone was Frederick Banting, an Orthopaedic Surgeon, aided by Charles Best, a medical student brought in to measure blood glucose. Professor John Macleod in whose laboratory this work was done, showed exceptional insight (or tolerance) in letting such rank amateurs loose in his laboratory[3]. They performed several failed experiments on dogs that they had to buy dogs in the black market. Eventually they did succeed in producing an "extract" which lowered blood glucose in dogs, but failed in its first human trial in a patient called Leonard Thompson. Macleod brought in James Collip, a chemist to help with the extraction and in January 1922, Collip hit upon an extraction procedure that caused insulin to be

precipitated and thus became the first person to "see insulin". For this Macleod and Banting were awarded the Nobel prize[1].

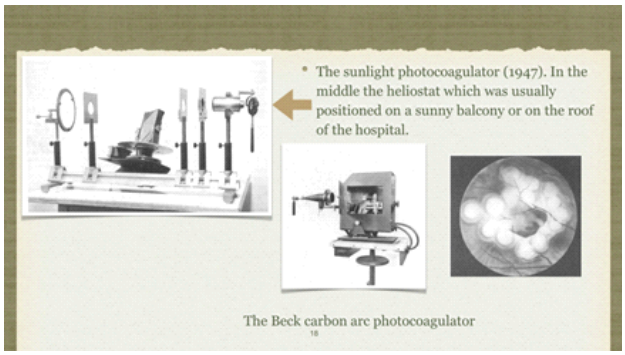
Introduction of insulin and later other oral hypoglycemics (in 1992) significantly improved the life expectancy of diabetics and there by kicked off an epidemic of microvascular complications of which lasts to this day.



The first successful treatment for diabetic retinopathy was the use of photocoagulation which was conceptualized by a 25-year-old German Ophthalmologist by the name of Gerhardt Meyer-Schwickerath in 1946[2]. The idea came to him while he was supervising a thesis of a medical student who described his own macular burn which he received whilst watching the sun at the eclipse of 11 July 1945.

Meyer-Schwickerath

After several animal experiments he developed a new apparatus which used the sun as light-source. Of course, the sunshine in Essen, Germany was unpredictable. Treatment was done on the roof of the eye hospital and was possible only when a prolonged period of sunshine was expected. However setting up the apparatus took time and when it was ready and the patient came in the sun disappeared and treatment had to be postponed.



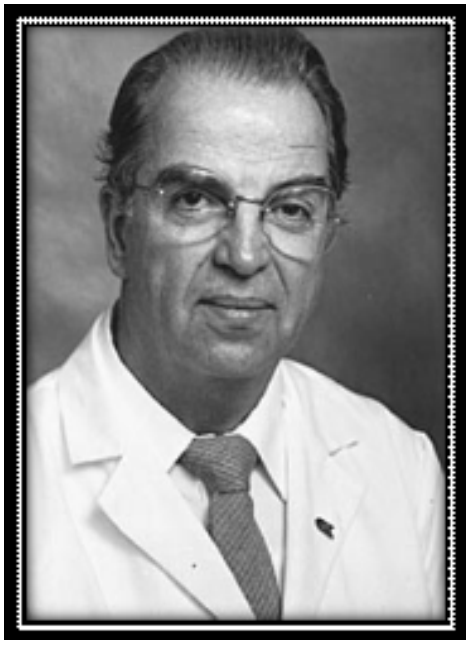
The dependence on the season and unpredictable weather was extremely annoying and in 1949 Meyer started experiments with a high intensity arc known (after its inventor) as the Beck-arc. This new instrument was a great success and was used clinically on several hundred patients between 1950 and 1956[2]. The light source was replaced with a carbon arc lamp which was a more reliable but a short filament life span, liberation of soot and unpredictable retinal burns limited its usefulness.

In 1956 prototype of a xenon-arc coagulator made by Zeiss for Meyer, and this quickly came into widespread use by ophthalmologists for retinal photocoagulation. It emitted a light spectrum similar to sunlight, with a relatively high, uniform power output which made it very efficacious. However, its disadvantages included difficulty on focusing, and relatively long exposure duration. It was also very painful for the patient. Furthermore, many complications occurred, such as intense retinal burns which resulted in scarring, fibrous traction, visual field defects, and vitreous heamorrhage. Diminished transparency of ocular media was a contraindication to xenon arc photocoagulation because the absorption of the visible light by cornea, lens, or other media opacity caused tremendous heat generation in that area. Interestingly, Schiwkerath himself introduced the xenon arc to India and when I visited India in 1990 for a vitreoretinal meeting, the xenon arc was still in use there.

In 1990 Hughes Research Lab in California, successfully constructed the world's first working laser; made

of synthetic ruby. The following year, laser was used for the first time at the Columbia-Presbyterian Medial Centre. Although the ruby laser was attached to a monocular, direct ophthalmoscope, the development of argon and subsequently solid-state laser sources permitted ophthalmologists the flexibility of treating patients at the slit lamp, or with an indirect ophthalmoscope or the operating microscope, as we know it today. The value of laser was confirmed by diabetic retinopathy study.

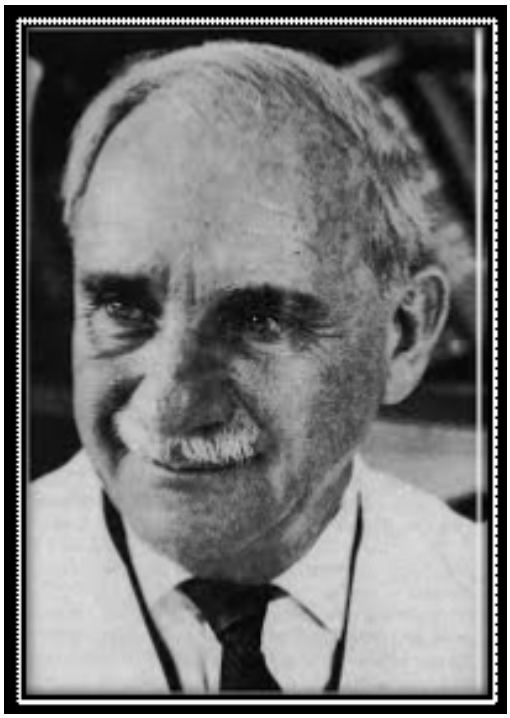
The next arm of treatment to develop was surgery. Robert Machemer developed pars plana vitrectomy to operate in a closed with controllable intraocular pressure. The technique of pars plana vitrectomy (PPV) was first reported in 1971 by Machemer et al[1]. using 17G instruments to clear diabetic vitreous haemorrhage. The Diabetic Retinopathy Vitrectomy Study which was a randomized controlled study examined early versus deferred vitrectomy following vitreous haemorrhage in 161 patients. After 2 years of follow up, 25% of the early vitrectomy group had visual acuity of 10/20 or better compared with 15% in the deferral group (P=.01). In patients with Type 1 diabetes, who were on the average younger and had more-severe proliferative retinopathy, there was clear-cut advantage for early vitrectomy, as reflected in the percentage of eyes recovering visual acuity of 10/20 or better, thus establishing the role of surgery in the treatment of DR. Although the techniques and technology has since evolved considerably, the basic goal of removing vitreous to relieve retinal traction and clear opacities remains the same.



Robert Machemer

By the end of the 20th century, diabetics had a considerably improved life span and treatment options in the form of laser and surgery for retinopathy were well established. So though the risk of blindness had considerably reduced for many who developed DR, the prevalence of impaired vision, specially from maculopathy had not.

The next development in the saga of treatment was anti VEGF agents[1]. As far back as 1948, Professor Michaelson postulated the presence of a secreted "Factor X", which was a soluble and diffusible growth factor which was responsible for retinal vascular growth in development and disease. Clinicians recognized that, damaged or ischemic retina secreted a factor that could leak out into other parts of the eye and cause new blood vessel growth, either in the retina, optic nerve, or on the iris. However, the exact identity of Factor X remained elusive for several decades.



Professor I C Michaelson

In the 1970s, Folkman's laboratory identified a tumor angiogenesis factor and Folkman published his seminal theory of tumor angiogenesis in the November 1971 issue at *New England Journal of Medicine*; that angiogenesis or the recruitment and growth of new blood vessels was required for tumor growth. However, Folkman's theory was met with skepticism.

In 1983, Harold Dvorak and Don Singer at Harvard Medical School isolated a Vascular permeability factor from ascites fluid and tumor cells. They demonstrated that it was a very potent and had a permeability 50 000 times that of histamine.

At the same time, Joan Millers group at Harvard collected ocular fluid samples form a model of ischemic retinopathy in a non-human primate in which experi'-mental retinal ischemia following laser vein occlusion leads to iris neovascularization. When they looked at VEGF/VPF levels with Dvorak, they saw that the protein which was virtually nonexistent before neovascularization appeared, and rose very quickly to high levels that correlated closely with increasing severity of iris neovascularization and levels decreased as the iris neovascularization regressed. This was the first time a correlation was made of increased VEGF levels with ocular neovascularization in vivo.

They continued working with Ferrara, used the ischemic retinopathy and iris neovascularization model to test the full-length anti-VEGF antibody (essentially the precursor to Avastin) and discovered that intravitreal injection of the antibody prevented iris neovascularization. In 1989, Napoleone Ferrara and others cloned, sequenced and characterized VEGF, which turned out to be the same molecule as VPF.

The development of anti-VEGF agents continued, ultimately resulting in two molecules; Bevacizumab (Avastin) which was a full-length antibody and ranibizumab (Lucentis) the antibody fragment. The full-length recombinant humanized anti-VEGF mono-clonal antibody (lgG) was initially approved by the Food and Drug Administration (FDA) for treatment of metastatic colorectal carcinoma. It had twice the half-life of ranibizumab. Ophthalmic uses of bevacizumab are not FDA approved; however, its safety and efficacy have been shown in multiple neovascular age-related macular degeneration trials and DME trials, such as DRCR net protocol T. The RISE and RIDE studies, discussed later, demonstrated efficacy of ranibizumab in DME. Based on multiple trials the FDA approved ranibizumab in 2017 for all stages of diabetic retino-pathy.

Aflibercept (EYLEA) is a recombinant fusion protein and it has been shown to bind VEGF with greater affinity than other anti-VEGF agents. The VISTA and VIVID trails studied aflibercept use in DME.

DRCR protocol S was a randomized clinical trial designed to determine whether ranibizumab, 0.5 mg, was noninferior to PRP for PDR were identified through a post hoc analysis. A composite outcome was used to determine worsening PDR, including vitreous haemorrhage, neovascularization of the iris or angle, neovascular glaucoma, retinal detachment as well as need for further PRP or vitrectomy. Overall, the PRP group had a higher proportion (42 versus 34%, p=0.063) of outcomes associated with progression. When the analysis was adjusted for severity of PDR, there was a significantly higher proportion of outcomes associated with PDR progression in the PRP group, when compared to the ranibizumab group (HR 1.45, p=0.024). This became more apparent when assessing eyes with center-involving DME that were randomized to PRP. Those eyes that did not receive adjunct ranibizumab and had a higher hazard ratio for adverse outcomes (HR 1.73, p=0.004) compared to ranibizumab alone. However the cost and time of anti-VEGF monotherapy is a burden upon patients and the healthcare system. The efficacy of the two treatments is similar. Protocol S did not show a significant difference between PRP and ranibizumab in overall percentage of eyes achieving quiescent PDR.

In light of these studies, the American Academy of Ophthalmology (AAO) Preferred Practice Pattern Committee now states that there is sufficient evidence for the treatment of diabetic retinopathy with anti-VEGF treatment. Practice Pattern states, "It would be reasonable to consider use of ranibizumab in severe NPDR patients in settings where laser surgery would be considered," and in high-risk PDR, an anti-VEGF alternative to PRP could be considered for patients who can follow-up regularly, especially if there is macular edema. Anti-VEGF monotherapy can also be consi-dered as first-line therapy in PDR assuming that judicious oversight by the clinician is possible to monitor disease progression. It also has a role in situations where PRP is not possible, due to media opacity, dense cataract or non-clearing vitreous haemorrhage, or where the patient is unable to go to the operating room due to medical reasons

The role of anti-VEGF treatment in NPDR is also evolving. The AAO Preferred Practice Pattern recom-mends considering anti-VEGF treatment in severe NPDR where PRP would otherwise be considered. Anti-VEGF treatment has also been shown to reduce diabetic retinopathy severity and is associated with lower rates of PDR development. Currently, the management of NPDR consists of risk factor modification. Use of anti-VEGF medications in addition to risk factor modifi-cation may prevent development of PDR.

A Cochrane Review of 24 studies collected and analyzed data to find the efficacy of 3 anti-VEGF agents for diabetic macular oedema (DME).

- Approximately three in 10 people improve vision by 3 or more lines with ranibizumab and one in 10 additional people can achieve this with aflibercept.
- Anti-VEGF injections were administrated less frequently and were less effective than those in the ranibizumab registration trials. After each of the first 9 injections, <25% of patients achieved both BCVA of 20/40 or better and a dry macular (Binder et al ECHO Study 1 report)

So what is the future for patients with DR specially DME?

At the end of the 20th century the impression of clinicians was that DR was essentially a microvascular complication. The fundamental change was a combination of capillary occlusion and an increased capillary permeability. With the property of promoting both vascular permeability and angiogenesis, VEGF was a likely contributor to the vascular dysfunctions observed in severe DR.

I alluded the descriptive term, of diabetic retinitis and related to you that the term was dropped because it was believed that inflammation played no role in DR. However, diabetic microvasculopathy does not explain the early loss of retinal function. Those retinal abnormalities in neurons and glial cells are believed to drive a variety of functional changes that often precede clinically visible vascular lesions in DR. Among the functional changes are those pointing to ganglion cell deficits as demonstrated by alterations in the pattern electroretinogram (ERG), altered microperimetry and perimetric testing, as well as increased implicit times and reduction in oscillatory potentials in the multifocal ERG (mfERG). Other less specific alternations have also been reported and those include abnormal dark adaptation, contrast sensitivity and colour vision.

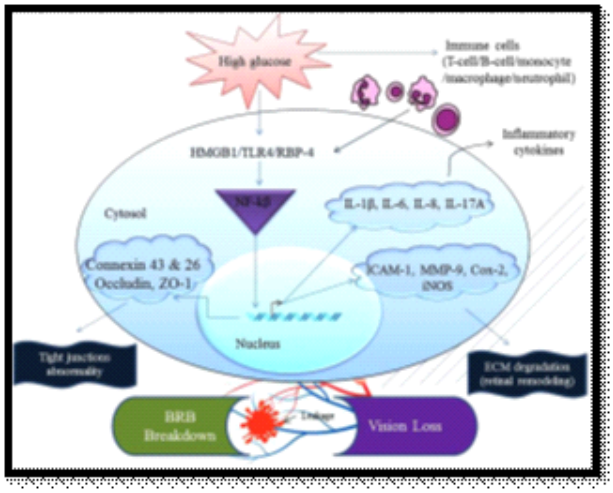
Beginning in the late 1990s, the concept that a proper function of a neurovascular unit was essential for normal retinal function developed. Furthermore the belief that low grade chronic inflammation was the key to changes in the vascular unit, as well as the neurodegenerative aspect of DR started to emerge and gain traction. This was followed by the postulate that glial cell dysfunction was a key element in the initiation and progression of DR. while retinal ganglion cells (RGCs) were the earliest cells affected and had the highest rate of apoptosis as a result.

An elevated rate of apoptosis has been also observed in the outer nuclear layer, with a reduction photoreceptors seen between 4 and 24 weeks after the onset of diabetes in addition to neuronal cell death.

Evidence of inflammation as a critical contributor to the development of DR is mounting as the mediating biomarkers such as inflammatory cytokines and chemokines are identified and found to be increased in serum and ocular samples from diabetic patients with DR.

These inflammatory cytokines include -lL-1β, lL-6, lL-8, TNF-a and MCP-1 which are elevated in ocular tissues from patients with DR. This low-grade inflam-mation plays a role in both the vascular pathology as well as the neuro degeneration.

Endothelial cells are extremely susceptible to cytokines, in vitro studies have demonstrated that endothelial cells respond more to cytokines rather than high glucose for induction of inflammatory pathways and apoptotic changes, suggesting that diabetes related endothelial injury is primarily due to glucose-induced cytokine released by neighboring cells rather than a direct effect of hyperglycemia on endothelial cells themselves.



This cytokine stimulation results in leukostasis, resulting in decreased vascular wall integrity leading to increased vascular permeability. This allows extravasation of vascular fluid and migration of additional immune cells (neutrophils, monocytes) into the tissue. Concurrently, loss of capillary pericytes causes endothelial cell degeneration, which has been associated with accumulation of vacuoles and debris in the basement membrane resulting in its thickening and ultimately vascular lumen occlusion. The resulting retinal ischemia and hypoxia are strong stimuli for endothelial and glial cells to promote the expression of VEGF and other pro-inflammatory cytokines such

as TNF-a, lL-6 and lL-1β and the inflammation becomes self-propagating.

In addition to the vascular perturbations, it has been shown that neurosensory retina is profoundly altered in diabetes. An emerging issue in DR research is the focus on the precise relationship between inflammatory alternations and the loss of neuronal function. Increased VEGF, and other factors can lead to alternations and the loss of alternation of the BRB and induction of inflammatory responses. In addition, it has been recently demonstrated that pro-inflammatory transcription factor is also activated in neurons during diabetes. Finally, photoreceptors contribute to the inflammatory response in DR. They are highly oxygen demanding cells and hence have shown to be the main sources oxidative stress in the retina in DR.

Role of glial cells in DR

The two main retinal glial cells are muller glial cells (MGCs) and astrocytes. Together with microglia, the main resident immune cells in the retina, they not only provide structural support, but they are also involved in maintaining the complex homeostasis of the retina by regulating the metabolism, the phagocytosis of debris and the cycling of neurotransmitters and trophic factors. Initiation of inflammation is now thought to be due to glial cell activation. Glial cells are the interface between the neurons and the vasculature and are thus key regulators of neuronal function. Diabetes also affects the neuro-glial unit by disrupting the communication between neurons and glia. In DR, accumulating evidence over the past decades have revealed that dysfunctional neuro glial crosstalk, in part associated with inflammation, plays a critical role in the early course of the disease[4].

How does all this help in the treatment of DR?

Considering the role of inflammation in the pathogenesis of DR, inhibiting the inflammatory pathway has been an appealing treatment option for DR in future practices. As a result, we understand the role of steroids in the management of DR in blocking some of the key pathways of inflammatory mediation. However, clinicians vary about using it due to its properties of cataractogenesis and the steroid response on the IOP. However other methods of blocking inflammatory pathways are being investigated. Preclinical studies with topical administration of NSAIDs such as specific COX-2 inhibitors were shown to reduce signs of DR. Canakinumab which is a selective lL-1β antibody(Novartis, Basel, Switzerland) has shown promising effects on diabetic macular edema reduction. Similarly, a clinical trial in DME patients comparing an oral inhibitor targeting the receptors for MCP-1, from (Pfizer, New York, NY, USA) to intravitreal anti-VEGF therapy showed non-inferiority of the study drug regarding gain in visual acuity and reduction in central retinal thickness. Other molecules targeting various mediations are also being investigated.

In conclusion, we should see the emergence of new molecules in the coming two decades which would not only target initiation of DR there by largely mitigating the dreaded clinical manifestations but also new drug delivery systems which will not only increase patient compliance but also reduce the economic burden.

References

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