Can Vitamin D agonists improve the treatment of Age-related Macular Degeneration (AMD)/Diabetic Retinopathy?

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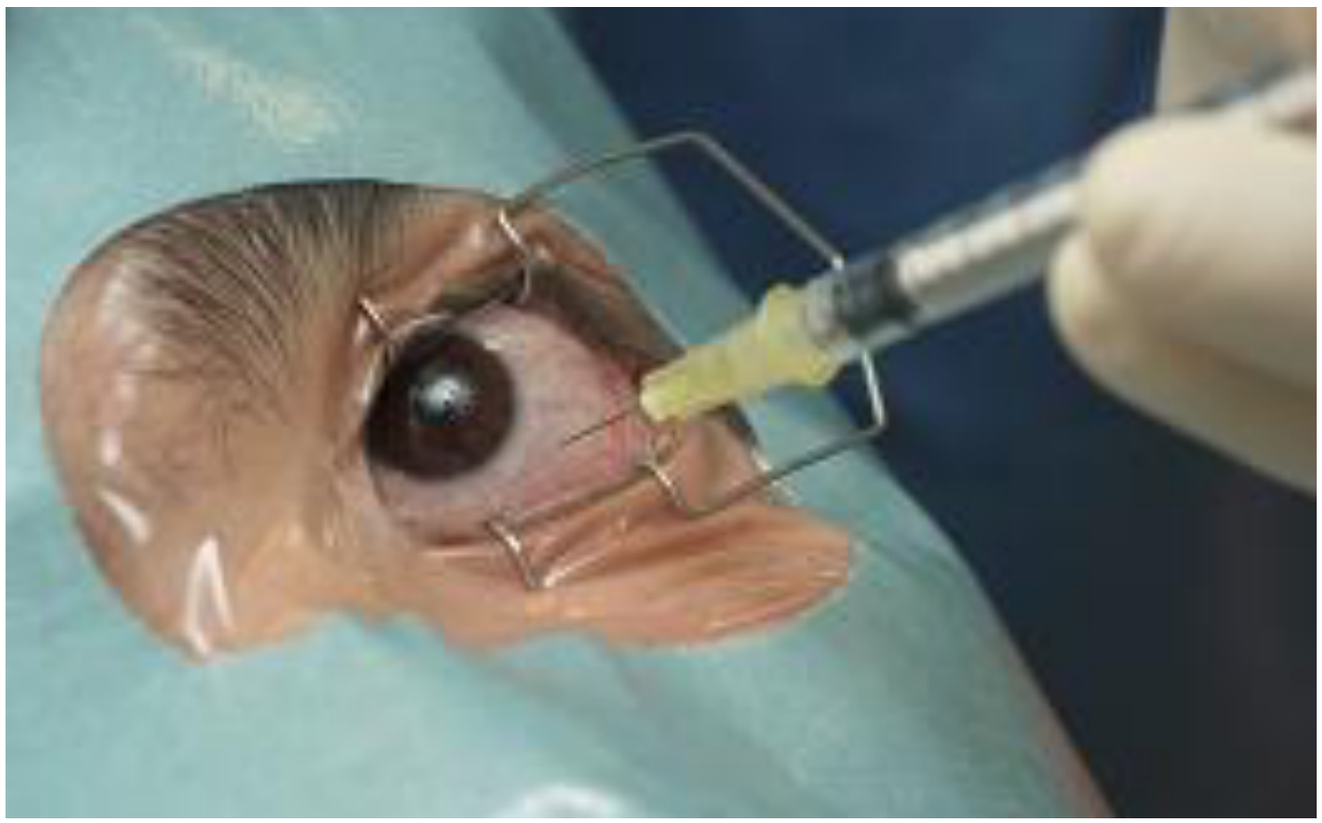
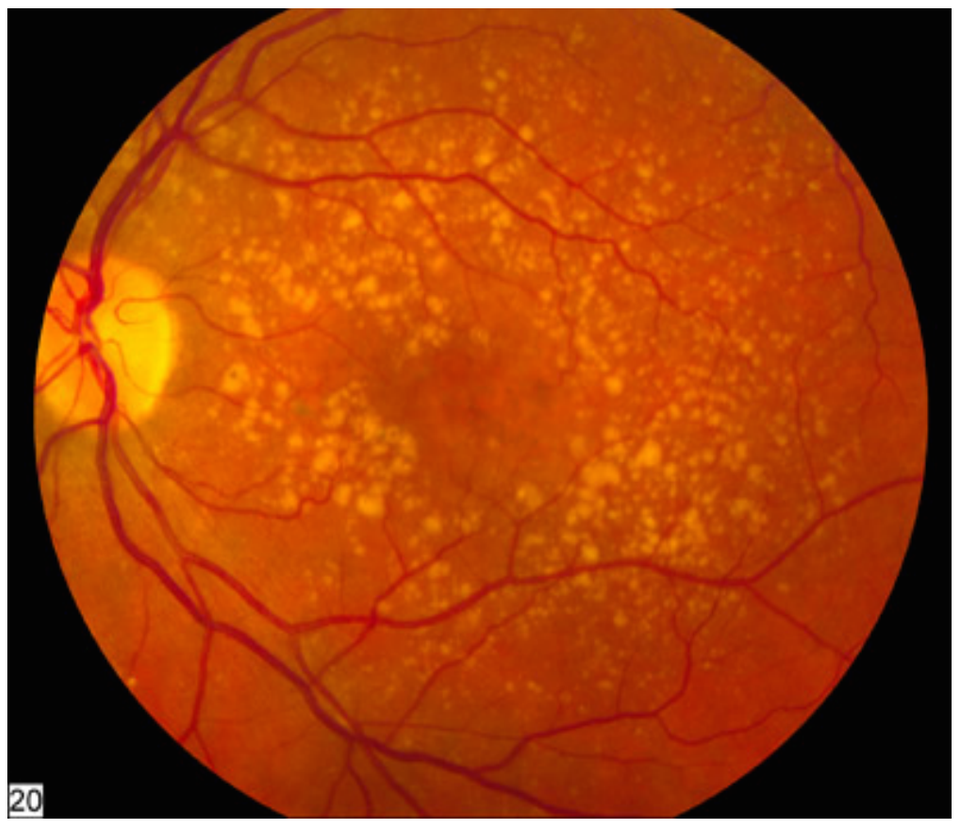


http://www.visioncentre3.net/new/index.php?page=4



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Objective

- ***To critically analyse evidence on Vit D agonists and their ability to improve the treatment of age-related macular degeneration and diabetic retinopathy.***

Outline

- Disease background of AMD and current treatments.
- What is Vit D?
- Vit D and AMD
- Future of Vit D & AMD
- Vit D and Diabetic Retinopathy
- Conclusion

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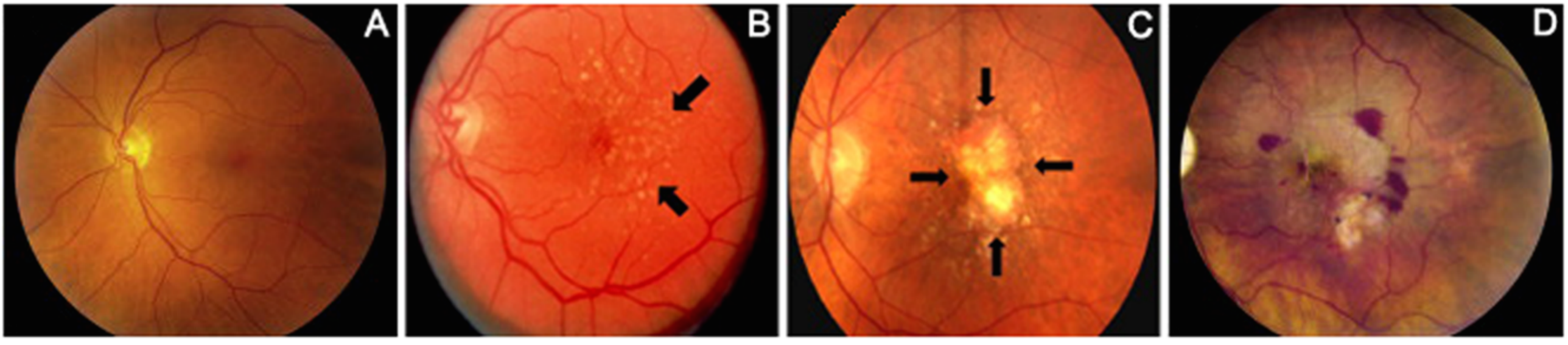
Age Related Macular Degeneration (AMD)

- Progressive degenerative disease of the retina
- Risks: increasing age, cigarette smoking, hypertension, family history
- Characterised by extensive drusen
- Immune components entrapped (Immunoglobulins, complement factors, fibrinogen)
- ***3 Stages;*** *Early, Intermediate & Late*
- **Dry AMD** - breakdown of photoreceptors in macula and surrounding tissue
- **Wet AMD**- neovascular growth, blood/ fluid leak



A. Healthy eye

B. Early- Small drusen

C. Dry -Loss of Retinal Pigment Epithelial

D. Wet - Chordial Neovascularisation

Marin-Castano ME. Ophthalmology

Current AMD Treatments

Dry AMD - no pharmacological treatment

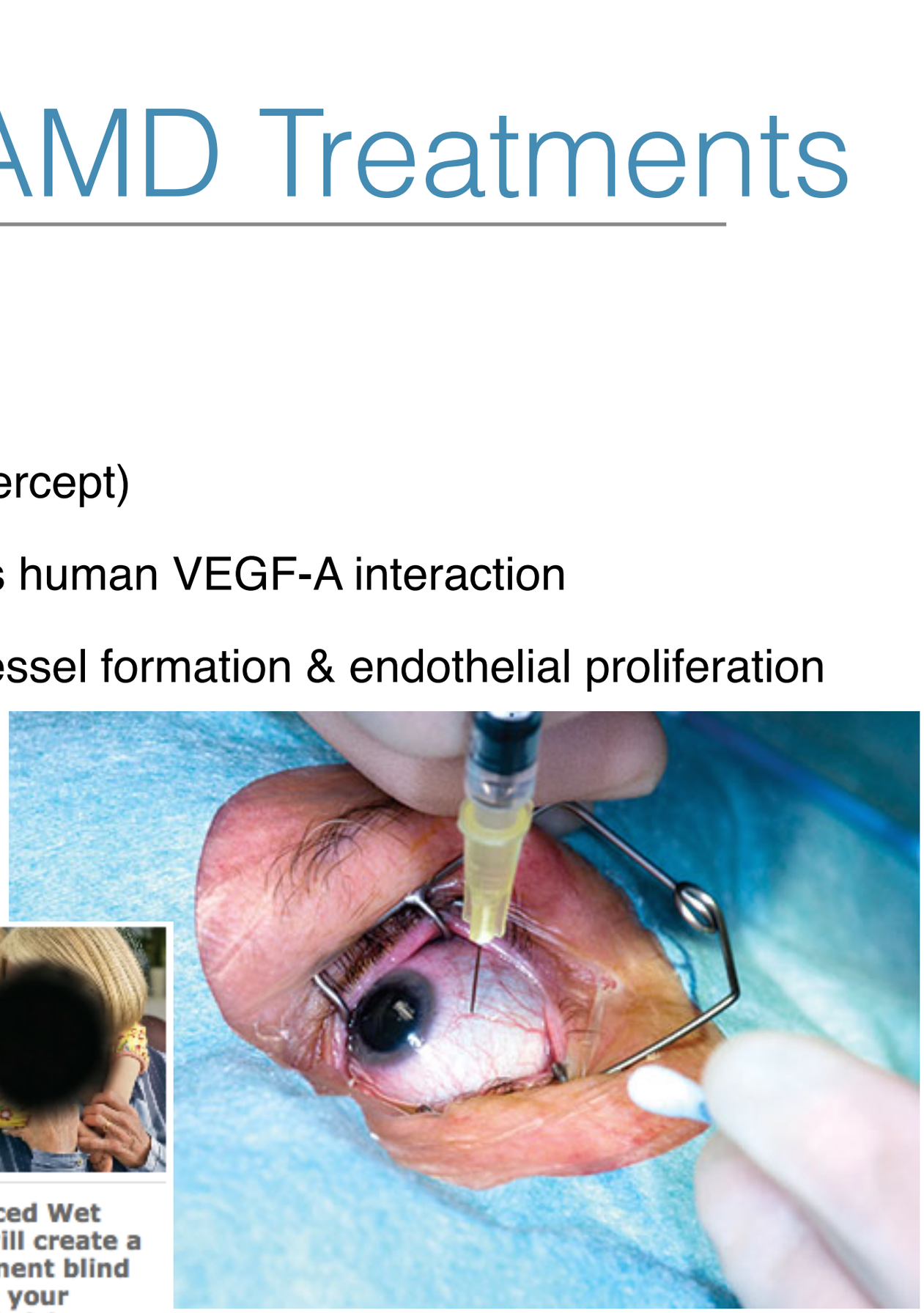
Wet AMD - Anti VEGF medication

- Lucentis (Ranibizumab) and Eylea (aflibercept)
- Lucentis is a VEGF-A antagonist; inhibits human VEGF-A interaction
- Reduces vascular leakage, new blood vessel formation & endothelial proliferation

Why look for a new treatment?

VEGF - neuroprotective

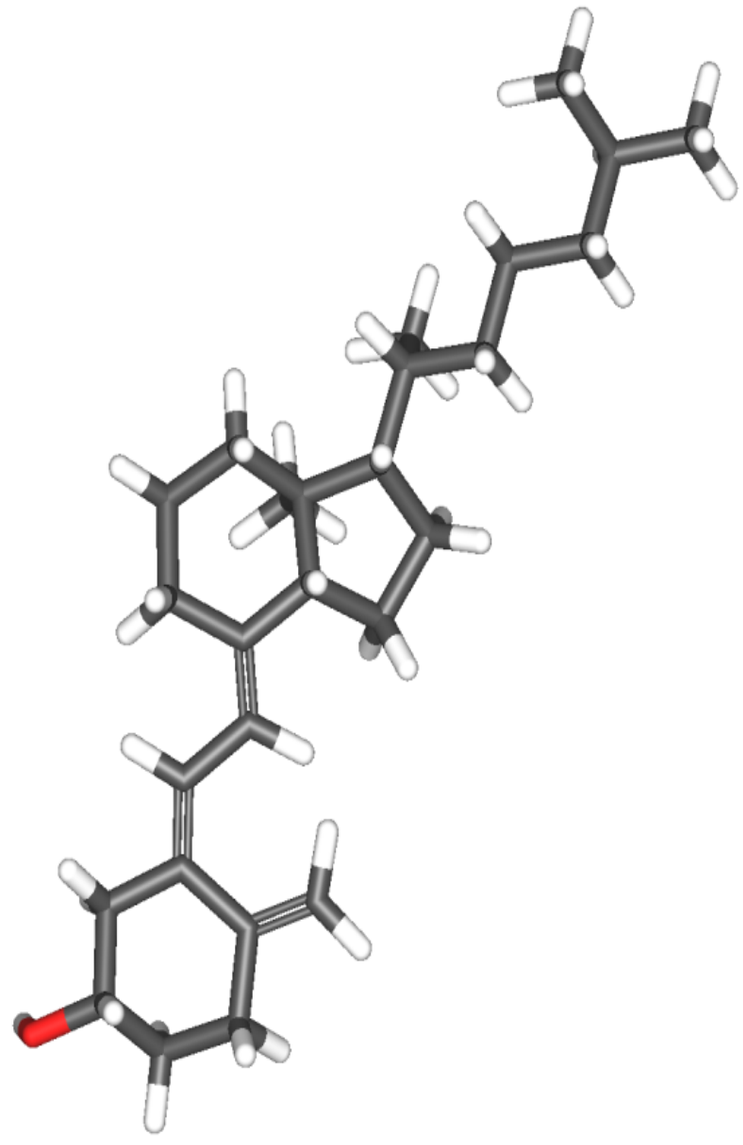
http://www.dublinopticians.ie/shop_eyecare



http://pixgood.com/intravitreal-injection.html

Vit D

- Group of fat-soluble secosteroids.
- Source: food, synthesis in skin (UVB radiation).
- Calcitriol is the biological active form, circulate in blood as an hormone.
- Act on nuclear VDR which is present on immune and retinal cells



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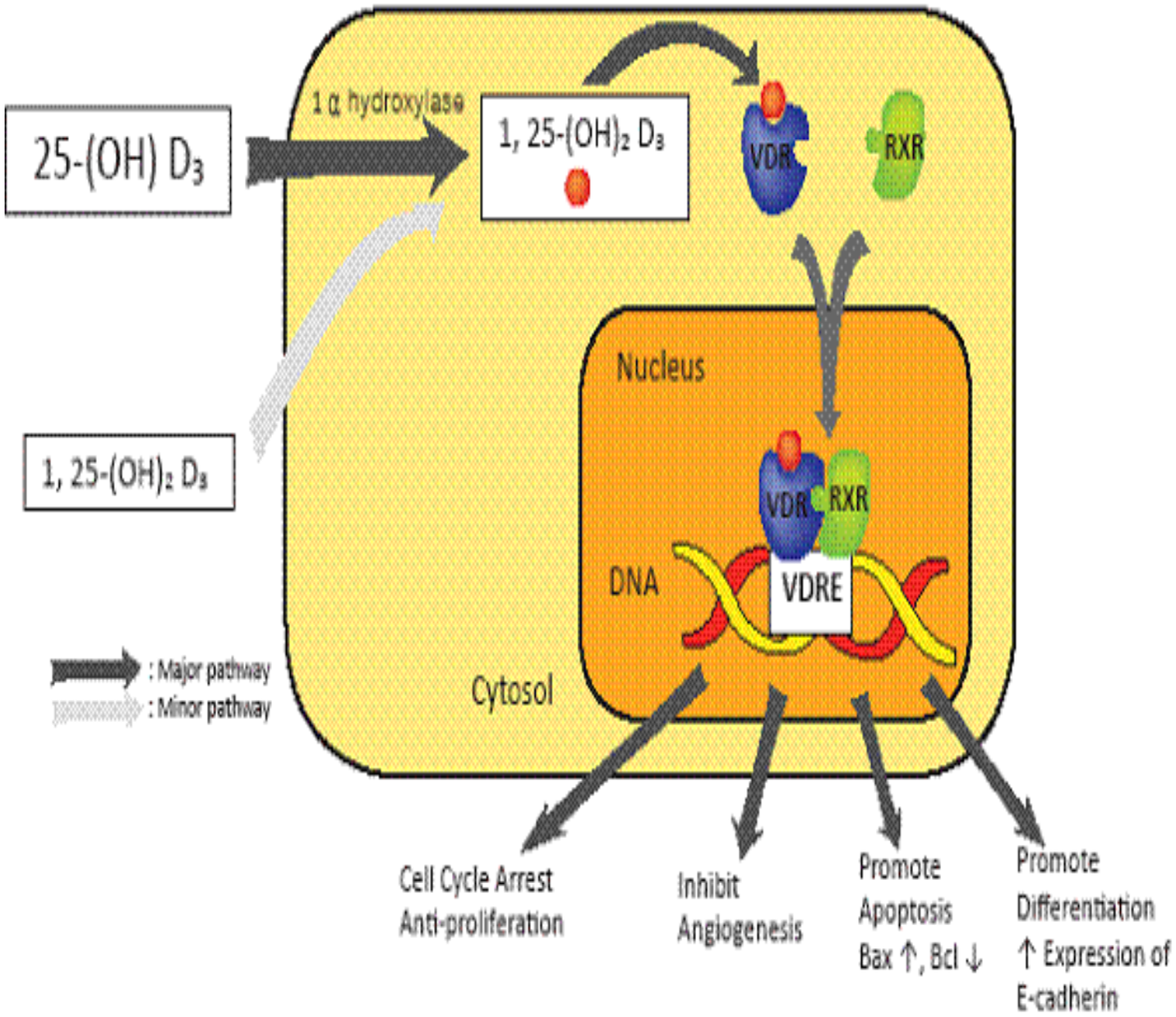
Vit D Receptor



www.redlandsfortnightly.org/papers/Baylink09.htm.

- Calcitriol + VDR complex binds retinoid X receptor (RXR).
- Act as transcription factor on Vit D response element (VDRE) in target genes.
- Vit D deficiency well established in many other chronic, age related illnesses e.g. autoimmune diseases, Alzheimer's disease, osteomalacia and rickets.

A role for Vit D in AMD

- Scientists have hypothesized a role for Vit D in AMD as Vit D has the ability to:

1. Act as an anti-inflammatory mediator via modulation of the immune system
2. Inhibit angiogenesis by possibly reducing VEGF expression and proliferation of endothelial cells.
3. Inhibit fibrosis by decreasing expression of profibrotic factors (TGF-β) and increasing expression of antifibrotic factors (BMP7).

Inflammation, angiogenesis and fibrosis underpin the progression and development of AMD.

Several studies have found an association between Vit D deficiency and AMD. However, the results have been very inconsistent.

Significant association

Vitamin D Status and Early Age-Related Macular Degeneration in Postmenopausal Women

Millen et al., 2011 (N = 1,313)

ASSOCIATION BETWEEN HYPOVITAMINOSIS D AND LATE STAGES OF AGE-RELATED MACULAR DEGENERATION: A CASE–CONTROL STUDY

Graffe et al., 2012 (N = 65)

No Association

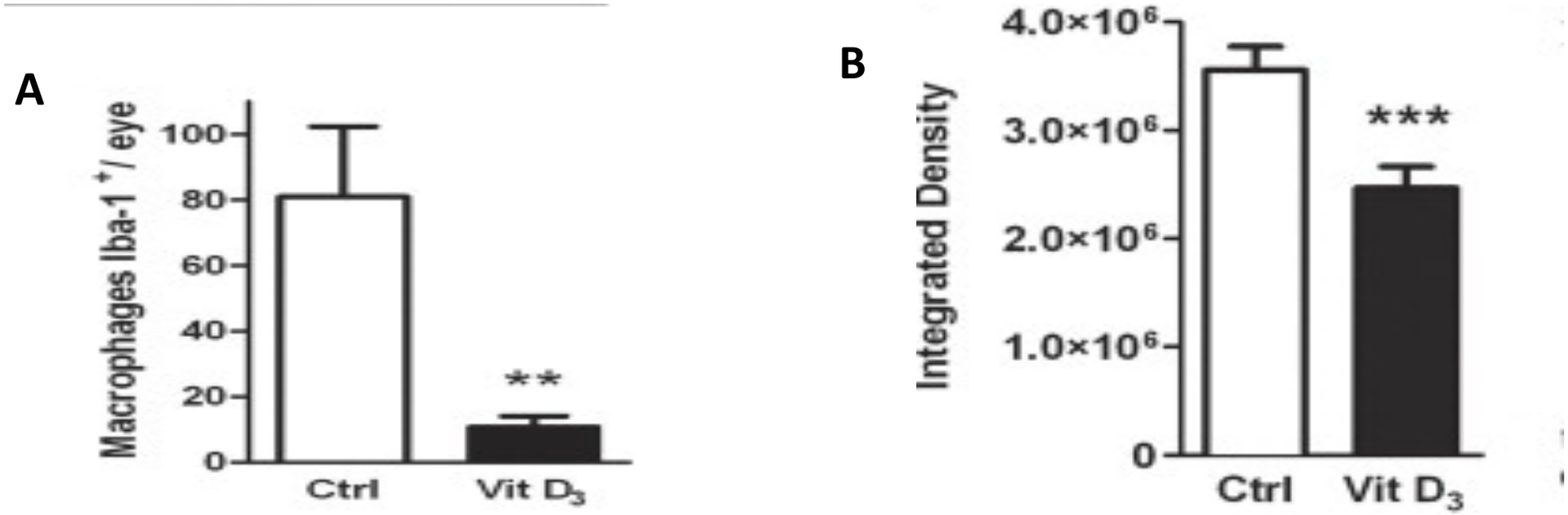
Association of Vitamin D Deficiency and Age-Related Macular Degeneration in Medicare Beneficiaries

Day et al., 2012 (N = 6966)

CME *Eye* (2011) **25,** 1122–1129; doi:10.1038/eye.2011.174; published online 5 August 2011

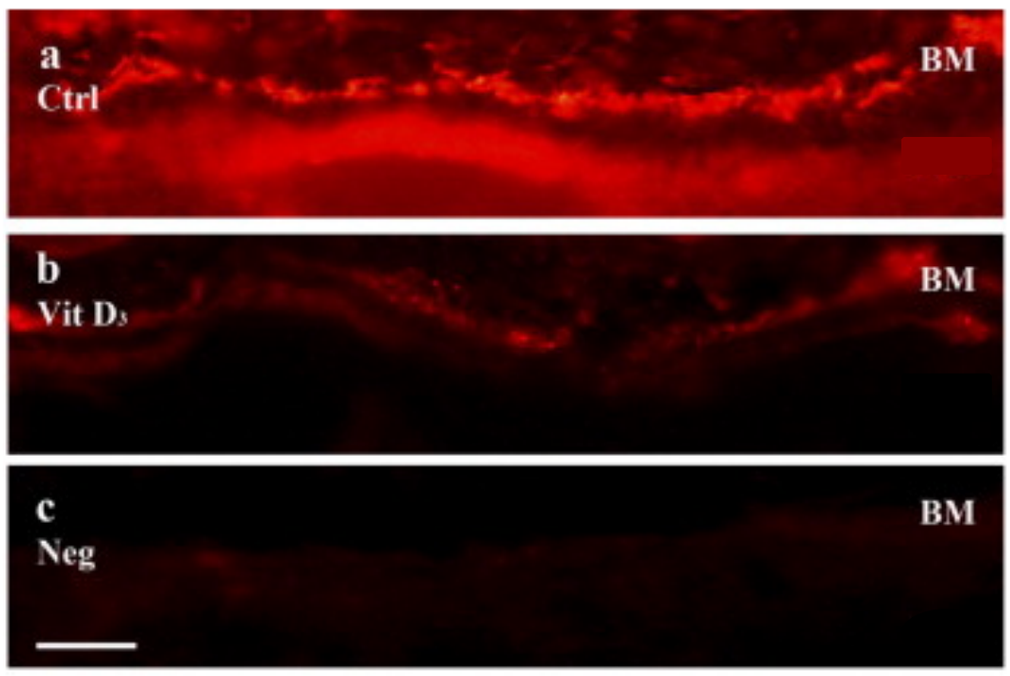
Reconsidering the connection between vitamin D levels and age-related macular degeneration

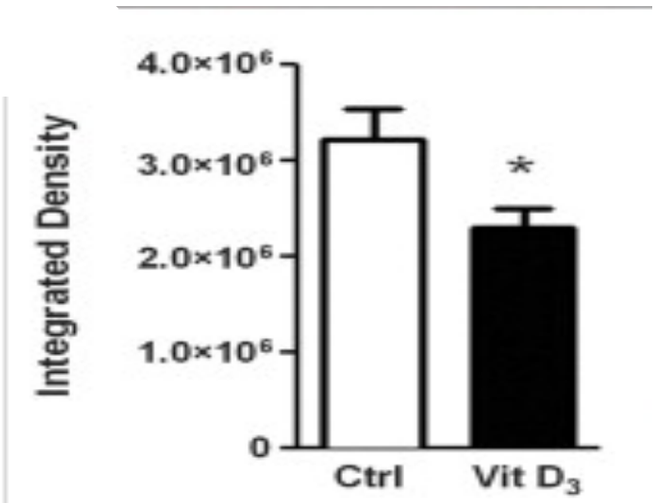
Golan et al., 2011 (N = 9169)



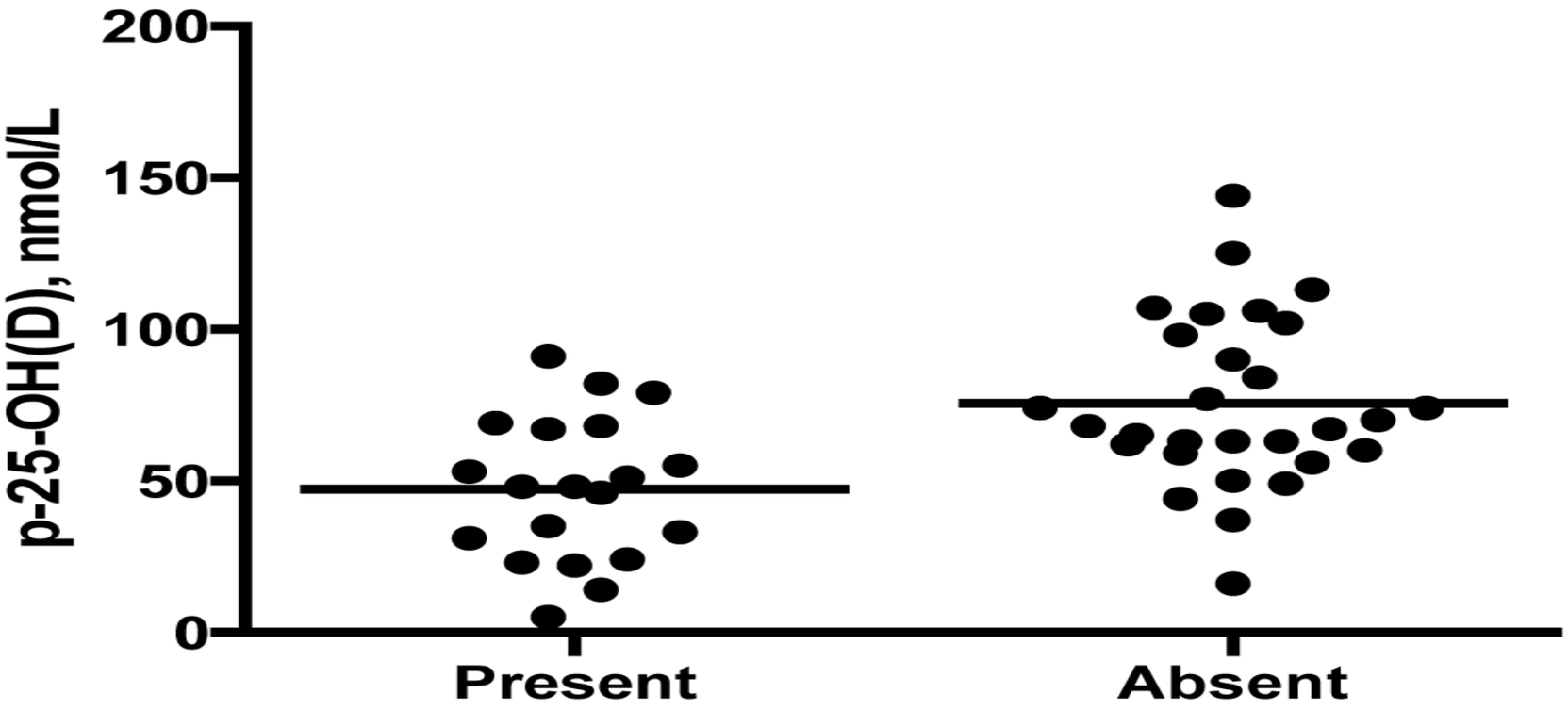
Lee et al. 2012 (**A**)There are significant reductions in the number of macrophages following Vit D_3 administration.

(**B**) Levels of C3d expression determined by immunostaining were significantly different between the 2 groups.

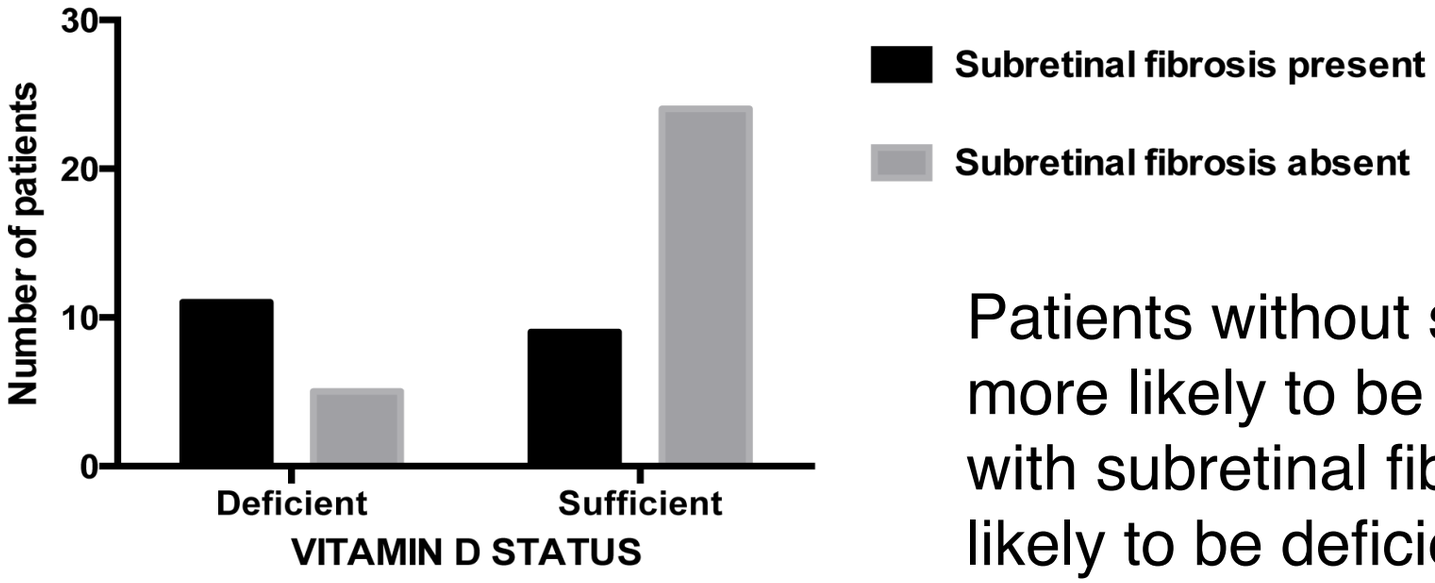




Retinal sections immunostained for Aβ. Differences between the groups were significant, with less Aβ in treated mice than in controls



Singh et al. 2013. Patients with subretinal fibrosis had significantly lower plasma Vit D concentrations compared to patients without subretinal fibrosis.



Patients without subretinal fibrosis (light filling) were more likely to be Vit D sufficient compared to those with subretinal fibrosis (dark filling) who were more likely to be deficient.

Future Strategies

- Detecting and preventing Vit D deficiency could prove helpful when managing patients with wet AMD to reduce incidence of fibrosis
- Potential for Vit D as an anti-inflammatory agent in conjunction with already available therapies (VEGF inhibitors)

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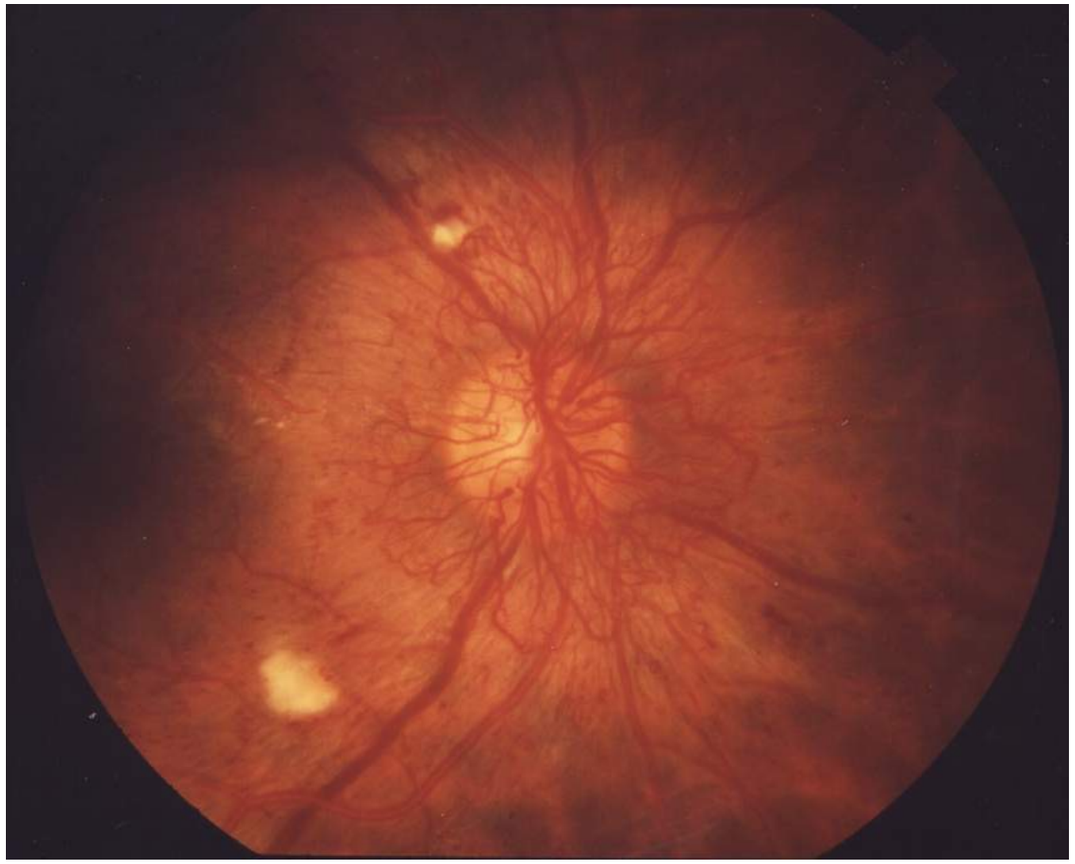
Diabetic Retinopathy

- Diabetic Retinopathy is the result of microvascular retinal changes
- Leading cause of blindness for people aged 20-64
- After 10 years or more, 80% of diabetic patients affected
- Treatments: laser surgery, anti-VEGF injection, vitrectomy, diabetes management



http://www.medindia.net/patients/patientinfo/general-info-about-diabetic-retinopathy.htm

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Vit D and Diabetic Retinopathy:

Degree of retinopathy	Mean level of 1,25(OH) 2 D3 (pmol/L)	P value
Mild NPDR	67.4 ± 13.7	($p < 0.001$)
Moderate NPDR	59.3 ± 11.2	($p < 0.001$)
Severe NPDR	45.7 ± 16.6	($p < 0.001$)
PDR	34.1 ± 17.2	($p < 0.001$)

(Reheem and Fattah, 2013)

“A single large dose of oral Vit D2 improves endothelial function in patients with Type 2 diabetes and Vit D insufficiency.” (Sugden, et al. 2008)

“VDD is associated with an increased prevalence of retinopathy in young people with type 1 diabetes.” (Kaur, et al. 2011)

“Current evidence is insufficient to assess the balance of benefits and harms of screening for Vit D deficiency in asymptomatic adults” (USPSTF, 2014)

Conclusion

- High Vit D levels have shown to be associated with lower risk of AMD but results are inconclusive and conflicting.
- Potential as an anti-inflammatory.
- Inconclusive evidence that Vit D may be therapeutic for diabetic retinopathy.
- **<u>Going forward, to gain more conclusive evidence:</u>**

• Less specific samples

• Categorise AMD by severity

• Record important factors e.g. D supplementation