
بسم الله الرحمن الرحيم
"وما أوتيتم من العلم إلا قليلا"
)الإسراء ٨٥(

Pathophysiology of Diabetic Retinopathy

Now and then

By
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MD Cairo University
FRSC Glasgow.

The aim of this presentation is to introduce

A new understanding
of the disease mechanisms

New methods for early Detection of DR

Novel treatment approaches

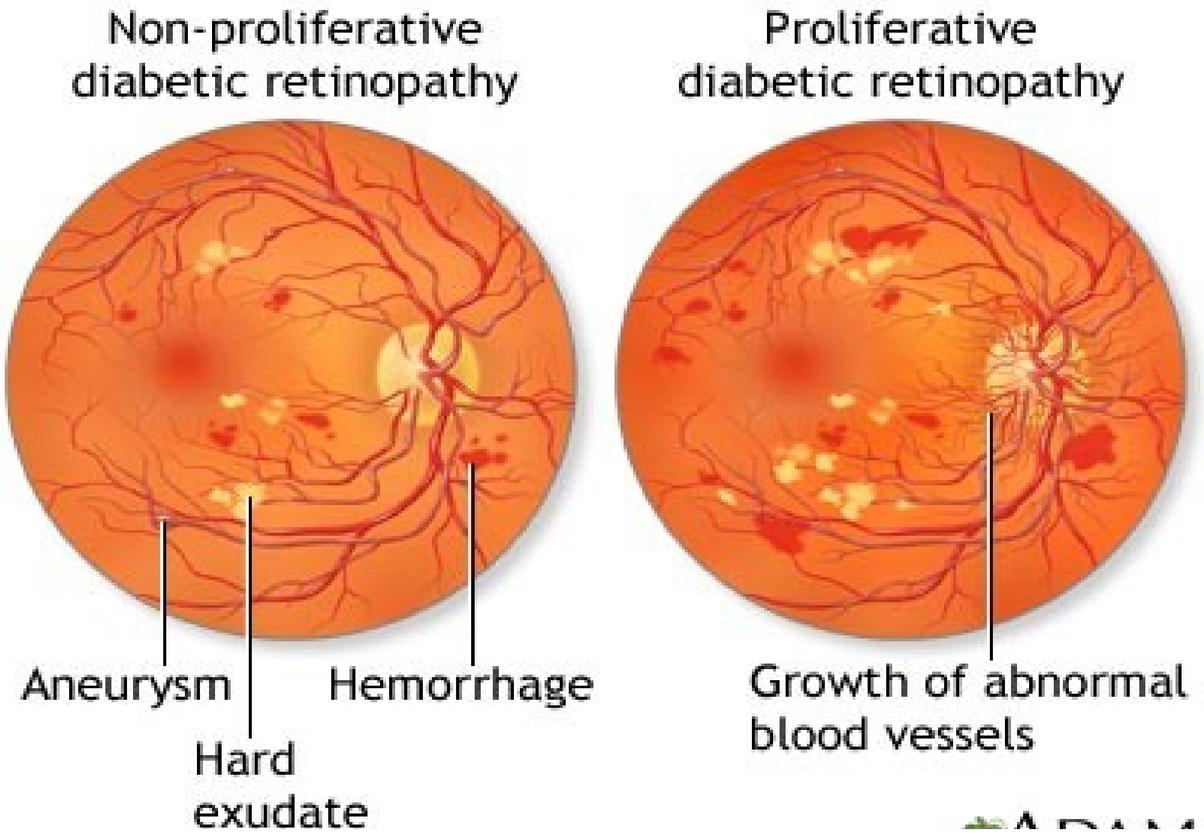
The aim of this presentation is to introduce

A new understanding
of the disease mechanisms

New treatments for early Dementia of IBM

New treatments for others

Now



DR has been traditionally regarded as purely microvascular disease in the retina , and clinically the diagnosis and classification of DR depends on retinal microvascular lesions observed by ophthalmic fundus examination.

Then

Recent studies have shown that DR is a complex neurovascular disorder that affects not only vascular structures but also neural tissue of retina i.e. The retinal neurovascular unit.

What is The Neurovascular Unit ?

Pathophysiology of Diabetic Retinopathy , Now and then

The Neurovascular Unit

- The term neurovascular unit was first applied to the blood-brain barrier on 2005.
- It describes the relationship between brain cells and their blood vessels, with regulating cerebral blood flow and blood-brain barrier.
- The term was then applied by Dr.Eric Newman to the retina on 2007.
- In the retina refers to the detailed functional relationship between neurons, glial cells and blood vessels.
- In DR, these interactions are disturbed leading to both vascular and neuronal dysfunction.

The Retinal Neurovascular Unit

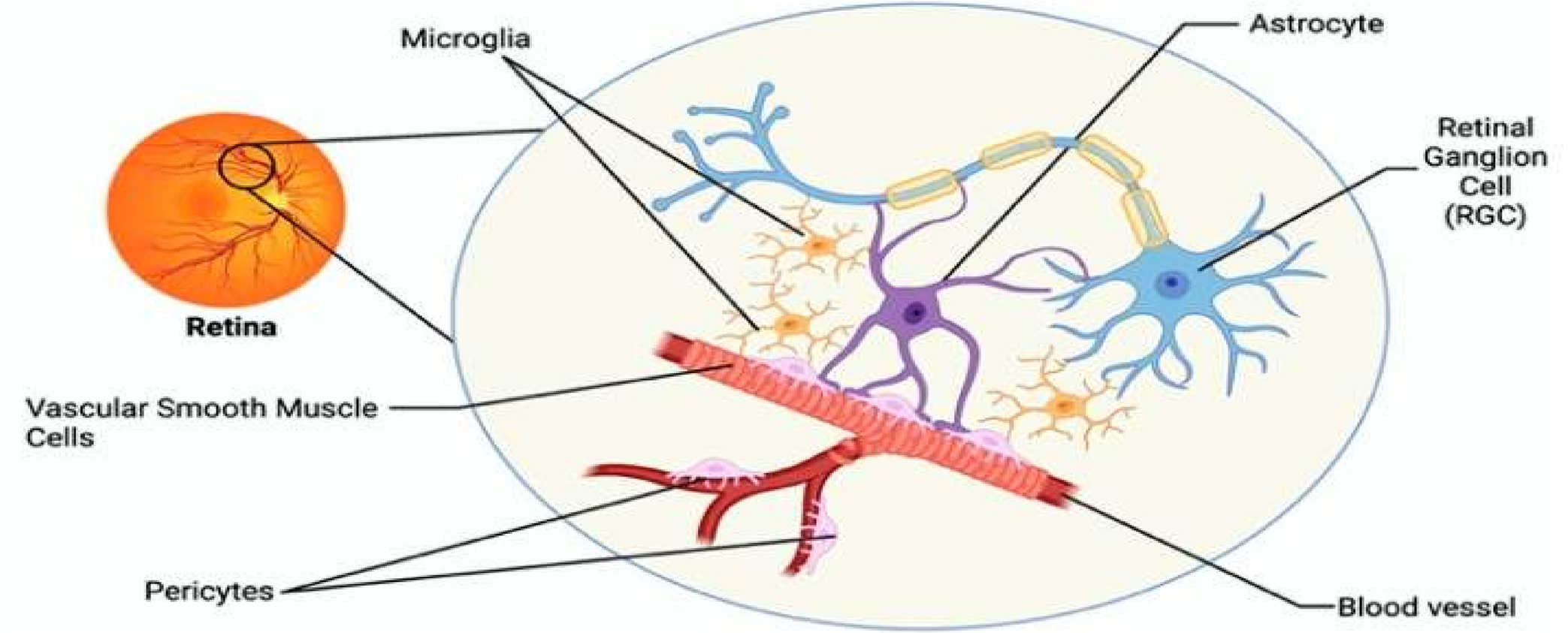


Figure 1. The retinal neurovascular unit. The retinal NVU consists of three main cell types: neurons (retinal ganglion cells; RGCs), glial cells (including astrocytes and microglia), and vascular cells (including endothelial cells, vascular smooth muscle cells, and pericytes).

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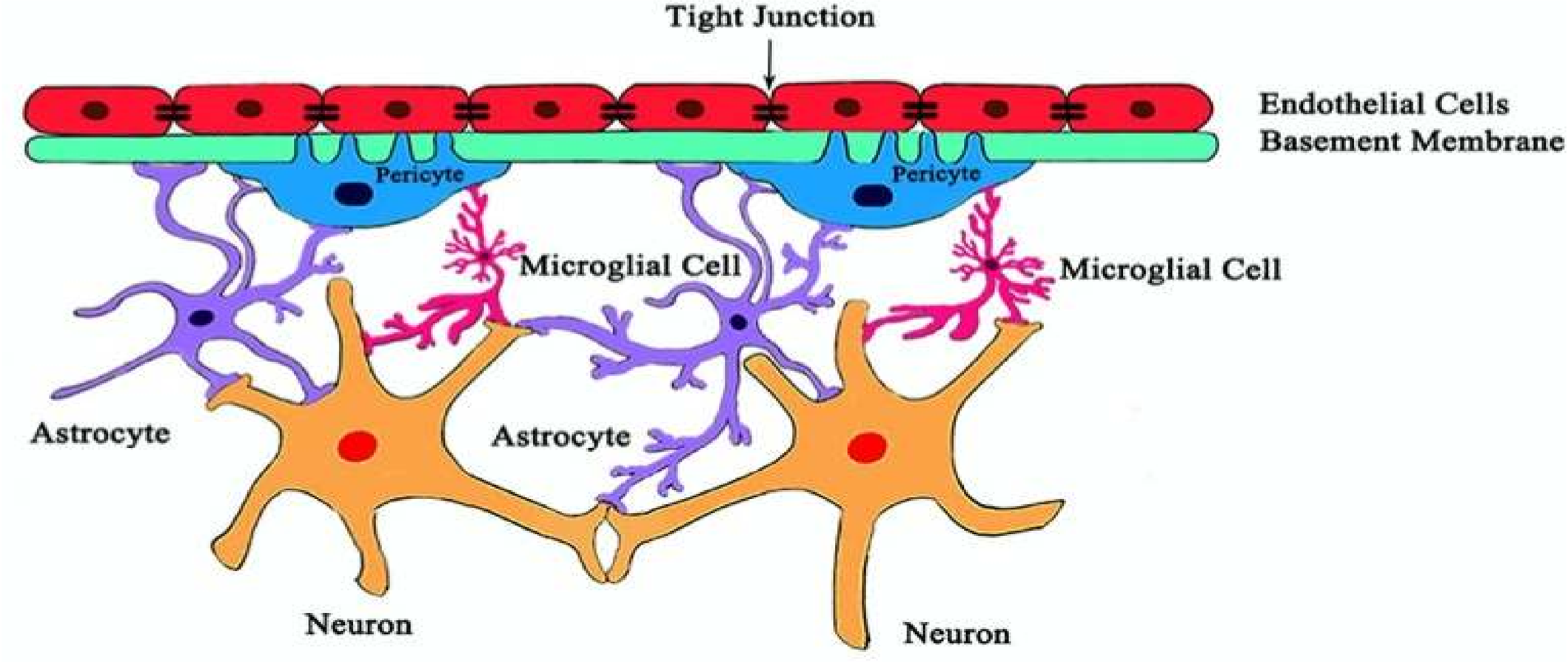
The Retinal Neurovascular Unit



Neurons are closely associated with neighboring pericytes, glial cells and microglial cells. Pericytes directly communicate with endothelial cells through peg-socket contacts. Glia and microglial cells are connected with both neurons and retinal pericytes.

Pathophysiology of Diabetic Retinopathy , Now and then

What is the function of The Neurovascular Unit?

Pathophysiology of Diabetic Retinopathy , Now and then

The function of The Neurovascular Unit

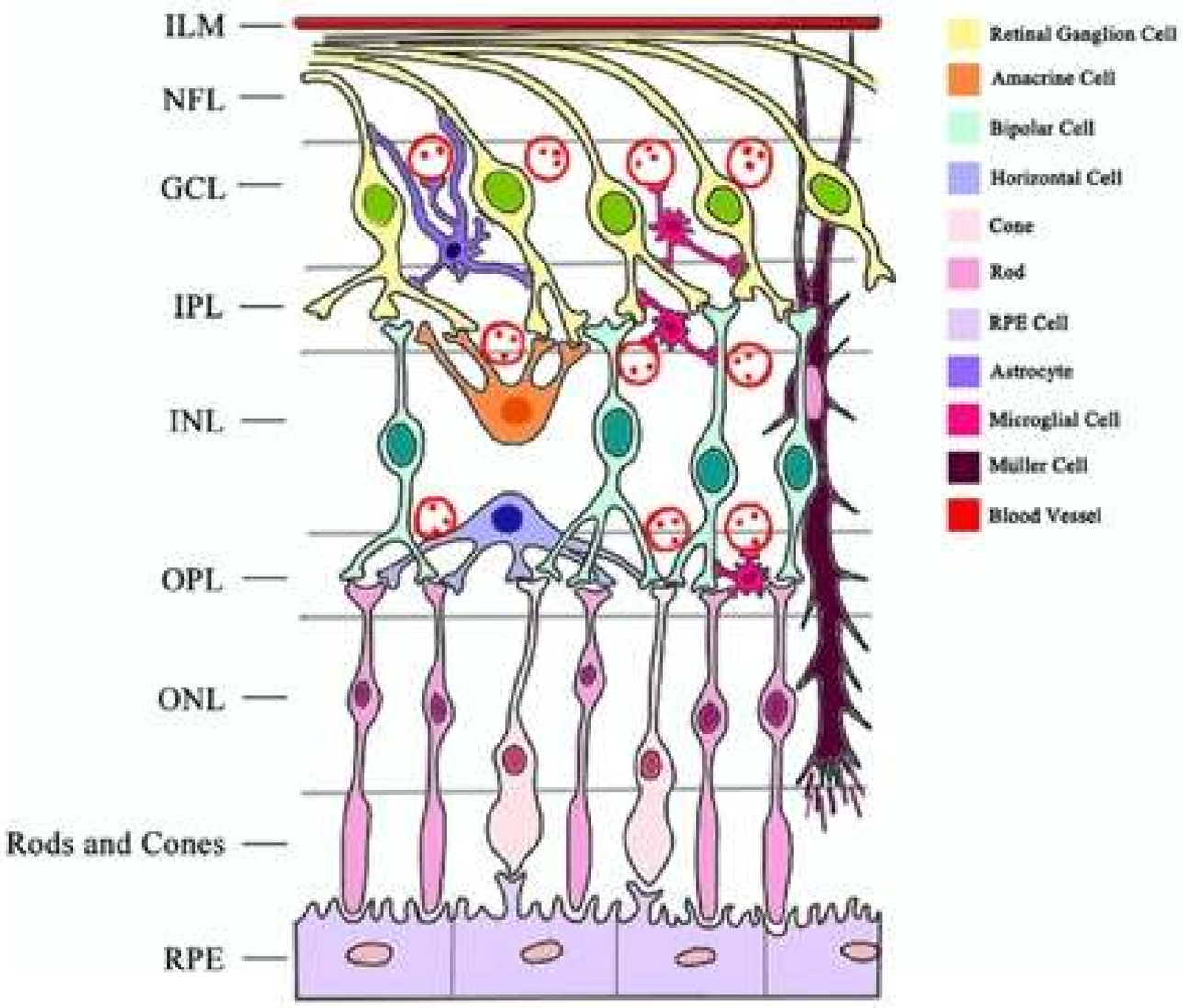
The neurovascular unite plays a crucial rule in **:**

- Maintaining the **blood retinal barrier** .
- **Regulating blood flow** to meet the metabolic demands of the retinal tissues.
- **Supporting** communication between the vascular and neural tissues.

The function of The Neurovascular Unit (NVU) in Retina

1- The Neurons

Transmit the electrical impulses converted by photoreceptors from light signals to the brain to form vision.



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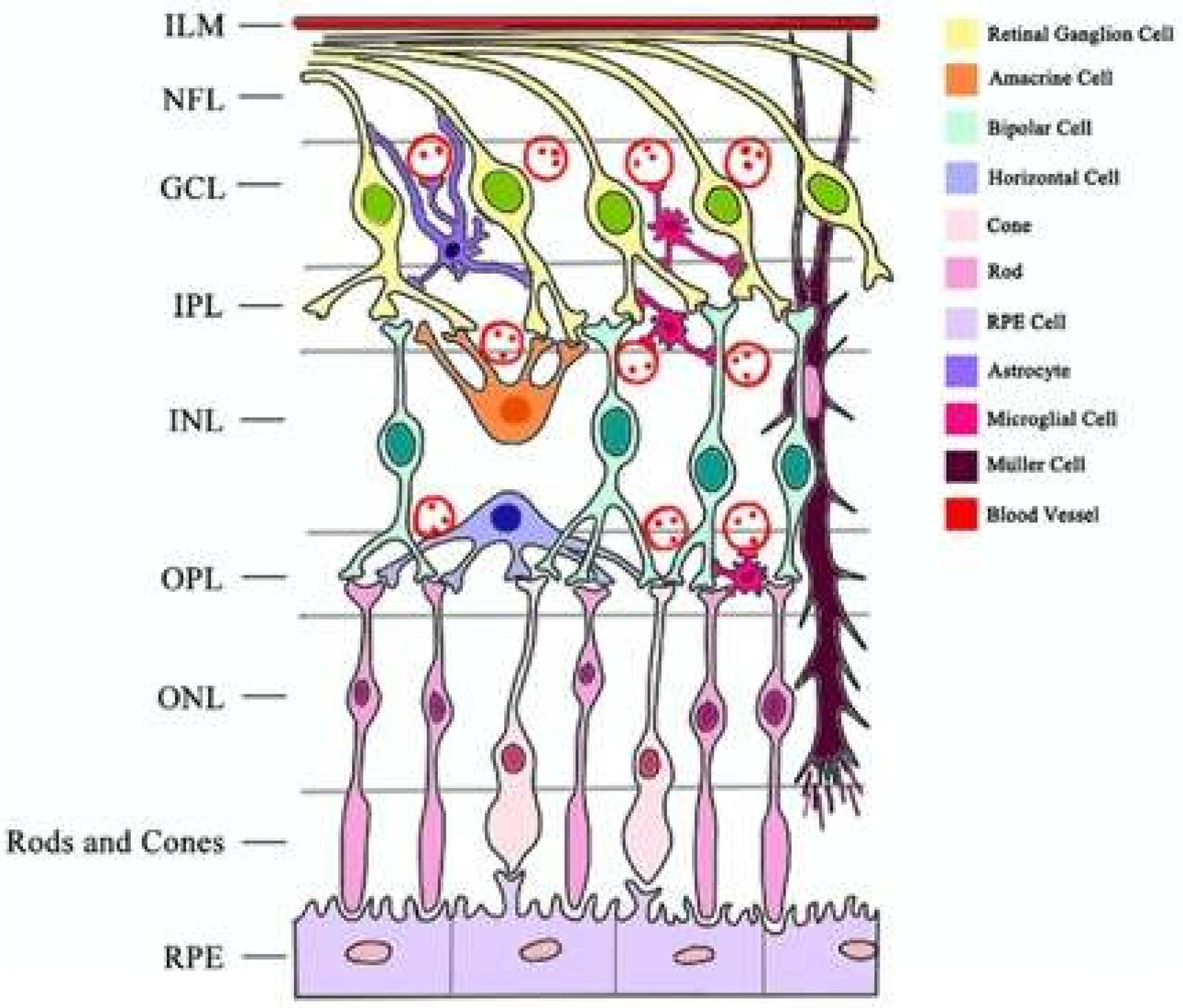
The function of The Neurovascular Unit (NVU) in Retina

2- Muller Cells

The major support glial cells in the Retina.

(glia from the Greek word meaning glue)

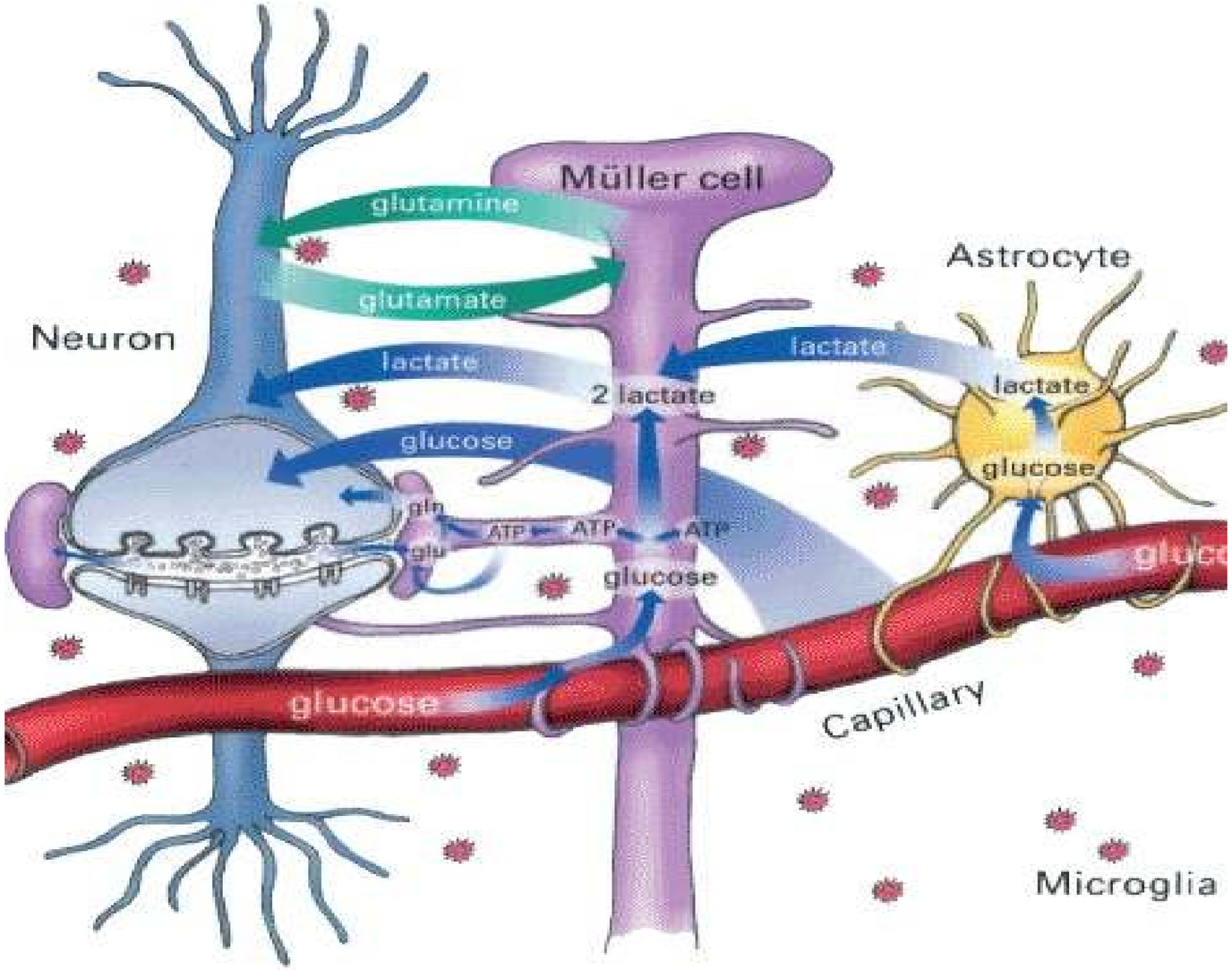


Pathophysiology of Diabetic Retinopathy , Now and then

The function of The Neurovascular Unit (NVU) in Retina

2- Muller Cells

- Their processes wrap around the BV and coordinate vascular responses to provide nutrients to the outer retina.
- Maintain the extra cellular PH value.
- Recycle transmitter.



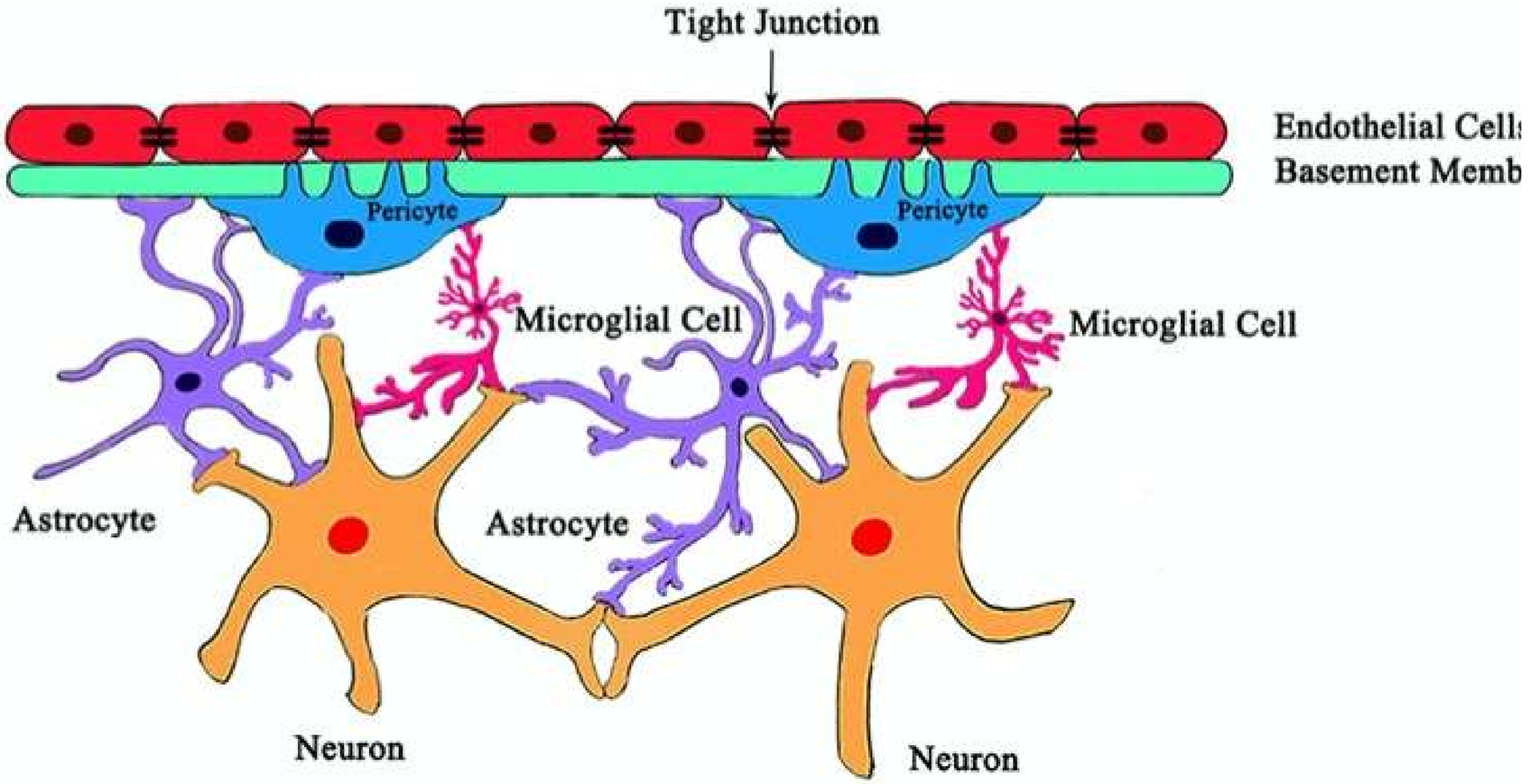
Pathophysiology of Diabetic Retinopathy , Now and then

The function of The Neurovascular Unit (NVU) in Retina

3- Astrocytes

Encircle the neuronal axons and vessels to form an irregular network to:

- ❖Support the integrity of inner BRB.
- ❖Play a role in the maintenance of vascular tone by autoregulation.



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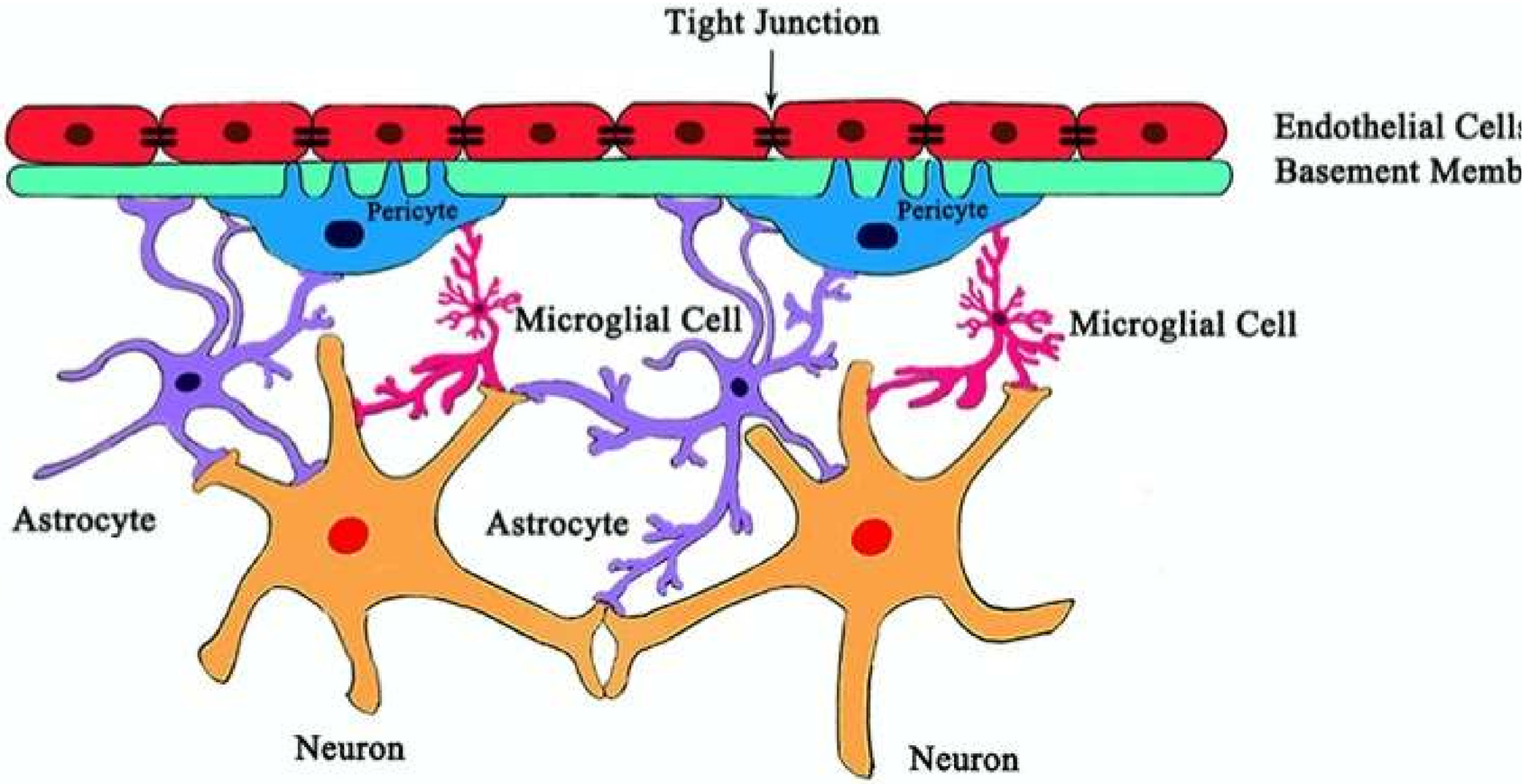
The function of The Neurovascular Unit (NVU) in Retina

4- Microglial cells

Are in direct contact with neurons and retinal pericytes.

- ❖ They are phagocytic cells (considered the local immune cells of the retina).
- ❖ In physiologic condition and in acute inflammation it produce anti-inflammatory cytokines and neurotrophic factors that support neural retinal health.
- ❖ But in chronic retinal diseases like DR it secrets a large numbers of pro inflammatory cytokines, affecting hemostasis of NVU.



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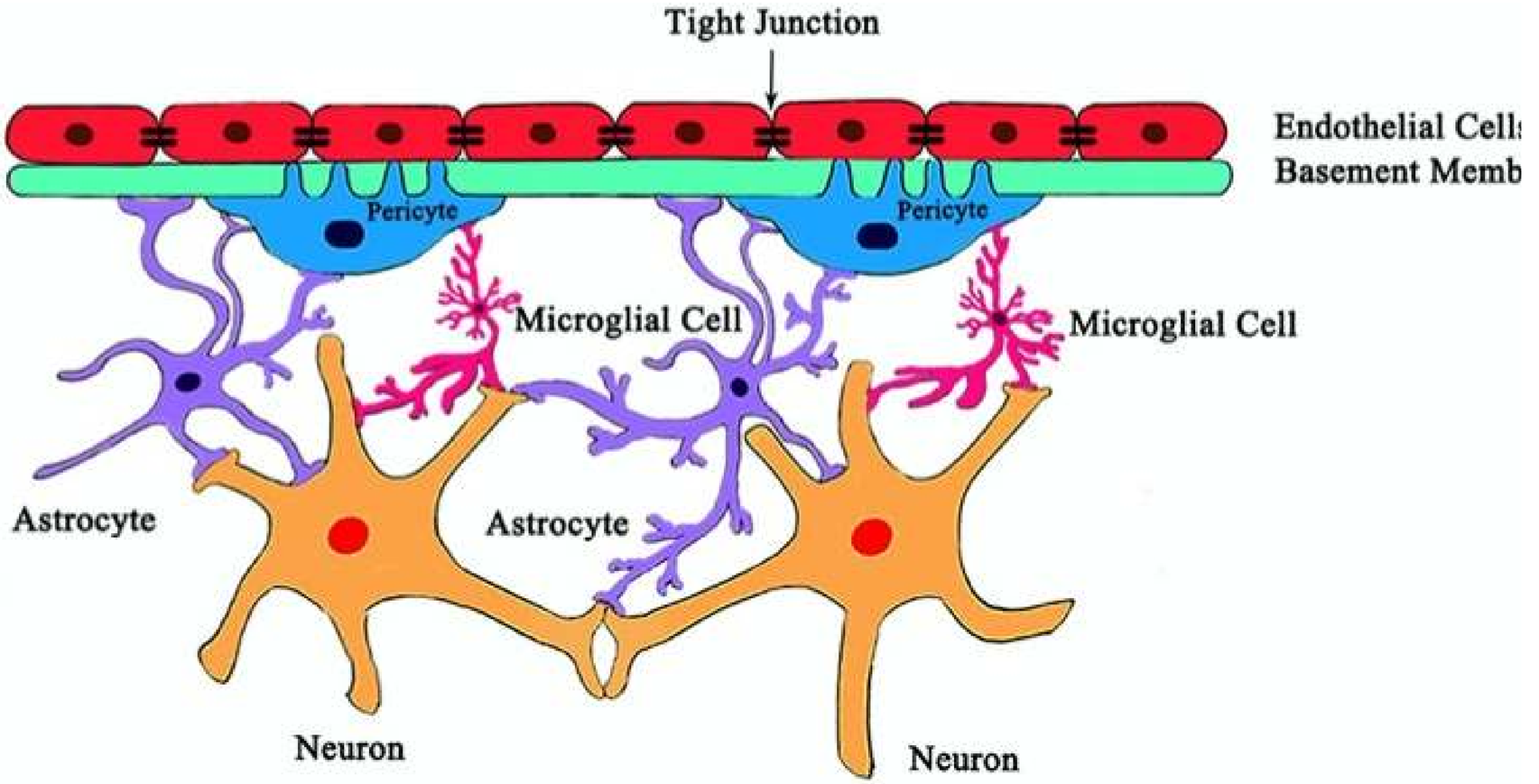
The function of The Neurovascular Unit (NVU) in Retina

5- Vascular cell

- ❖ Endothelial cells: form the inner BRB.
- ❖ Pericytes (contractile): envelop retinal capillaries to:
- Maintain the inner BRB and neurovascular unit (structural support of BV).
- Control blood flow in response to initial systemic and local messenger molecules.



Pathophysiology of Diabetic Retinopathy , Now and then

Pathological feature of Neurovascular Unit in DR

Pathophysiology of Diabetic Retinopathy , Now and then

Pathological feature of Neurovascular Unit in DR

1. Neurodegeneration
2. RPE and Choroid Pathology
3. Reactive gliosis
4. Immuno-inflammation
5. Microvascular Pathology

Pathological feature of Neurovascular Unit in DR

Impact on the retina clinically

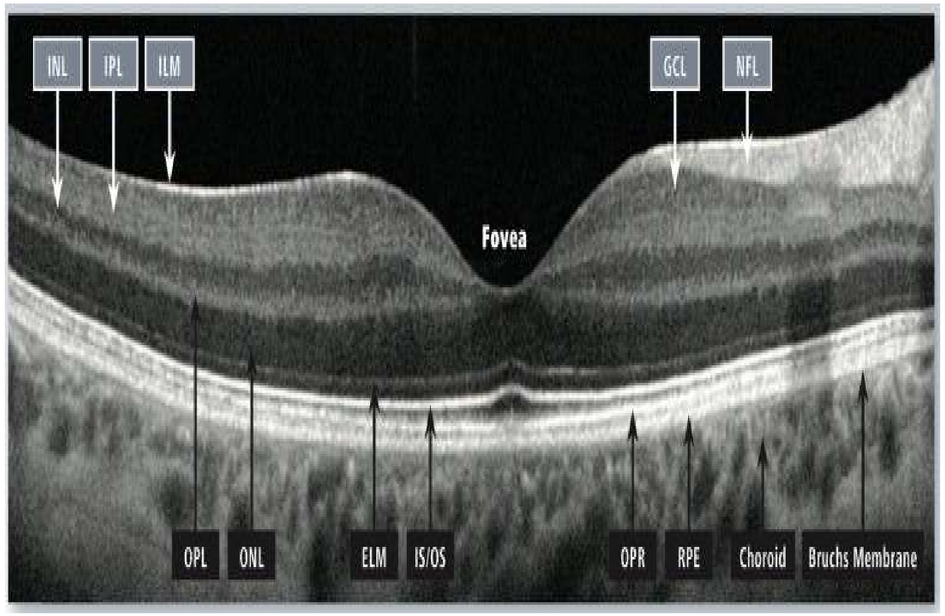
1. Adaptive changes (Compensated- NO DR)

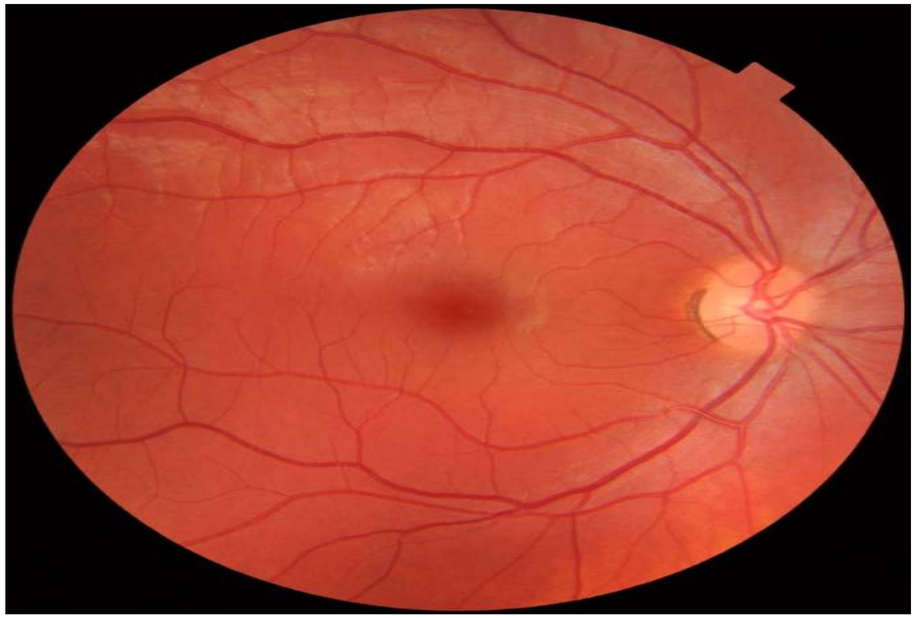
Occurs within the first few weeks to months after the onset of Diabetes.

- Reduced electrical activities.
- Reduce synthetic activities (protein , lipid, autophagy and apoptosis).
- Impaired auto regulation.

This reduce retinal energy demand and allow retinal neurons to survive in the face of diabetes

Vision Intact





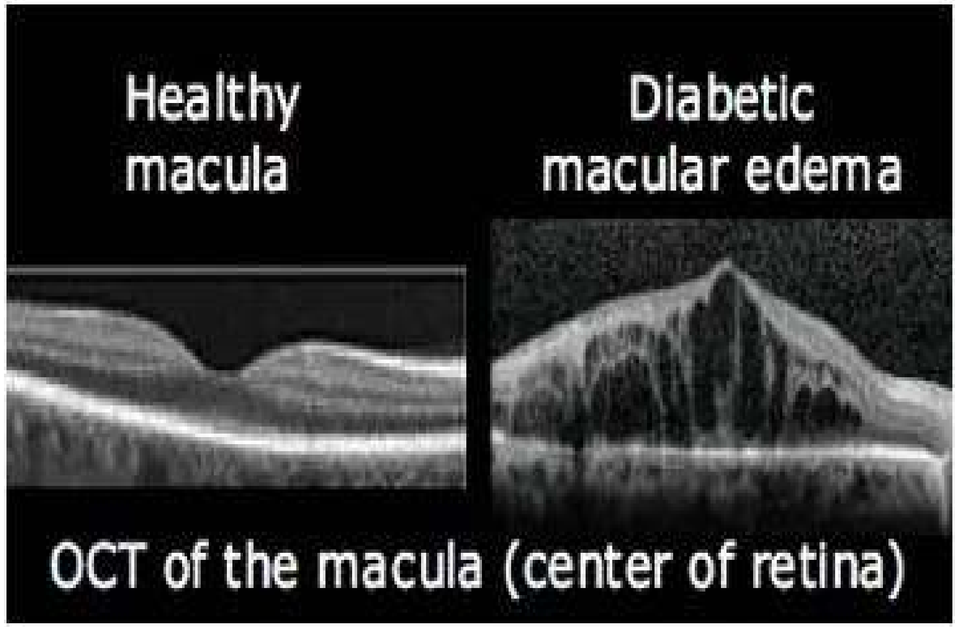
Pathophysiology of Diabetic Retinopathy , Now and then

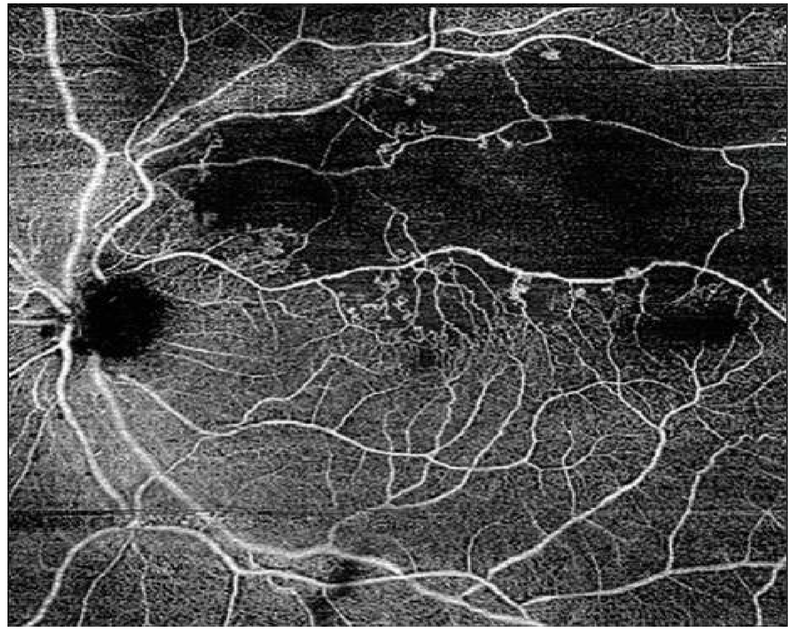
Pathological feature of Neurovascular Unit in DR

2. Adaptive changes (Decompensated- NPDR)

- Occurs after 5 - 10 years.
- Venous dilatation, Retinal Hemorrhage,
- Micro aneurysms, cotton wool spots ,
- ME and vascular non- perfusion.

Vision impaired





Pathophysiology of Diabetic Retinopathy , Now and then

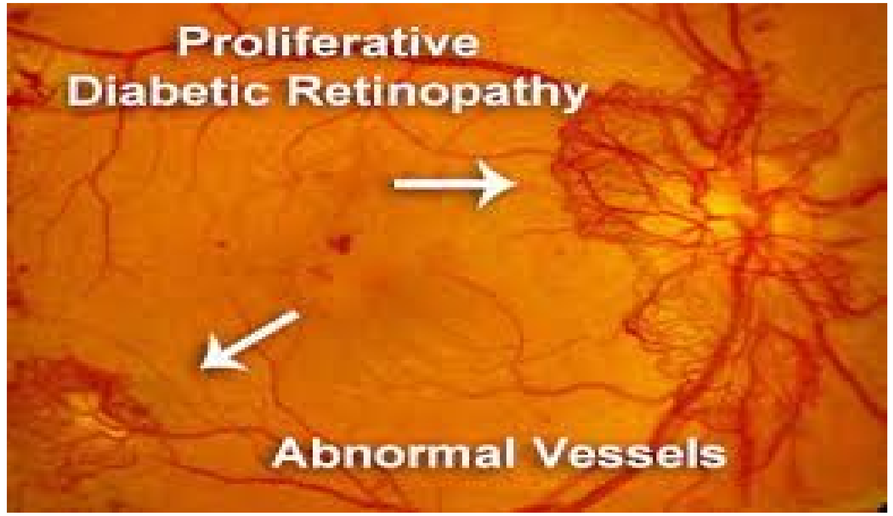
Pathological feature of Neurovascular Unit in DR

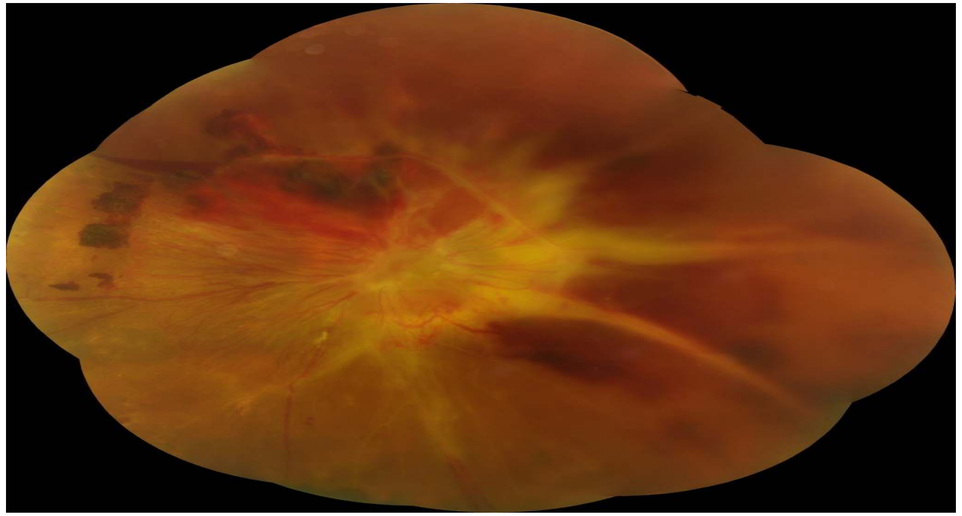
3. Maladaptive changes

Aberrant repair= PDR

Neovascularisation.

- Gliosis.
- Fibrosis.
- **Loss of Visual Acuity.**





Pathophysiology of Diabetic Retinopathy , Now and then

A new understanding of the disease mechanisms

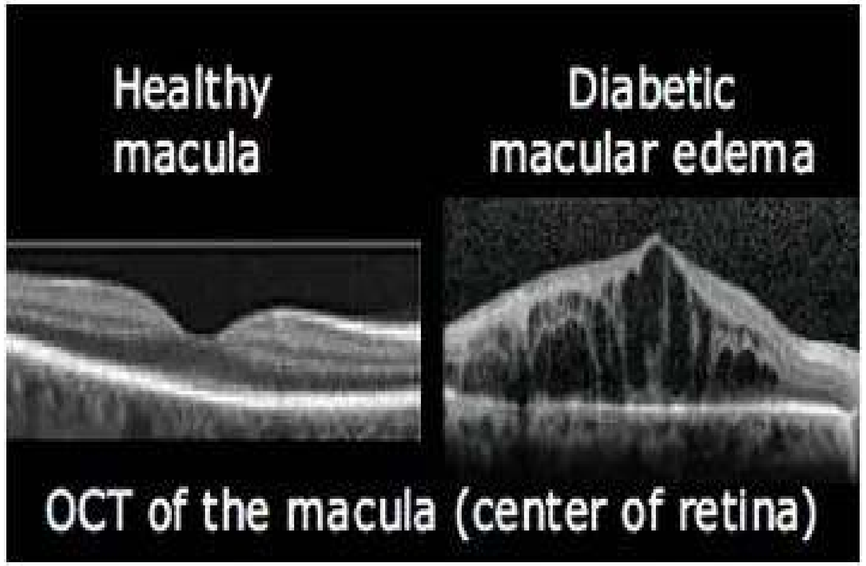
New methods for early Detection of DR

New treatment modalities

Pathophysiology of Diabetic Retinopathy , Now and then

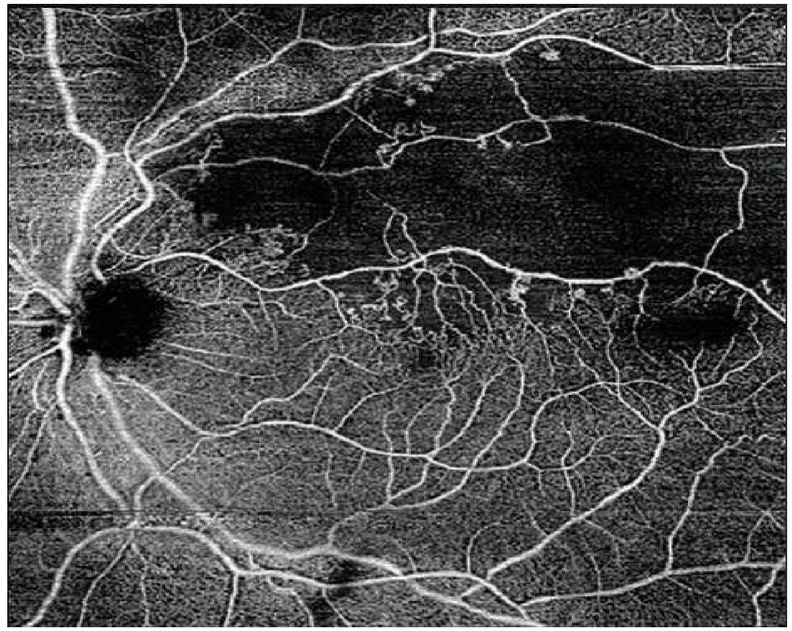
Now

Fundus examination



OCT

FFA



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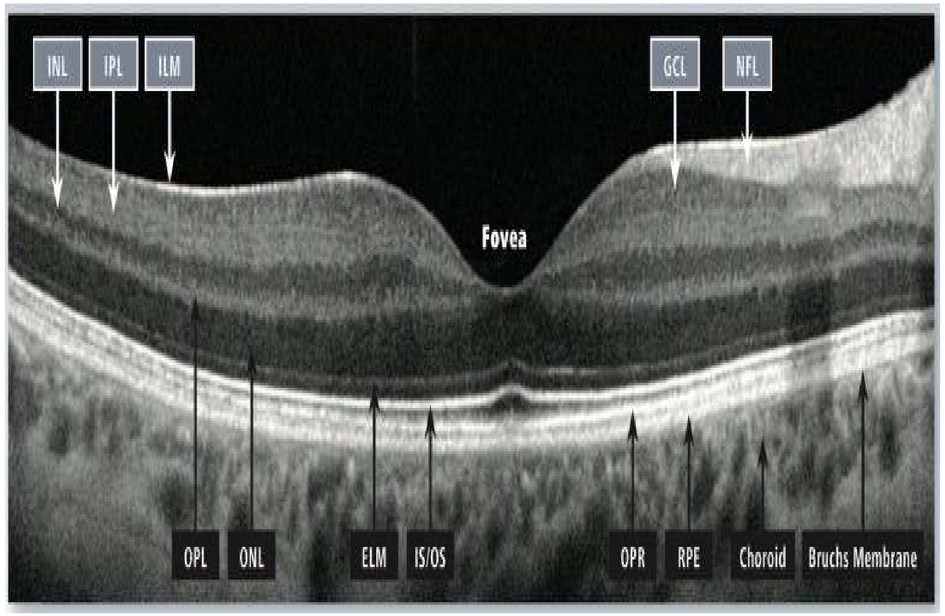
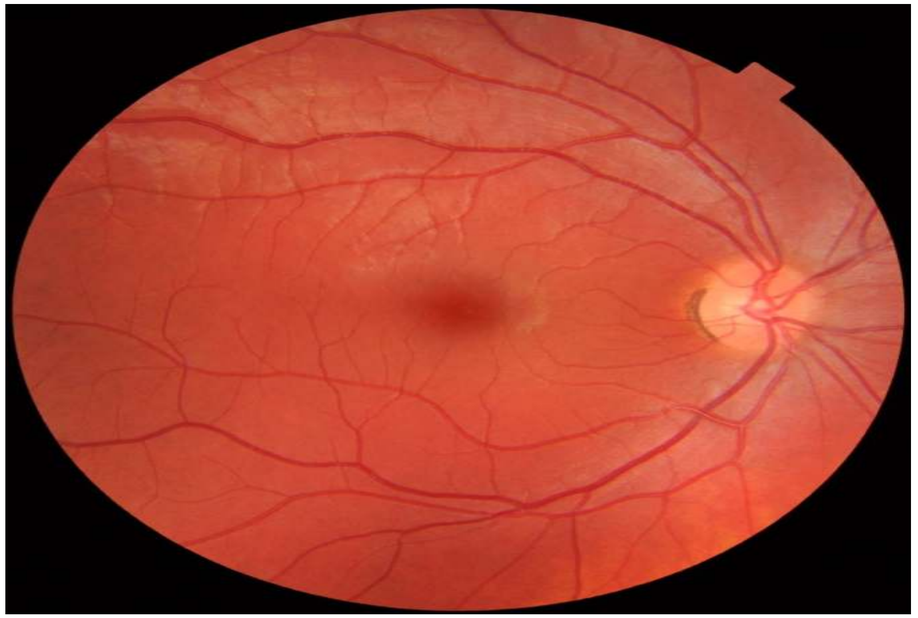




Pathophysiology of Diabetic Retinopathy , Now and then

Then

Early Diagnosis=Detecting the very early changes

1) **Electrophysiological changes:**

- **Reduced dark adaptation** (both photoreceptors and RPE cells are impaired).
- **Frequency doubling perimetry** (assesses primarily the inner retina) : marked loss of visual field sensitivity.
- **Standard photopic perimetry**: marked loss of visual field sensitivity.

2) **Retinal imaging:**

- **SD- OCT:** thinning of the macula.

3) **Artificial intelligence application in screening.**

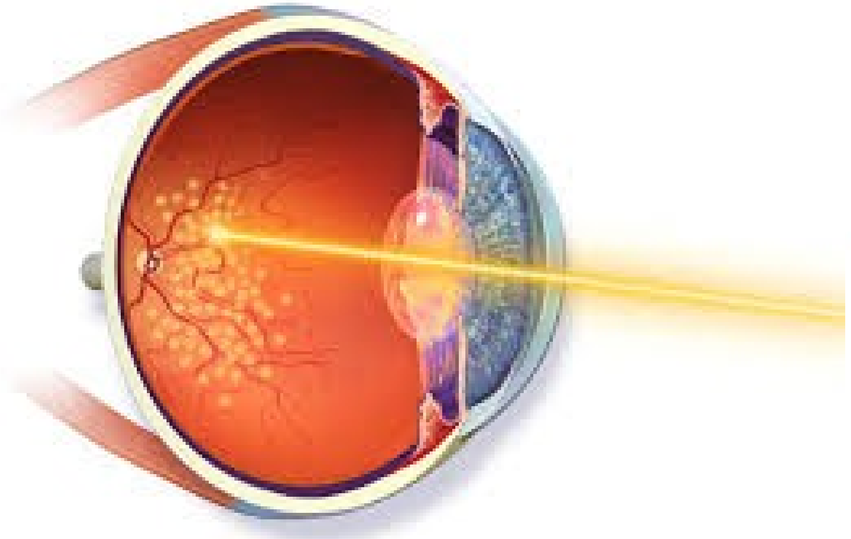
A new understanding of the disease mechanisms

New methods for early detection of DR

New treatment modalities

Now

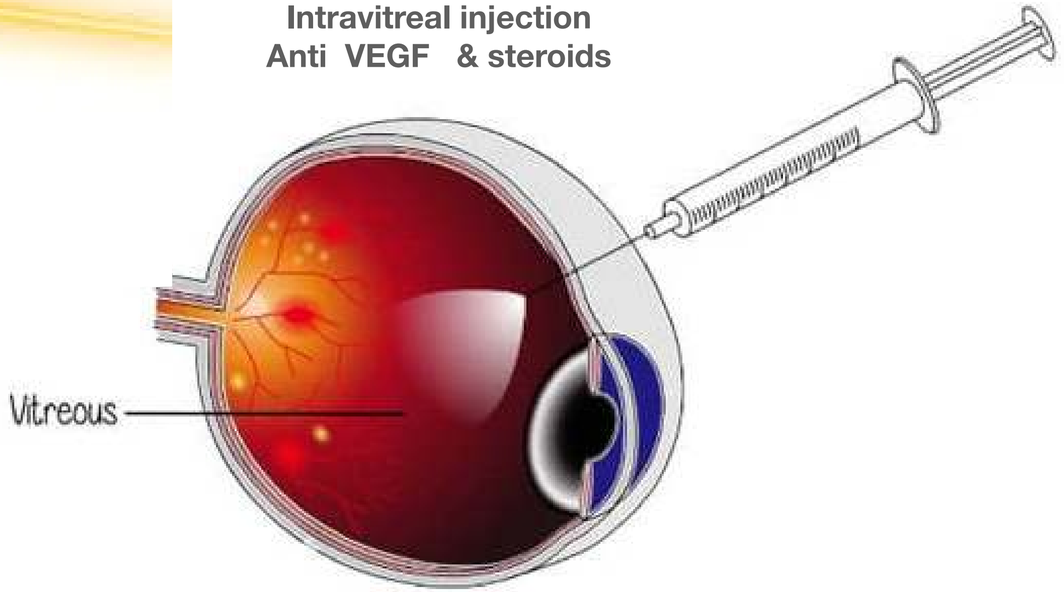
Traditional treatment Methods

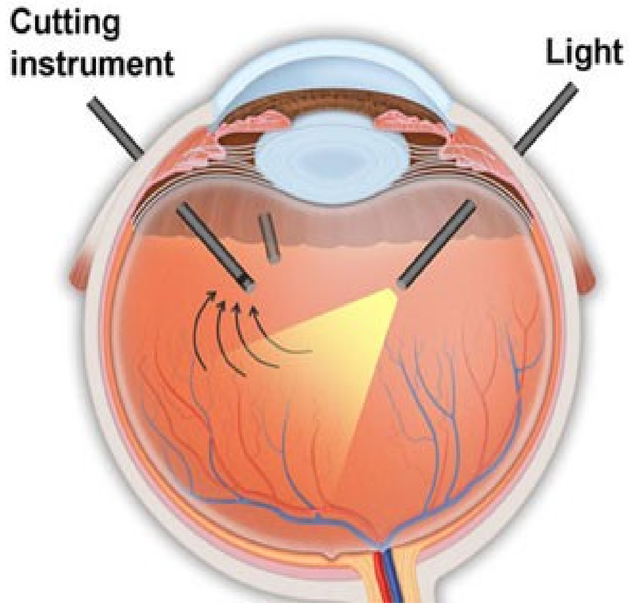


Retinal photocoagulation

Irreversible tissue damage

Intravitreal injection
Anti VEGF & steroids





Vitrectomy

Pathophysiology of Diabetic Retinopathy , Now and then

Then

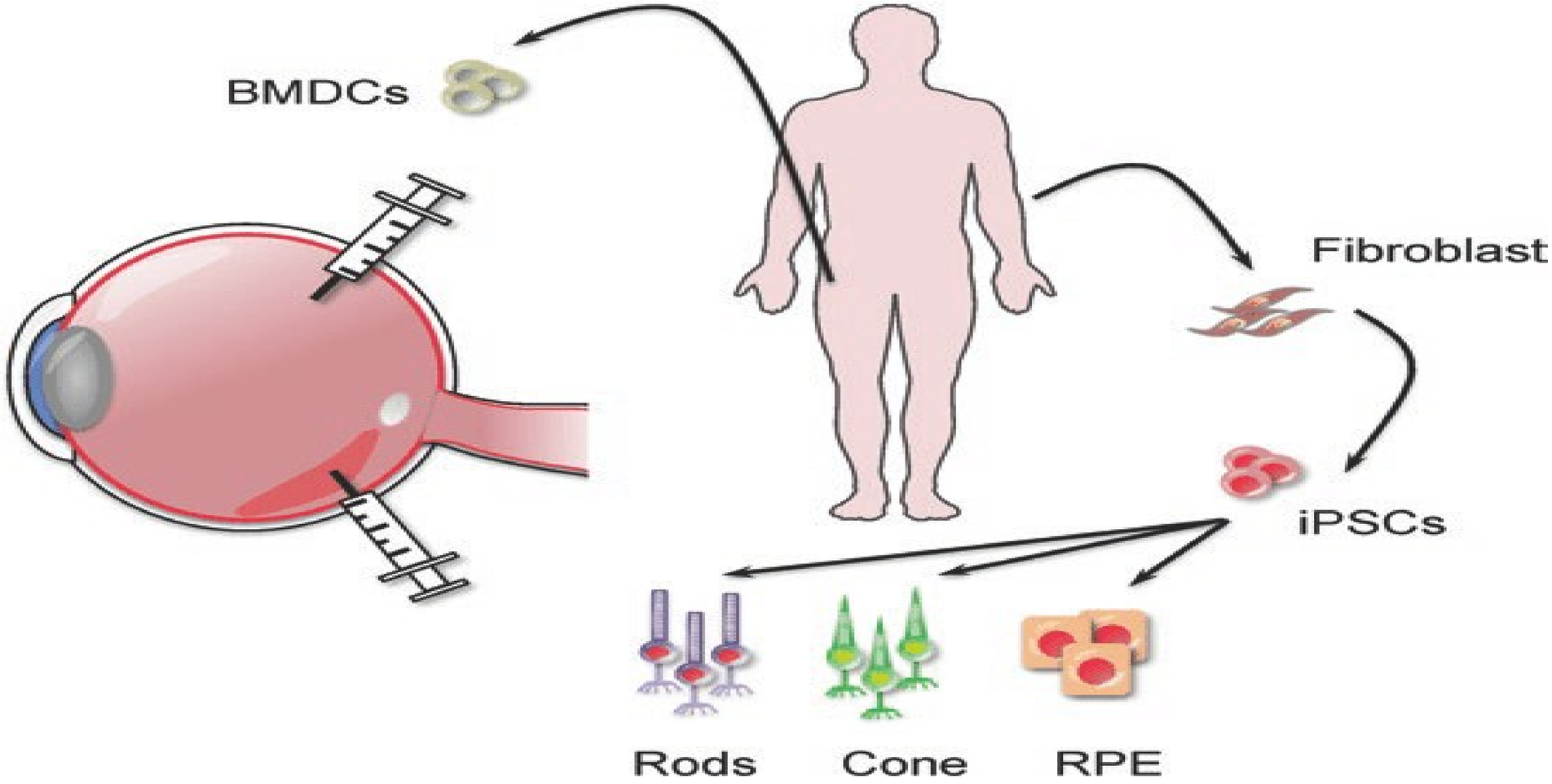
Novel treatment approach

- Gene therapy and regenerative medicine.
- Stem cell research in retinal repair.
- **Subthreshold micro pulse laser treatment.**
- **Photo biomodulation.**

Novel treatment approach

Gene therapy and regenerative medicine.

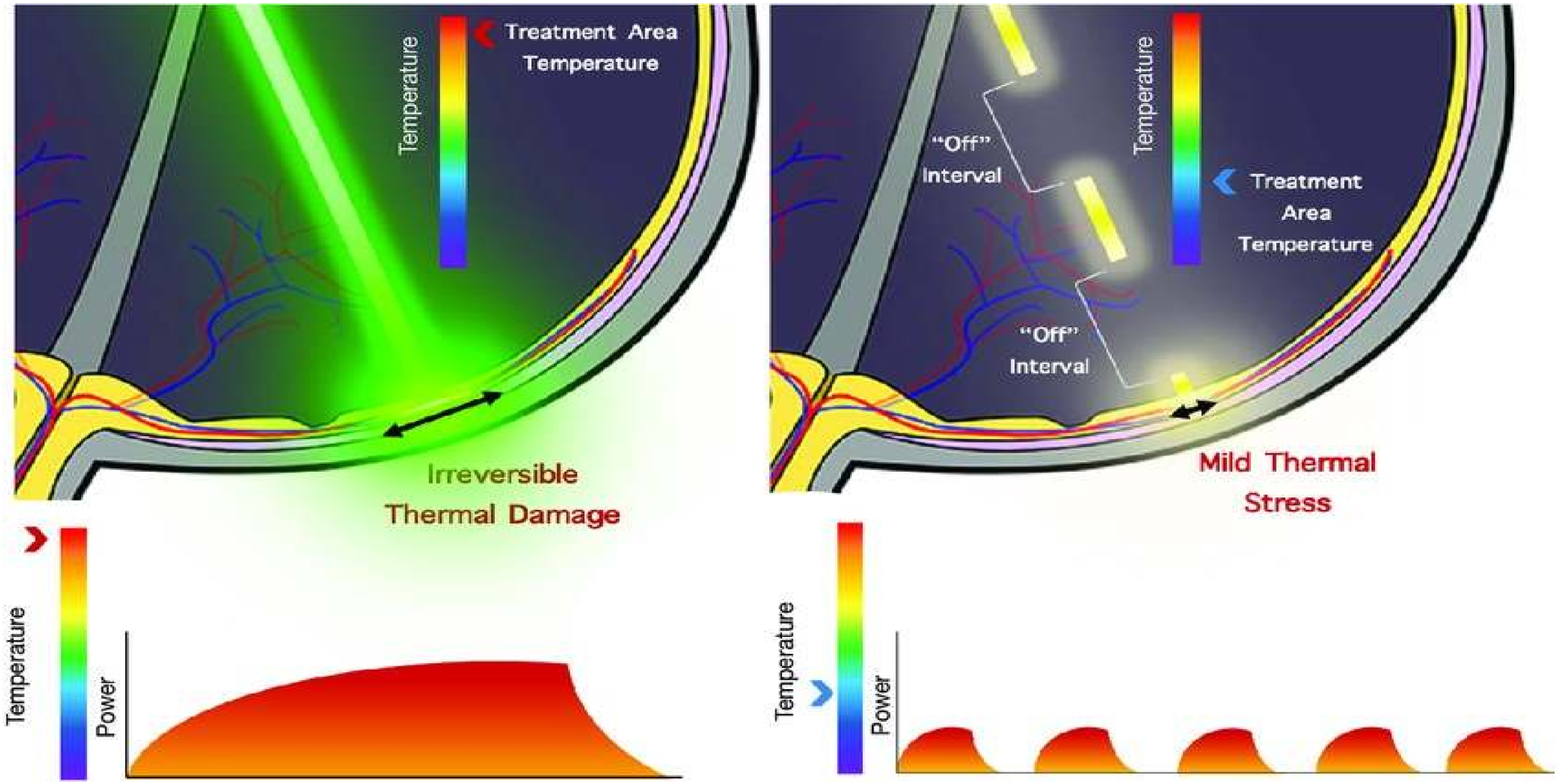
Novel treatment approach



Stem cell research in retinal repair

Pathophysiology of Diabetic Retinopathy , Now and then

Novel treatment approach



Subthreshold Micro Pulse Laser Treatment.

Pathophysiology of Diabetic Retinopathy , Now and then

Novel treatment approach

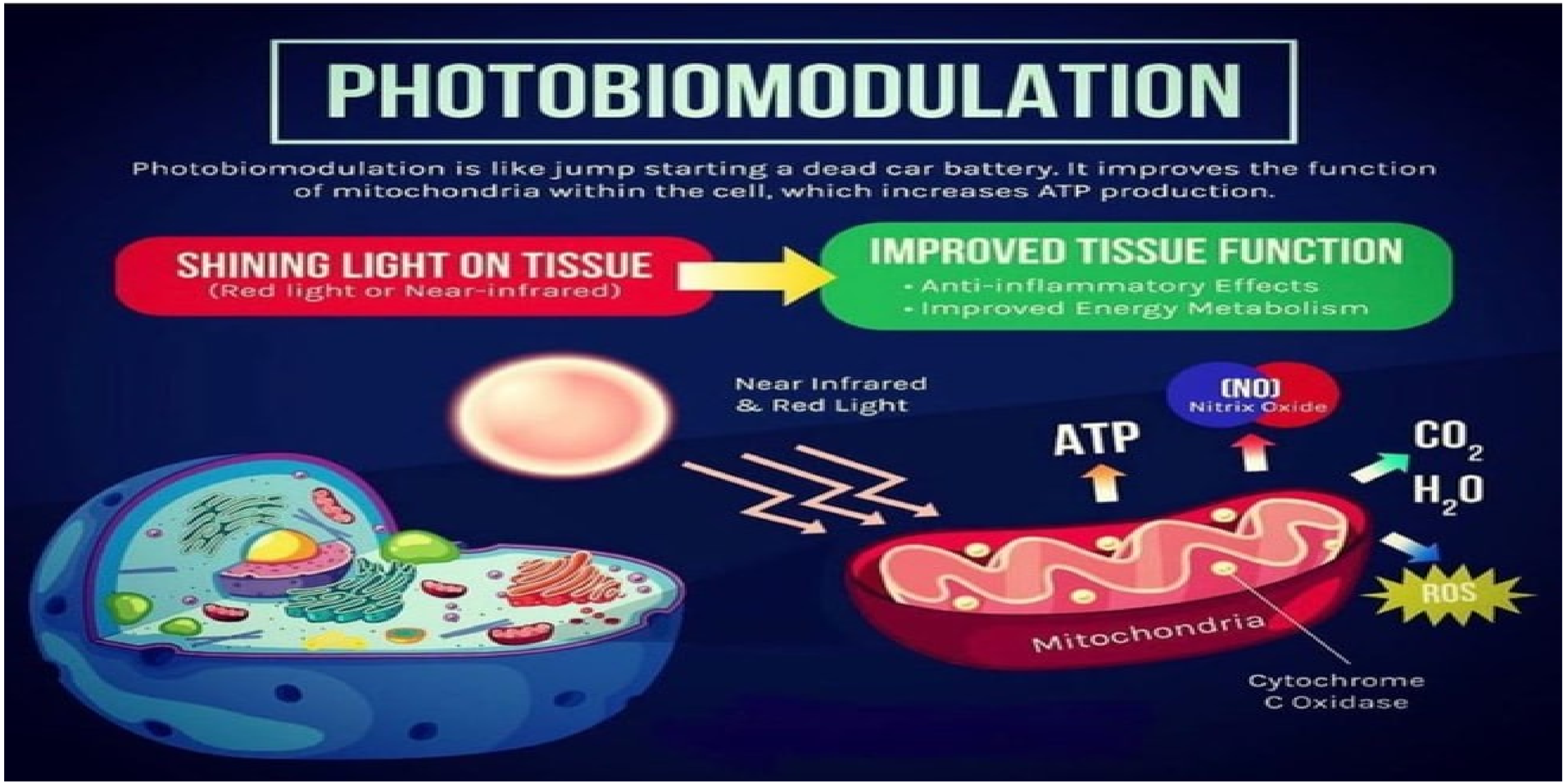


Photo biomodulation

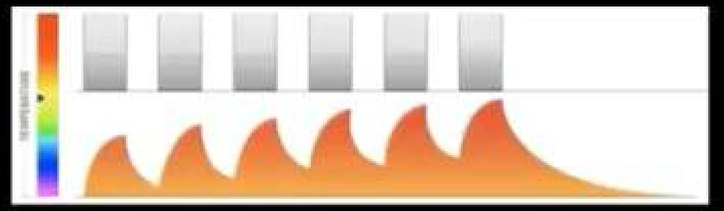
Pathophysiology of Diabetic Retinopathy , Now and then

Subthreshold Micro Pulse Laser Treatment

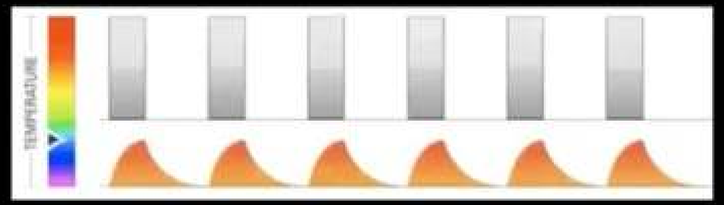
MicroPulse

- Continuous wave laser is chopped into spaced micropulses
- Lower energy per pulse
- Allows for tissue cooling between pulses
- Decreasing power of continuous wave NOT equivalent to MicroPulse
  - Less tissue heating with MicroPulse

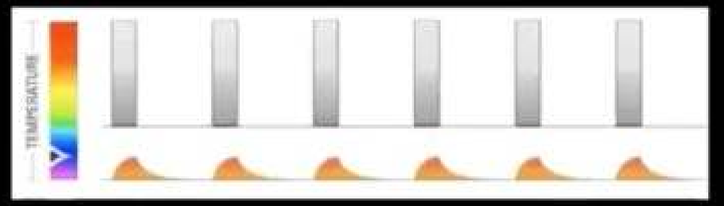
CW Laser Exposure: 100% Duty Cycle (DC)



MicroPulse High DC (15%)

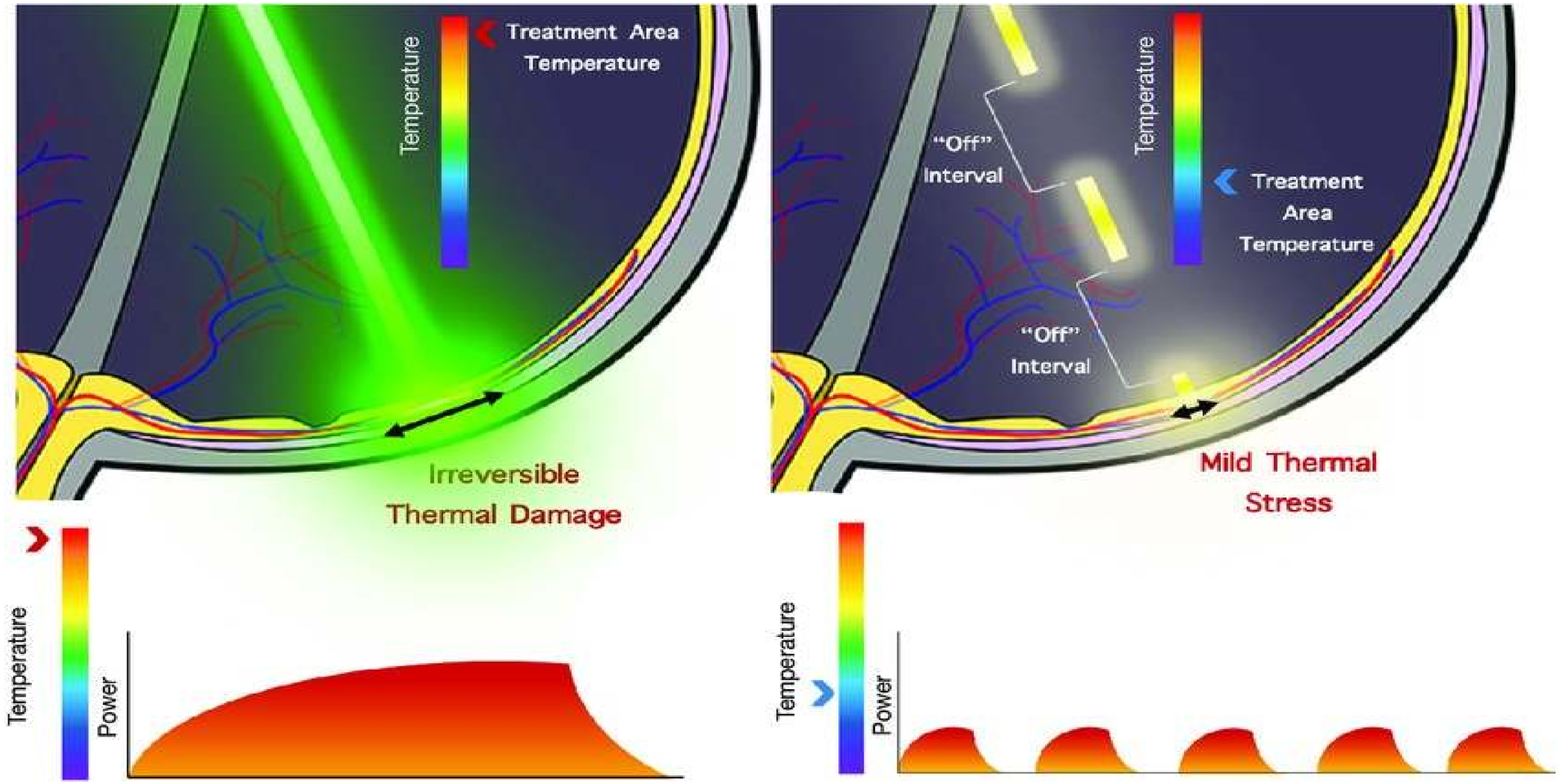


MicroPulse Medium DC (10%)



MicroPulse Low DC (5%)

Novel treatment approach



Subthreshold micro pulse laser treatment.

Pathophysiology of Diabetic Retinopathy , Now and then

	810	577	532
Maximal Absorption	RPE	Melanin Oxyhemoglobin	Melanin Hemoglobin
Minimal Absorption	Media Opacity Luteal Pigment Hemorrhage	Xanthophyll	Xanthophyll
Power	Highest	Lower	Lowest
	Not attenuated by thickened neurosensory retina	Minimal spot expansion	Most widely used laser wavelength

Mechanism of action of subthreshold Micropulse laser treatment

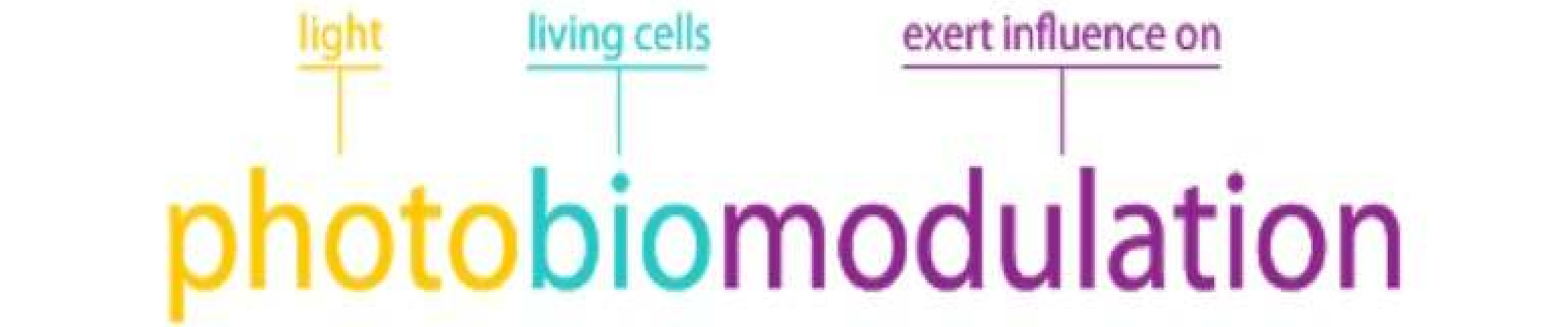
The exact mechanism is not understood, but some studies showed that:

- Micro pulse **stimulate heat shock protein production** in **the RPE** ,which protect cells from stress-induced damage and improve the function of RPE.
- It may **alter the metabolic activity of the RPE**, resulting in the release of cytokines that regulate angiogenesis and vascular leakage without any associated retinal damage.

Advantages

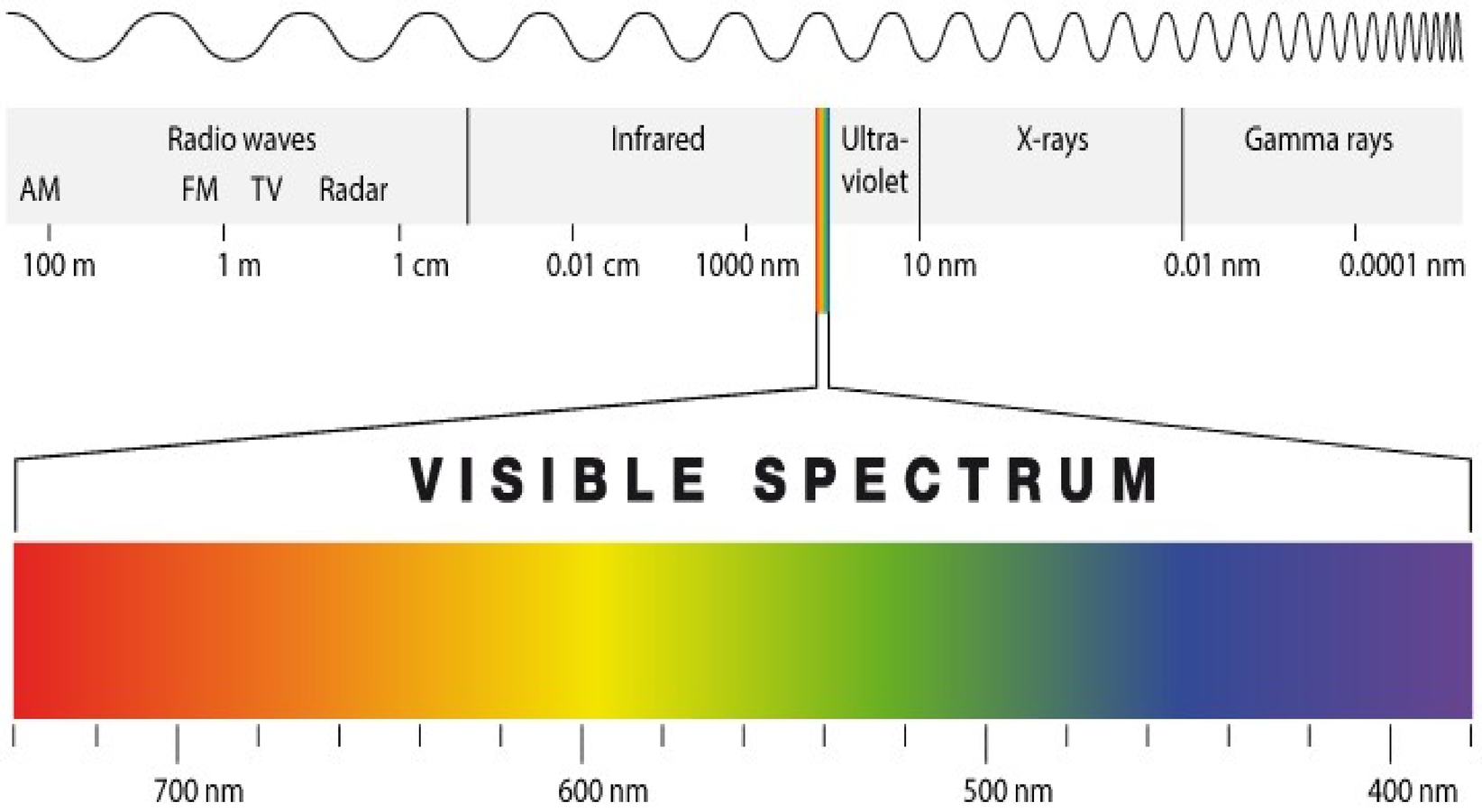
- It provide selective therapeutic targeting of the RPE while sparing of the neurosensory retina.
- It is applied with no visible intraretinal damage or scarring, either during or after treatment.

Photobiomodulation



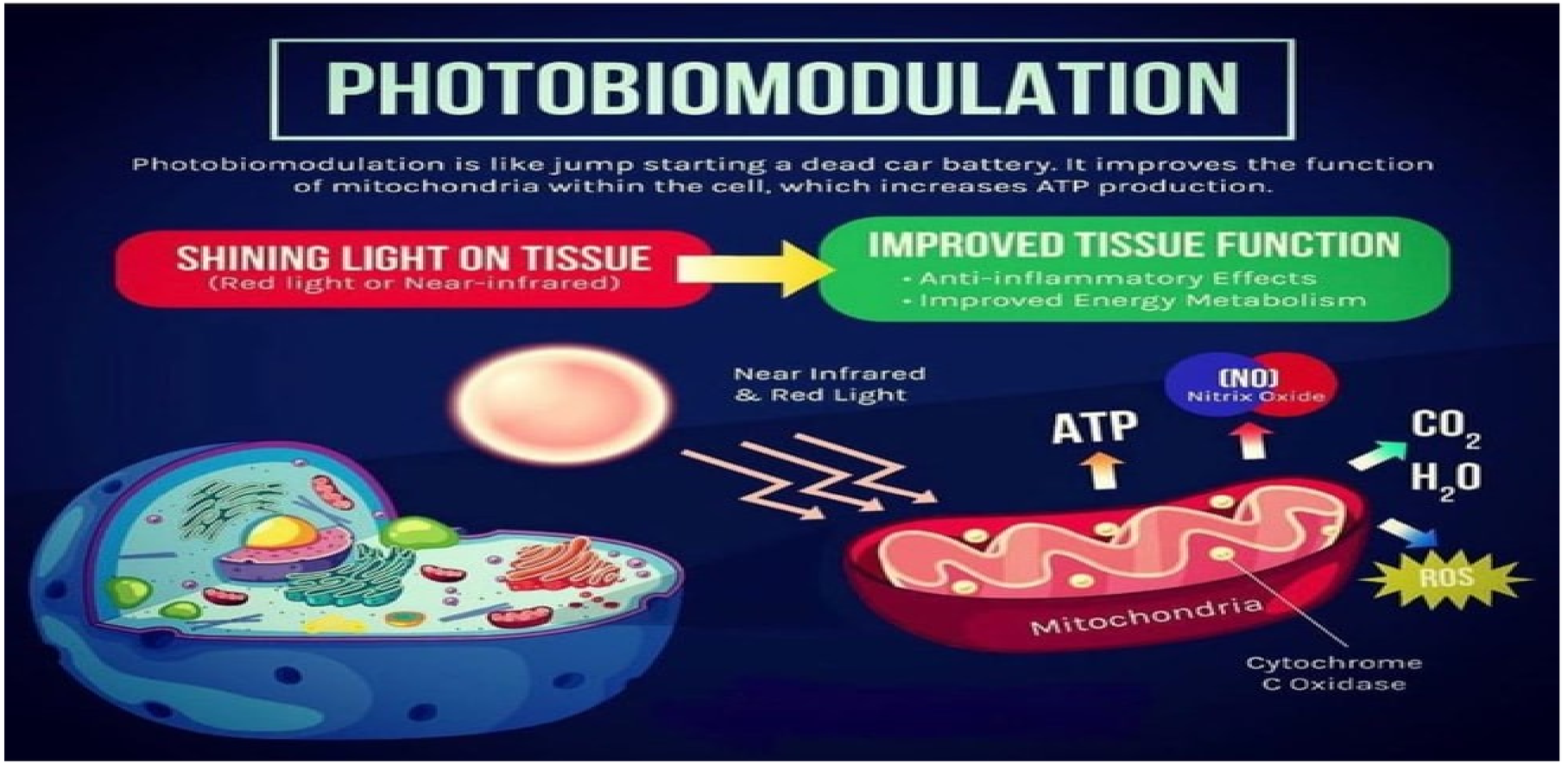
describes biochemical reactions that occur in living cells in response to light

Photobiomodulation



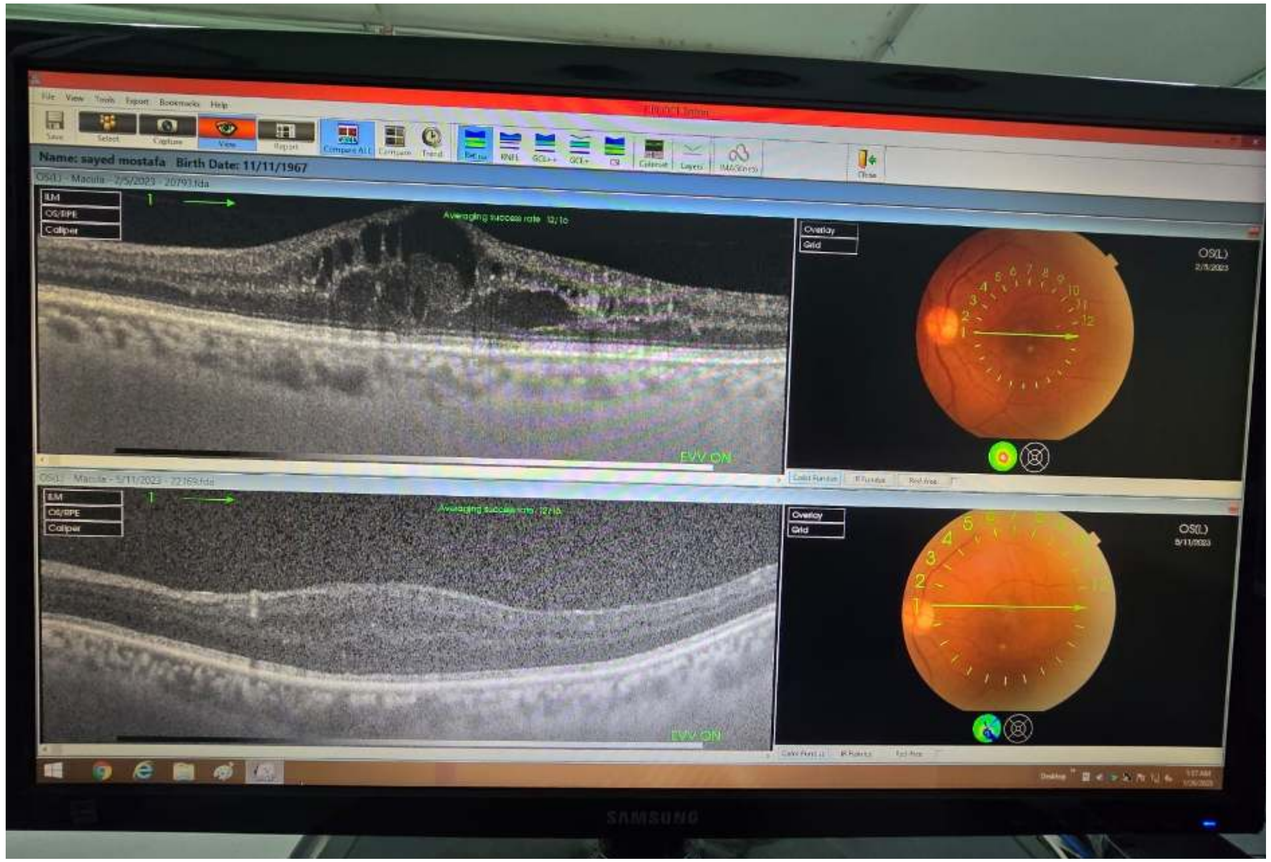
- Involves the use of visible light to near infrared light(NIR) **(500-1000nm)** produced **by a laser** or **non-coherent light** source applied to the surface of the body to produce beneficial effects in a wide range of disease states.

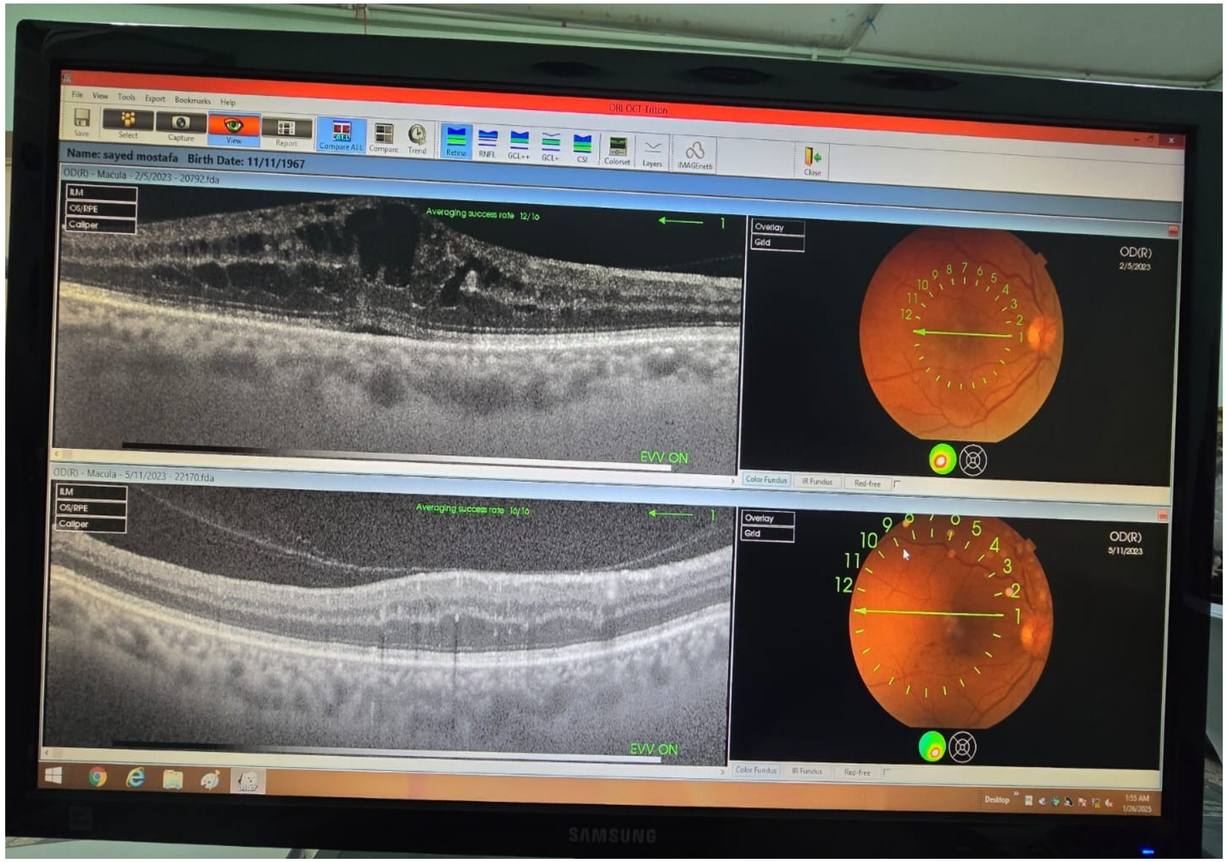
Mechanism of action of Photobiomodulation



- It is nonthermal process that induce photochemical effects on the cells.
- It activate the mitochondrial respiratory chain components resulting in promotion of cellular proliferation and cytoprotection.

57 years old male with diabetic maculopathy under went 29 injections both eye with no response



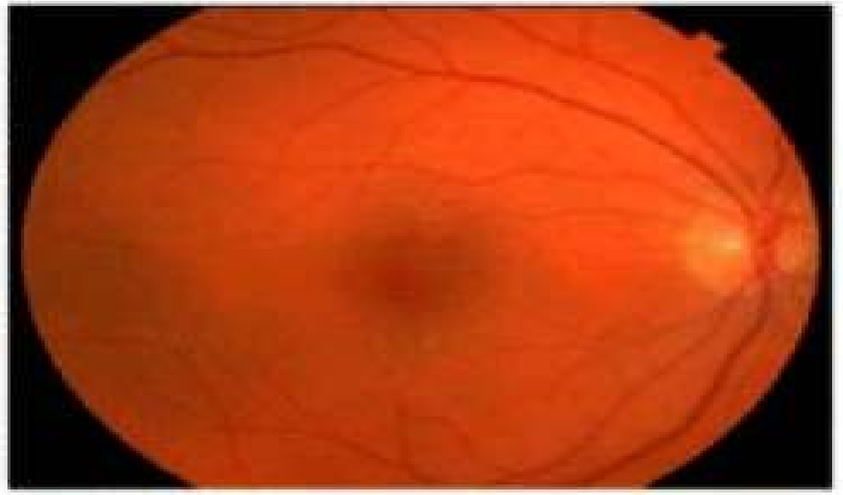


3 months after micropulse treatment

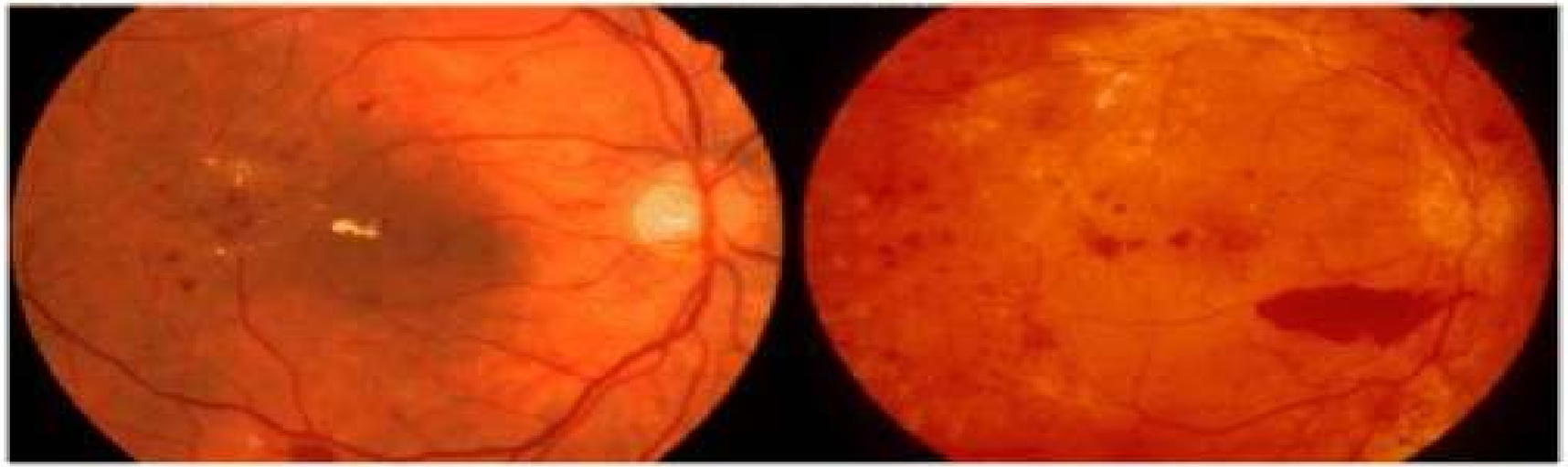

TAKE
HOME

Is it possible to diagnose and prevent progression of DR before it become detectable on fundus examination?

Compensated DR



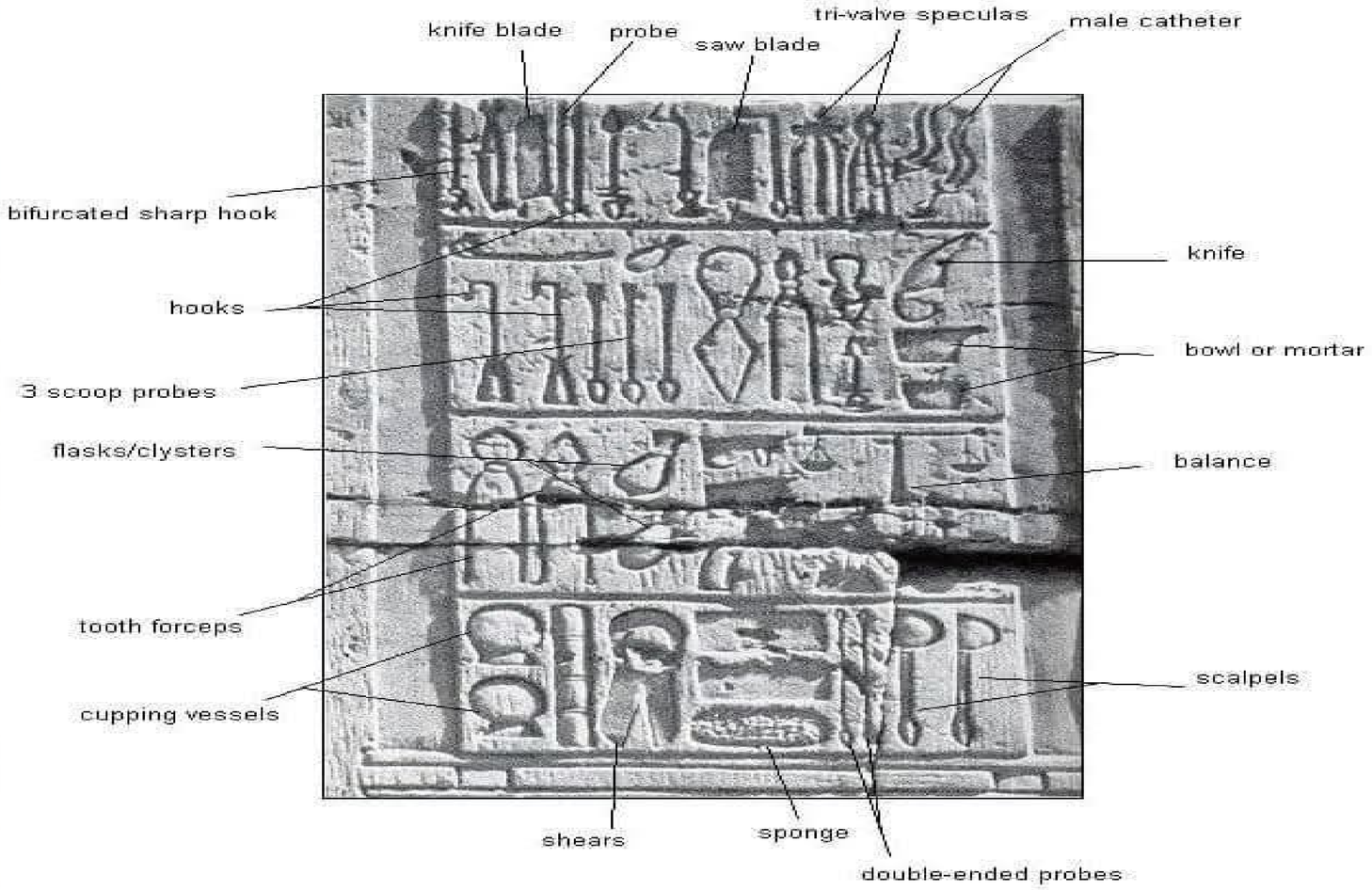
Decompensated DR



Since deterioration of neural retina could precede microvascular abnormalities in diabetic retinopathy (DR) , studying the electrical activities of the retina can provide valuable insight into the early stages of retinal damage.

This may also help in developing new therapeutic strategies to prevent or reverse retinal neurodegeneration, neuroinflammation and impaired cell-cell interactions of the neurovascular unit in early stages DR.

Medical kit , Temple of Kom Ombo, Egypt,circa 18 BC




Thank you
تحيا مصر