# The Role of Vitamin D (and Gender) in Optic Neuritis Study ("VitaDON")

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## Disclosures

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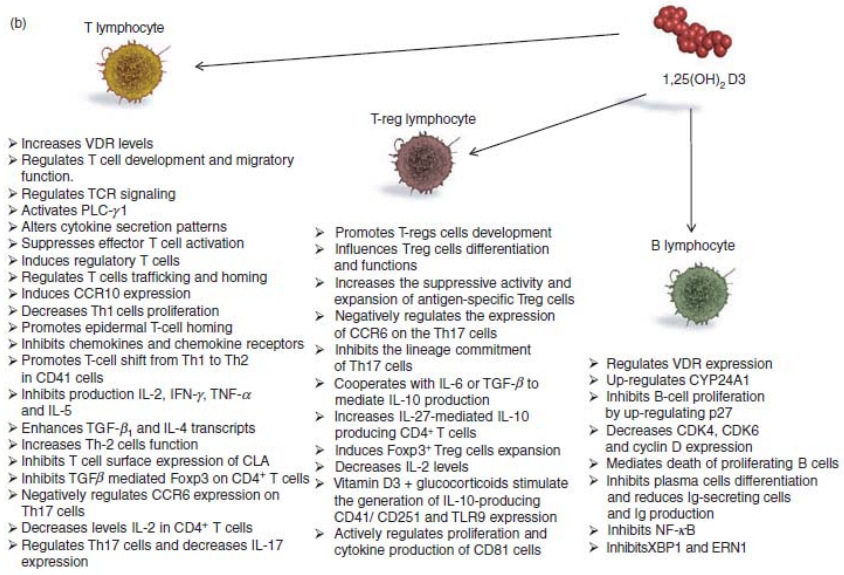
## Objectives

- Vitamin D in MS – a quick reminder
- A review of optic nerve physiology and optical coherence tomography (OCT)
- The design and results of Vitamin D in Optic Neuritis (VitaDON) pilot study
- Lessons learned and future plans

# Background

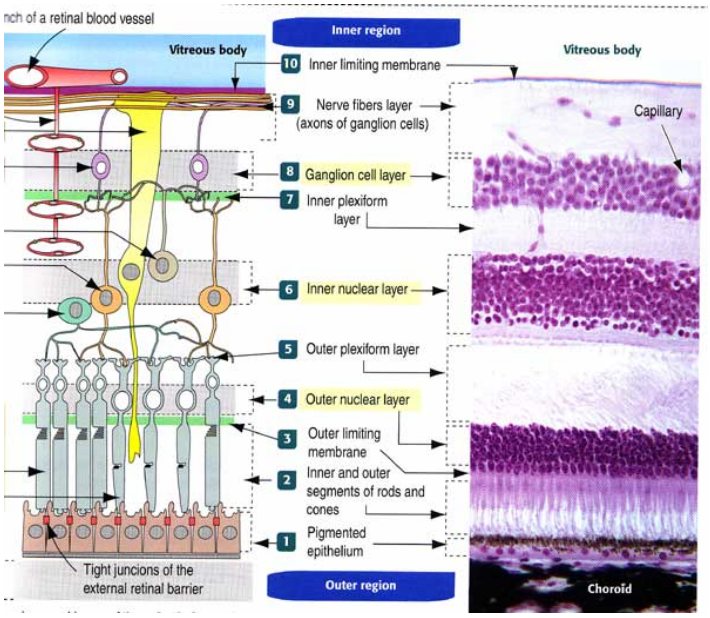
- Vitamin D insufficiency is a risk factor in MS development, and is common in MS patients
- Many studies have shown relapses and MRI lesion activity are associated with vitamin D
- Convergent evidence supports the anti-inflammatory effects of vitamin D, but there remains no definitive clinical proof of neuroprotection and/or factors associated with recovery

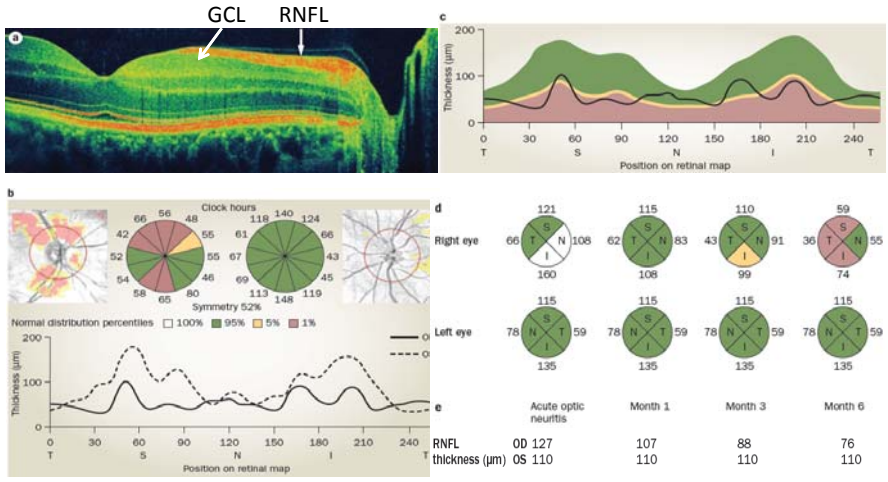


# A Little Information About the Optic Nerve and Optic Neuritis

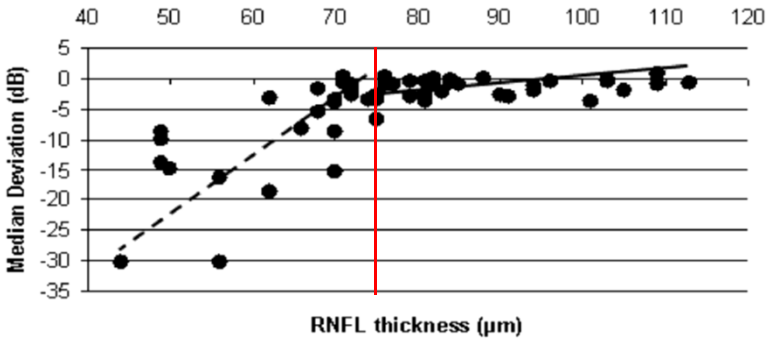
- The optic nerve is comprised of retinal ganglion cell axons originating in the retinal nerve fiber layer (RNFL)
- The absence of myelin in the RNFL makes it an ideal anatomical substrate within the CNS to quantify axon loss in the context of demyelination
- Optical coherence tomography (OCT) non-invasively measures optic nerve injury and recovery, quantifying subsequent loss of RNFL thickness, and chronic changes can be seen in as few as 6 months
- The ganglion cell layer (GCL), also measured by OCT, is not impacted by edema, thus it may be a less "messy" measure of thinning in the first 6 months of an optic neuritis event

# The Retina






(Taken from Barkhof et al, 2009, Nat Rev Neurol).




One regression line (dotted line) shows the relation between retinal nerve fiber layer (RNFL) values less than 75 um and visual field mean deviation; the other regression line (solid line) shows the relation between RNFL values greater than or equal to 75 um and visual field mean deviation. (Costello et al, 2006, Ann Neurol)

## So….

- If vitamin D has a multitude of immune actions
- And it clearly impacts the inflammatory clinical, radiological and other markers of demyelinating disease activity
- Maybe it can impact neurodegeneration and recovery?
- And…if the optic nerve provides a non-invasive substrate to look at not only inflammatory aspects of demyelination, but measures of axonal and neuronal loss as well
- And if this can be assessed in as little as 6 months
- Maybe we can use the optic nerve and OCT to study vitamin D's impact of neurodegeneration and/or recovery?

## Vitamin D in Optic Neuritis (VitaDON)

- Prospective 6 month pilot study of 50 patients typical optic neuritis event in a naïve eye
- Inclusion criteria: = > 18 years of age within 30 days of an episode of relatively typical optic neuritis in the context of demyelinating disease or an isolated event.
- Exclusions criteria: A previous optic neuritis or optic nerve injury in the same eye
- Vitamin D insufficiency defined as serum 25(OH)D < 80nmol/L
- Approved by University of Calgary Conjoint Health Research Ethics Board
- Start date: May 2011
- Last patient out: March 2014

## Primary Hypotheses:

-RNFL and GCL thickness (mean total, inter-eye difference) at **6 months post-optic neuritis** will show relatively less thinning in patients whose optic neuritis event occurred in the context of vitamin D sufficiency (25(OH)D > 80nmol/L)

## Secondary Hypotheses:

-RNFL thickness (mean RNFL, inter-eye difference) **at optic neuritis onset** will show relatively less thickening (i.e. edema) in patients whose optic neuritis event occurred in the context of vitamin D sufficiency

-Macular volume will follow the behaviour of RNFL

# Methods/Schedule of Activities

| | Baseline | Month 3 (+/- 1mo) | Month 6 (+/- 1mo) |
|---|---|---|---|
| **Consent, eligibility review** | • | | |
| **History** | • | • | • |
| **Chart/Meds/Lifestyle review** | • | | • |
| **Visual assessment, VEP, OCT*** | • | • | • |
| **25(OH)D** | • | • | • |
| **EDSS** | • | | • |

* Cirrus

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* Cirrus

# Results: Demographics

As of March 2014, 49 patients (50 eyes) of a targeted 50 patients have been enrolled with 42 having been evaluated at month 6.

| | Vitamin D Insufficient (25(OH)D < 80 nmol/L) (n=32) | Vitamin D Sufficient (25(OH)D > 80 nmol/L) (n=17) | p-value |
|---|---|---|---|
| **Age** | 35.3 | 35.2 | NS |
| **Gender (F/M)** | 22/10 | 14/3 | NS |
| **Diagnosis (CIS/MS/Other)** | 24/7/1 | 9/7/1 | NS |
| **Acute Steroid Therapy (Y/N)** | 12/20 | 6/11 | NS |
| **Baseline 25(OH)D** | **56** | **105** | <0.0001 |

# OCT Outcomes by Vitamin D Status

| | Vitamin D Insufficient (25(OH)D < 80 nmol/L) (n=32) | Vitamin D Sufficient (25(OH)D > 80 nmol/L) (n=17) | p-value |
|---|---|---|---|
| Baseline RNFL (µm) | 131 | 106 | 0.13 |
| Baseline RNFL IED (µm) | -36 | -9 | 0.04 |
| Baseline MV ($mm^3$) | 10.21 | 9.87 | 0.03 |
| Month 6 RNFL (µm) | 81 (n=29) | 76 (n=15) | NS |
| Month 6 RNFL IED (µm) | 12 (n=26) | 8 (n=15) | NS |
| Month 6 GCL IED (µm) | 14 (n=21) | 6 (n=12) | 0.066 |

# OCT Outcomes by Vitamin D Status: Baseline Measures

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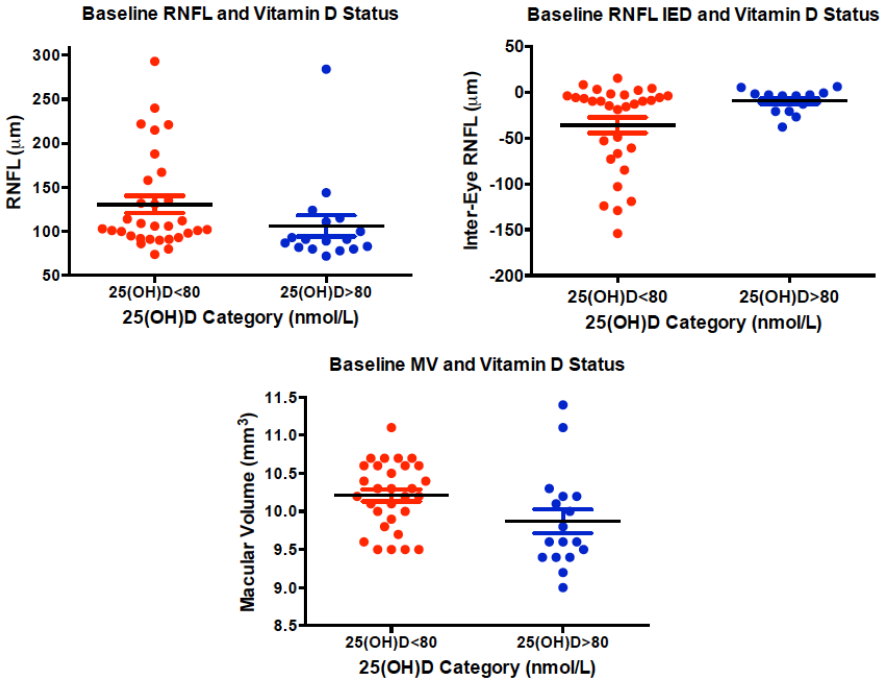


# OCT Outcomes by Vitamin D Status: Month 6

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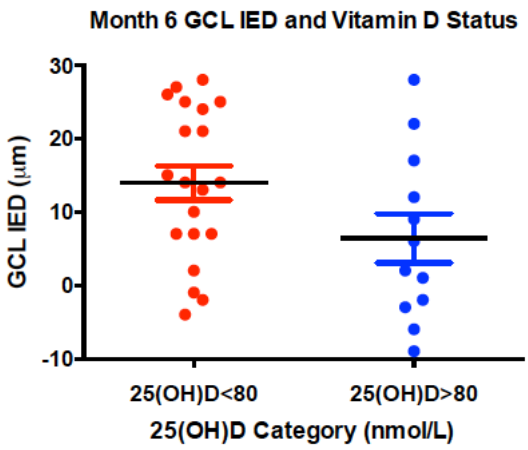


# Results by Gender

| | Male (n=13) | Female (n=36) | p-value |
|---|---|---|---|
| **Age** | 35.9 | 35.2 | NS |
| **Baseline 25(OH)D (nmol/L)** | 64 | 75 | NS |
| **Baseline RNFL (μm)** | 121 | 128 | NS |
| **Month 6 RNFL (μm)** | 70 (n=11) | 81 (n=32) | 0.018 |
| **Month 6 RNFL IED (μm)** | 21 (n=10) | 7 (n=31) | 0.003 |
| **Month 6 GCL (μm)** | 60 (n=8) | 67 (n=25) | 0.040 |
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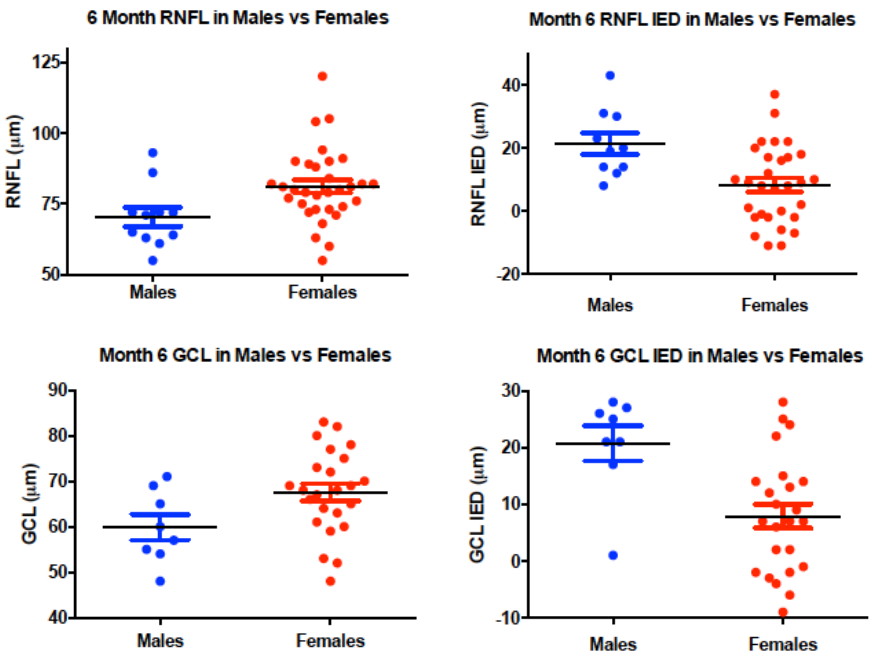

## Lessons Thus Far

- Our OCT results suggest vitamin D does impact optic neuritis outcomes acutely and chronically
- In acute optic neuritis, regardless of gender, disease subtype or steroid use, vitamin D insufficiency is associated with greater edema in the RNFL and macula
- By 6 months, both vitamin D insufficiency and male gender are associated with relatively greater thinning in the RNFL, but more so in the ganglion cell layer (GCL), which is unaffected by the initial edema
- These results suggest that vitamin D sufficiency and female gender may confer either neuroprotection and/or improved recovery in the optic nerve after optic neuritis. It is possible that these two factors interact and work synergistically.

## Future plans

- An additional 50 patients will be enrolled to take this from a pilot study to a properly powered prospective cohort study
- Use of this design and model to study other putative influences and therapies for demyelinating disease with respect to neuroprotection, neurodegeneration and recovery
- A possible trial of acute high-dose vitamin D therapy in relapse/optic neuritis (e.g. vs placebo, vs. high-dose steroids…)

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