Detecting Tomorrow’s Macular Degeneration Today

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Of cases missed, 39.9% had intermediate disease: large drusen

A missed opportunity for treatment


Visual acuity in AMD

Beaver Dam Study: Early-intermediate disease

Relatively good visual acuity: loss of two or fewer letters

Visual acuity is a simple, common measurement but lacks diagnostic value


Photoreceptor damage in AMD

Normal macular anatomy

The macula is cone-enriched but not cone-dominated. Rods outnumber cones in the macula by 9:1

Only the center 0.80 mm of the macular (the fovea sub-region) is exclusively cones

Photoreceptor damage in AMD

Rod pathology occurs before cone pathology

*Normal fovea*  *Dry AMD fovea*

*Relative retention of foveal cones*

*No change in peak cone density or total foveal cones*


Photoreceptor damage in AMD

Rod pathology occurs before cone pathology

Degeneration of para-foveal rods

60-70% reduction


Normal dark adaptation

Functions shift to the right with increasing decade, indicating a slowing of the rate of dark adaptation during aging.
Rod-mediated dark adaptation

A shorter protocol

Less bleach: 0.80 ms light delivered 5 degrees inferior to fixation
  • 76% bleach of rods

Endpoint: Rod intercept
  • Amount of time necessary after bleach offset for the patient’s sensitivity to recover to $5 \times 10^{-3}$ scot cd/m$^2$
  • Entirely mediated by rods

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Test region: 2° area, 5 degrees superior to visual meridian

Rod-mediated dark adaptation

Use as a diagnostic tool

Healthy controls took 5.5 minutes to recover a sensitivity of $5 \times 10^{-3}$ scot cd/m$^2$ (‘rod intercept’) after a 76% rod bleach

AMD subjects of all severity did not reach the rod intercept during the testing duration

Diagnostic sensitivity: 90.6%

Diagnostic specificity: 90.5%
Rod-mediated dark adaptation

Correlation with clinical findings

Damage within four degree testing area in the superior retina correlated with impaired dark adaptation recovery:

Rod-mediated dark adaptation

Use as a diagnostic tool

Over the course of three years, older patients (by four years) and smokers were more likely to have abnormal dark adaptation recovery.

When age and smoking status were controlled, however, adults with a healthy macula but an increased rod-intercept were twice as likely to develop early AMD than those with normal dark adaptation.

Physiological basis for dark adaptation deficiencies

Photochemical damage may exacerbate oxidative damage


Macular pigment is protective against AMD

Protective (antioxidant) properties of lutein and zeaxanthin


Macular pigment is protective against AMD

Heterochromatic flicker photometry: an optical measurement of macular pigment density

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Macular pigment density levels in Midwest

Humans, n = 280
Heterochromatic flicker photometry

Mean macular pigment density: $0.211 \pm 0.013$

40% lower than the rest of the country

Macular pigment co-varies with serum carotenoid levels and dietary intake

Macular pigment is protective against AMD

Can a diet high in carotenoids make a difference?

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Summary Effect</th>
<th>95% Lower Lmiter</th>
<th>95% Upper Lmiter</th>
<th>p Value</th>
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<tbody>
<tr>
<td></td>
<td>RR</td>
<td></td>
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<tr>
<td>Fish types</td>
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<td>Dark meat fish</td>
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<td>Non-dark meat fish</td>
<td>0.82</td>
<td>0.65</td>
<td>1.03</td>
<td>0.088</td>
</tr>
</tbody>
</table>

\[ n = 128,988 \text{ humans from 8 cohorts} \]

Weekly consumption of dark meat fish reduced the risk of AMD (any stage) incidence over ten years.


Looking into the future

Diagnostic aid from artificial intelligence

*Deep neural network*: computer program with many repeated processing layers that take input data (color fundus photographs) and process them via a cascade of operations with the goal of producing an output class label for each image.

*Deep Learning*: when a deep neural network is able to learn task-specific image features with multiple levels of abstraction without relying on manual feature selection.
Goal: classify color fundus photos as either healthy or having early, intermediate, or advanced AMD

Deep learning systems had similar performance metrics to human graders.

n = 130,000 images from AREDS
Conclusions

• Many cases of early age-related (AMD) macular degeneration go undiagnosed

• Clinical tests that target rod function, including dark adaptometry, may provide early detection of AMD

• Due to its antioxidant and light-absorbing properties, macular pigment plays a protective role against AMD

• Measurement of macular pigment optic density may identify patients at risk of developing AMD or progressing with the disease

• In the (near?) future, artificial intelligence programs will likely aid in the diagnosis and monitoring of AMD