Is it straight forward ????

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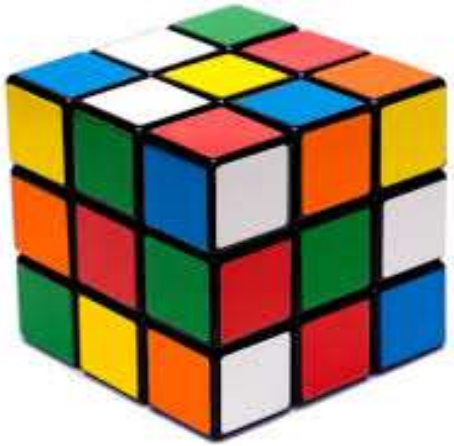


Diabetic retinopathy (DR) - **Introduction**

Major cause of blindness- Worldwide, there are approximately

A) 93 million - DR

B) 17 million - proliferative diabetic retinopathy (PDR)

C) 21 million with diabetic macular edema (DME)

D) 28 million with vision threatening DR

Treatments

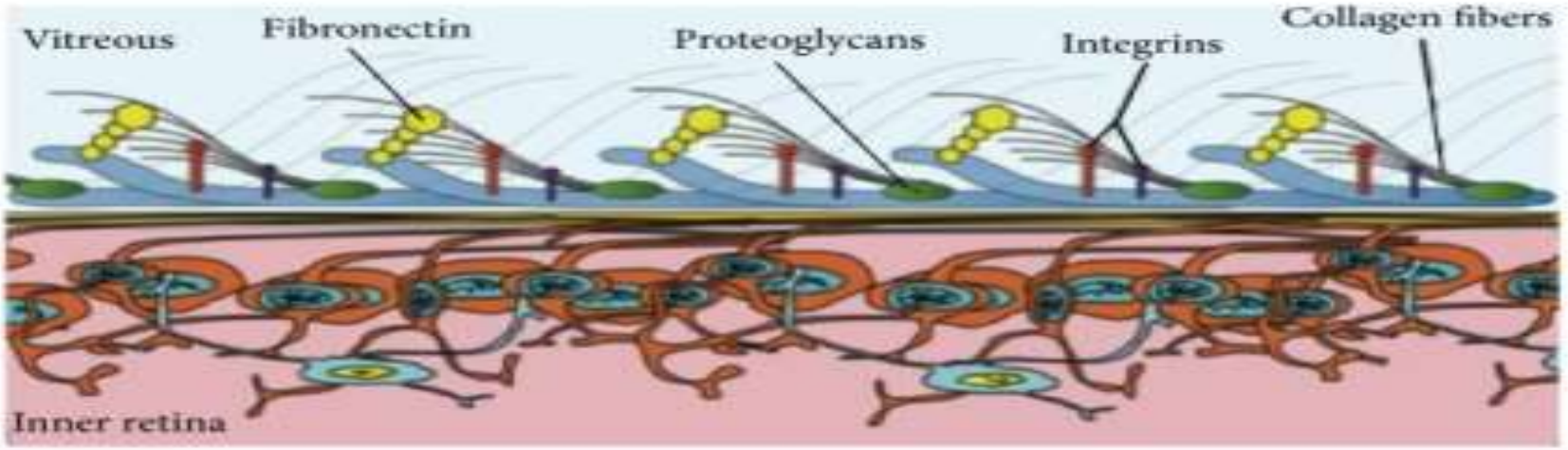
A) Photocoagulation of retinal tissue,

B) Intravitreal therapy - steroid compounds and anti VEGF

C) Surgical intervention for vitreous hemorrhages and repair of tractional formation of retinal detachment.

In DR patients, the VMI (Vitreo macular interface) can significantly influence the emergence, progression, and response to treatment of DR.

Vitreoretinal attachments at the vitreoretinal interface



In normal eyes, the posterior vitreous is attached to the internal limiting membrane (ILM) by collagen at the VMI. Collagen fibers fuse with ILM and help anchor the vitreous cortex to the retina along with laminin, fibronectin, and chondroitin

Posterior Hyaloid and Vitreous

- Ultrastructure of the VMI in eyes with diffuse DME reveals a layer of vitreous collagen covering the ILM, **fibroblasts, and astrocytes** embedded in vitreous collagen in prominent premacular cortical vitreous and single or multilayers cell membranes on a layer of vitreous collagen in eyes with vitreomacular traction
- Histologic examination of vitreoretinal tissue of ILM and epimacular tissue in patients with diffuse DME -Thickened premacular cortical vitreous , epimacular membrane, retinal striae and vessel distortion consistent with vitreomacular traction
- Vitreous may provide traction on the macula during the perifoveal PVD leading to DMO
- Higher incidence of complete PVD in patients with nonproliferative DR versus those with PDR

- ***Importance of the vitreous in the development and progression of diabetic retinopathy***
- ***Statistically significant relationship between posterior vitreous detachment (PVD) and lack of macular edema***
- ***Resolution of macular edema was faster in patients with vitreomacular separation***

OCT Imaging

- Increasingly important tool to help better understanding of the VMI in DR.
- DME - diffuse retinal thickening, cystoid macular edema, serous retinal detachment ,posterior hyaloid traction, and tractional retinal detachment (improved visual acuity after vitrectomy). Increased retinal thickness, macular edema, and posterior hyaloid traction are associated with worse vision
- Definite VMI abnormalities including vitreoretinal adhesions and epiretinal membrane (ERM) were found in around 50% of patients with persistent DME after at least one session of focal laser treatment
- **Higher resolution OCT imaging, including 3D visualization** demonstrated vitreoretinal traction and tangential fine folds
- Swept-source OCT (SS-OCT) have inner and outer layers of vitreoschisis, taut ILM, cortical vitreous separation, and vitreoretinal adhesions in proliferative diabetic retinopathy

Immune and Molecular Pathways Mediating the VMI in DR

DMO

- Elevated ***VEGF, ICAM-1, IL-6, and MCP-1*** in vitreous fluid, (with VEGF and ICAM-1 having a stronger influence on retinal vascular permeability and DME severity)
- Chemokines including ***CCL2*** - inflammation of the diabetic retina, including the activation of retina microglia and macrophages (disruption of the blood-retina barrier)
- The breakdown in the blood-retina barrier ->increased concentrations of chemoattractants in the vitreous cavity ->stimulate cell migration -> glial and epithelial cell infiltration -> tractional forces found in DR

Immune and Molecular Pathways Mediating the VMI in DR

PDR

- Increased levels of ***IL-6 , IL-8, IL-1B,VEGF, CCL2, EDN1 and TNF***
- Higher levels of 11 chemokines, including ***CCL17, CCL19, and TGFβ3***
- Elevated levels of ***D-serine and glutamate*** → retinal ganglion cell excitotoxicity
- elevated IL-8 levels were independently associated with worse visual outcome in PDR
- ***T-lymphocytes, B-lymphocytes, and macrophages*** were found in the fibrovascular membranes of PDR patients with B-lymphocytes only in active PDR patients. The authors demonstrated a relationship between the density of inflammatory cells and activity of retinopathy
- Statistically significant association was shown between high levels of lymphocyte infiltration into the ERM and poor visual prognosis after vitrectomy because of reproliferation of the ERM

Vitrectomy for DME

- Separation of the thickened posterior hyaloid and taut posterior hyaloids→ improvement in vision with resolution of macular traction and edema
- Vitrectomy → tractional forces on the retina
- ILM peel → eliminates the scaffold for proliferating astrocytes on the retinal surface and resolution of macular edema (accelerated the absorption of edema in severe DME but did not further improve visual acuity)
- ***Pars plana vitrectomy and ILM removal*** for chronic DME → Reduced leakage within the macula and a decrease in macular thickening were and visual acuity improved significantly (2+ lines) in 43% of patients. (chronic DME may cause structural changes that are difficult to reverse)
- Even without signs of traction on exam, vitrectomy in DME could help to resolve macular edema and improve vision

Effective treatment for DME but chronic changes might still persist

Retinal Oxygenation

- Vitrectomy in patients caused a statistically significant increase in oxygen tension both near the lens and in the vitreous.
- In patients undergoing repeat vitrectomy, the oxygen tension was significantly higher than in eyes undergoing vitrectomy for the first time, indicating a lasting effect of vitrectomy on ocular oxygen levels
- Oxygen tension in PDR found that oxygen tension in the midvitreous was 46% lower in PDR patients than in controls, with increased oxygen levels in PDR patients near the posterior pole likely from extensive neovascularization.

Retinal Laser Photocoagulation

- Retinal laser photocoagulation has been used as a treatment for DME to help reduce visual loss.
- The Early Treatment Diabetic Retinopathy Study →efficacy of combination of focal and grid photocoagulation to arrest loss of visual acuity in patients with DR
- **PPV and removal of the ILM** were superior to grid laser photocoagulation in the treatment of DME, with greater reductions in foveal thickness and greater improvement in visual acuity
- High-risk PDR patients -**combining intravitreal bevacizumab with PRP** → a)provided better short-term regression of retinal neovascularization b)rapid clearance of vitreous hemorrhage c)visual improvement

  d) more durable effect of laser PRP
- PRP induces a decrease in ambient mitogen (promitotic signal) and activates apoptosis in diabetic fibrovascular membranes, suggesting an additional mechanism by which PRP helps treat DME [48].

Complications-

- Chronic macular edema and vision loss (biweekly treatments allowed for faster recovery of macular thickening after PRP)
- In DME- PRP induced a statistically significant increase in central foveal thickness that persisted for 3 months.
- Normal macula - morphologic changes after laser including cystoid macular edema, vitreomacular traction, ERM, and subfoveal serous detachment

Intravitreal Corticosteroids

- Glucocorticoids (reduce macular edema)

  a) inhibit macrophages promoting angiogenesis and ICAM-1 mediating leukocyte adhesion [

  b) suppress basement membrane degradation and strengthen tight junctions

- ***IVTA***

A) inhibit the degradation of capillary basement membranes

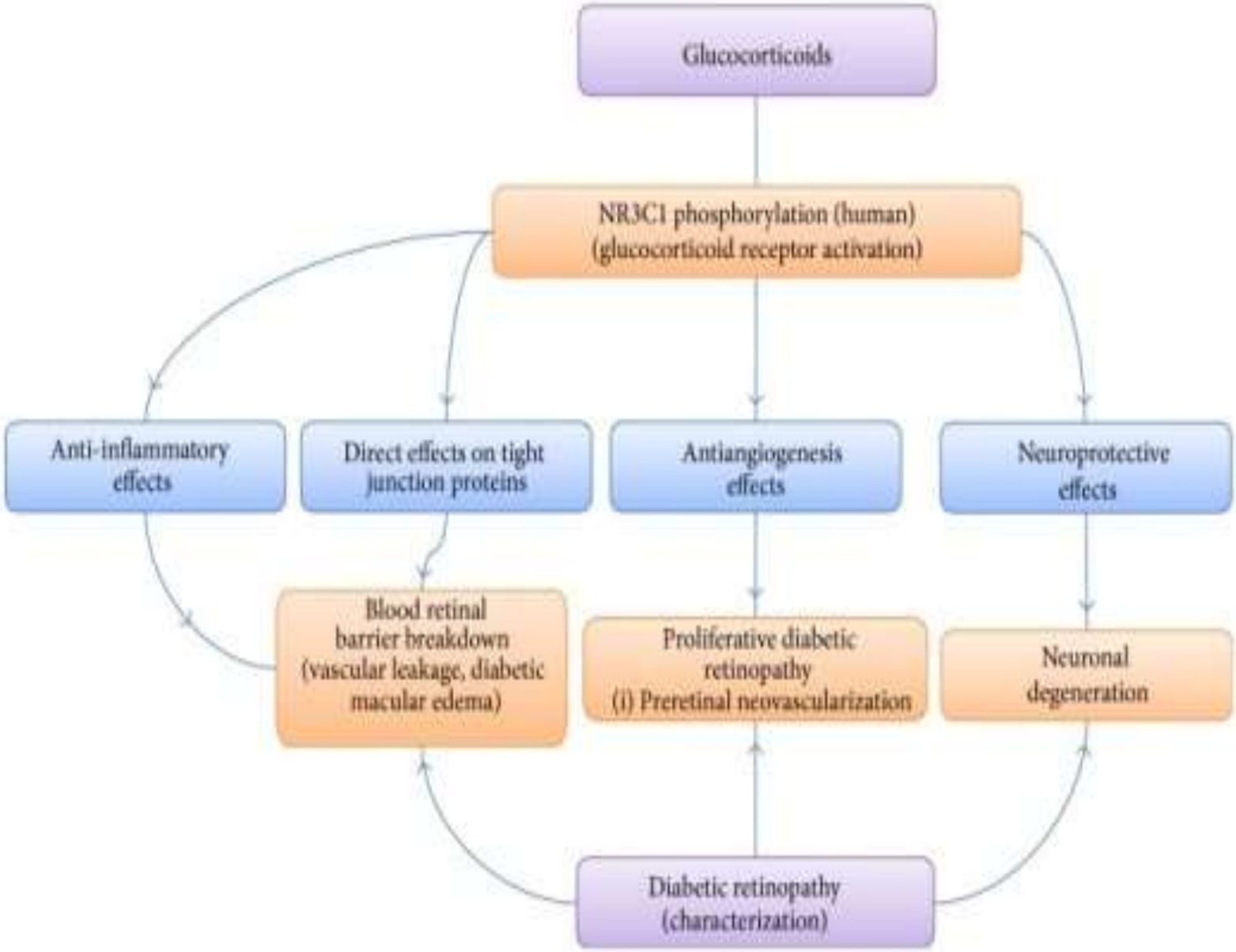
b) reduced VEGF and TGF-β expression

c)reduction in choroidal thickness while downregulating basal expression of COX-2 and VEGF

d) stimulates activation of protein kinase A and helps open pathways for K^+ and Cl^- ions to help quickly resolve edema in human patients

e) help inhibit inflammation, strengthen tight junctions

- reduced central macular thickness in patients with DME.
- reduced not only central macular thickness, but also subfoveal choroidal thickness lasting 12 weeks


Glucocorticoids
NR3C1 phosphorylation (human)
(glucocorticoid receptor activation)
Anti-inflammatory effects
Direct effects on tight junction proteins
Antiangiogenesis effects
Neuroprotective effects
Blood retinal barrier breakdown (vascular leakage, diabetic macular edema)
Proliferative diabetic retinopathy
(i) Preretinal neovascularization
Neuronal degeneration
Diabetic retinopathy
(characterization)

VEGF

- ***VEGF***

a) Promote neovascularization of the retina

b) Decline in response to laser photocoagulation

c) Predictive factor for progression of PDR after vitrectomy in patients with PDR

- ***Bevacizumab***

A) Reduce not only VEGF, but also other inflammatory cytokines including IL-1RA, IL-5, IL-10, IL-12, IL-13, and interferon-γ

B) Reduces neovascularization of the retina and resolution of vitreous hemorrhage

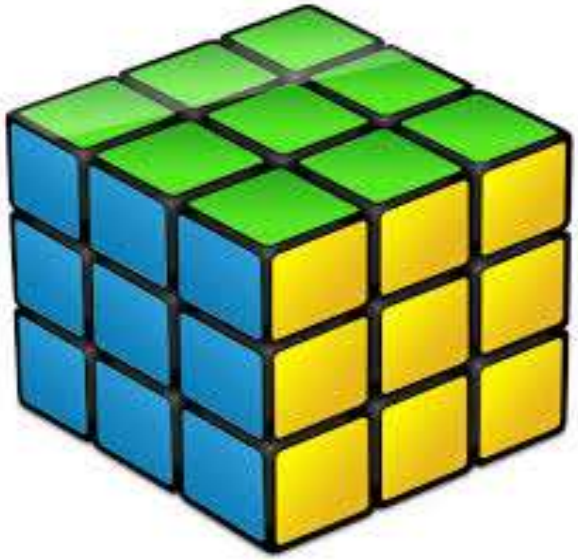
C) Preoperative treatment (5–7 days before surgery) with bevacizumab in patients undergoing pars plana vitrectomy for complications of PDR → surgical time and intraoperative bleeding were both reduced

D) Patients injected multiple times with anti-VEGF treatments for DMO who had vitreomacular interface abnormalities such as ERMs or vitreomacular adhesions had less change in best-corrected vision than those with only DME after 3 injections.

Possible role of vitreomacular interface abnormalities in reducing the therapeutic effects of anti-VEGF agents

Conclusion

- Multiple treatments that alter the VMI, including ILM/posterior hyaloid peeling, PRP, triamcinolone acetonide, and VEGF inhibitors, have been shown to help in various degrees to arrest the progression of PDR and/or improve vision.
- Complete PVDs seem to improve macular edema in some cases, possibly by reducing traction
- ***Overall, there are multiple elements and significant interplay in the vitreomacular interface of diabetic retinopathy***



Thank You