

## The Importance of Physiologic Mechanisms in the Treatment of Diabetic Macular Edema

### *Diyabetik Maküla Ödemi Tedavisinde Fizyolojik Mekanizmaların Önemi*

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#### ABSTRACT

There are multiple different treatment options of diabetic macular edema. Therefore it is important to understand the physiological mechanism of these treatment modalities when deciding the appropriate combination of treatment options. We herein present a brief review of available treatment options of diabetic macular edema with particular consideration of the mechanisms of action.

**Keywords:** Diabetes, Macular edema, Starling's law

#### ÖZET

Diyabetik maküla ödeminde tedavi seçenekleri fazladır. Bu yüzden diyabetik maküla ödemi tedavi seçenekleri arasında doğru kombinasyona karar verirken altta yatan fizyolojik mekanizmaları anlamak önemlidir. Burada altta yatan fizyolojik mekanizmaları göz önünde bulundurarak diyabetik maküla ödeminin tedavi seçeneklerini kısaca gözden geçirdik.

**Anahtar Kelimeler:** Diyabet, Maküla ödemi, Starling yasası

#### INTRODUCTION

Diabetic macular edema (DME) is the most common cause of reduced vision in diabetic patients. About one in four diabetic patients has a risk of developing DME during a lifetime<sup>1</sup>. Most frequently used follow up test for macular diseases are Amsler grid test, 10/2 visual field testing<sup>2</sup>. Optical coherence tomography (OCT) is a new retinal imaging technique that produces cross-sectional images of the retina and is frequently used in DME<sup>3</sup>. Photocoagulation was established as an effective treatment in the 1980s and is still being one of the options for DME<sup>4</sup>. Other treatment modalities which have emerged in the more recent years are intravitreal steroids, anti-vascular endothelial growth

factor (VEGF) drugs and the release of vitreoretinal traction by means of surgical pars plana vitrectomy.

Generally, edema is defined as an abnormal accumulation of water in a tissue. Starling in 1896 defined the forces that transport water between the vascular space and tissue interstitial space. The forces are hydrostatic and osmotic. In homeostasis, the hydrostatic pressure gradient and the osmotic pressure gradients between blood vessel and tissue are balanced. But this balance can be disturbed if either pressure gradient is changed. Either an increase in the hydrostatic pressure gradient or a decrease in the osmotic pressure gradient induces edema.

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Due to the concentration of albumin, the osmotic pressure in blood is higher than that in the tissue interstitial space and this pulls water back from the tissue interstitial space into the blood circulation and reduces edema. DME is associated with increased leakage of the macular capillaries, as is seen on fluorescein angiography and fluorophotometry<sup>5</sup>. The physiological importance of capillary leakage is the leakage of macromolecules, predominantly albumin, not just water from the blood into the tissue interstitial space. The accumulation of albumin in the tissue interstitial space increases the osmotic pressure in the tissue and reduces the osmotic pressure difference between the interstitial space and blood. The smaller osmotic pressure gradient is less effective in pulling water back to the blood stream from the tissue interstitial space and consequently water accumulates in the tissue interstitial space and edema develops. VEGF is very effective in increasing the permeability of retinal capillaries and reduces the osmotic gradient that should pull water back into capillaries. VEGF is a growth factor for new blood vessel formation. The newly-formed blood vessels are very leaky and this results in edema. Therefore anti-VEGF agents are used in the treatment.

#### **Treatments Available that Increase Osmotic Pressure Gradient**

##### a) Photocoagulation

Vascular endothelial growth factor production is controlled by oxygen tension in the tissue; the production of VEGF is induced by hypoxia. It is shown that breathing pure oxygen reduces DME<sup>6</sup>. Retinal laser photocoagulation also raises the oxygen tension in the retina and reduces hypoxia. This is because the destruction of the photoreceptors located in the peripheral retina reduces the oxygen consumption of the retina overall and allows an oxygen flux to diffuse from the choroid through the glial laser scar into the inner retina in the macular area without being consumed by the photoreceptors located in the peripheral retina. This increases the oxygen tension in the inner retina and thus decreases the VEGF production.

##### b) Vitrectomy

In vitrectomy, the viscous vitreous gel is replaced by low viscosity saline, and that allows faster transport of other molecules, such as VEGF, which can diffuse more readily from the retina into the vitreous cavity. This reduces the VEGF concentration in the retina<sup>7</sup>. Reducing VEGF concentration in the retina reduces, in turn, capillary leakage of high molecular weight proteins such as albumin.

##### c) Anti-VEGF treatment

The injection of VEGF antibodies into the vitreous cavity, such as bevacizumab and ranibizumab, has similar consequences to vitrectomy, because effective free VEGF concentration is reduced. Free VEGF in the vitreous gel is bound by the antibody, thus lowering the

concentration of free VEGF in the vitreous cavity and increasing the diffusion and clearance of VEGF from the retina, thus lowering its concentration. In addition, ranibizumab penetrates deeper into the retina and also binds VEGF in the retina itself.

##### d) Steroids

Corticosteroids suppress inflammation by inhibiting multiple inflammatory cytokines, resulting in decreased migration of inflammatory cells and capillary leakage. Moreover, corticosteroids may also have an inhibitory effect on the VEGF pathway<sup>8</sup>. New intravitreal implants that provide sustained release of steroids at therapeutic levels for 6 months to 3 years are currently being evaluated for the treatment of DME.

#### **Treatments Available that Reduce Hydrostatic Pressure Gradient**

##### a) Arterial Blood Pressure

Arterial hypertension is a risk factor for DME. It is also established that reducing arterial blood pressure lowers the hydrostatic pressures that push water out of capillaries and therefore reduces DME<sup>1</sup>.

##### b) Vitreoretinal Traction

Vitreoretinal traction reduces interstitial tissue hydrostatic pressure and therefore the hydrostatic pressure gradient causing water to go out of the capillaries increases. Procedures like intracapsular cataract extraction as an example produces loss and therefore vitreous traction and complications like cystoid macular edema more frequently seen<sup>9</sup>. It is known that releasing any of the vitreoretinal tractional forces by means of vitrectomy, improves resolution of the macular edema and restores visual acuity<sup>10-12</sup>.

##### c) Vasoconstriction

Retinal laser photocoagulation and vitrectomy increase the oxygen tension in the inner retina. Increased oxygen tension results in an autoregulatory vasoconstriction, where arterioles constrict and their resistance increases. This results in a decrease in hydrostatic pressure in capillaries and a decrease in the hydrostatic gradient between the vascular compartment and tissue interstitial space, thus reducing water flux from vessel to tissue and decreasing edema. Vasoconstriction in the retina is seen not only following laser treatment but also following intravitreal triamcinolone and bevacizumab injections.

#### **CONCLUSION**

The pathogenesis of macular edema includes multiple insults to normal retinal function and there are multiple treatment options available, but still as a first step we must take the main physiologic mechanisms into consideration while deciding on the best form of treatment, though this step is easily overlooked.

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