

Age-Related Macular Degeneration and Metformin

Kimberly Nguyen, MD

1

Objectives

- Understand the basics of Age Related Macular Degeneration (AMD)
- Understand the relationship between metformin use and AMD
- Counsel patients with AMD on the potential ocular effects of metformin use

2

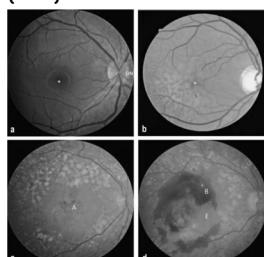
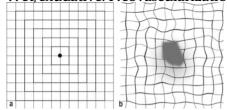
Outline

- AMD: Definition, epidemiology, pathophysiology, management, prognosis
- Metformin: Mechanism, indications, adverse effects
- Clinical trials demonstrating the relationship between metformin and AMD

3

Age-Related Macular Degeneration (AMD) Definition

- Chronic progressive degenerative disorder of the macula due to age related changes leading to loss of central vision
- Dry/nonexudative: small drusen → geographic atrophy
- Wet/exudative: Neovascularization



Stahl et al.

4

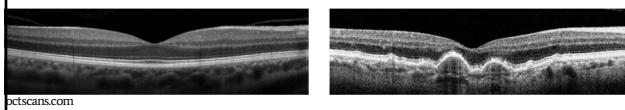
AMD Epidemiology

- Third most common cause of blindness worldwide
- Rare in pts under 55 yo
- More commonly in pts older than 75 years
- F>M
- Risk factors: light irides, age, smoking, hyperopia, hypertension, hypercholesterolemia, family history

5

AMD Pathophysiology

- RPE failure to process cellular debris
- Lipids deposited in Bruch's membrane
- Drusen (lipid, amyloid, complement factors, cellular components)
- Thickening of Bruch's, degeneration of collagen and elastin within Bruch's, increased glycation end products, accumulation of lipids and cellular debris form barrier between choroid and retina → relative ischemia with subsequent CNV



octscans.com

6

AMD Management

- Dry AMD: AREDS2
 - Decrease progression to wet AMD
 - Smoking cessation
- Wet AMD:
 - Anti-VEGF: bevacizumab, aflibercept, ranibizumab

7

AREDS

- Objective: Reduce the risk of vision loss in intermediate/stage 3 to advanced/stage 4 nonexudative AMD
- Intermediate/stage 3 = 1 large druse $\geq 125\text{um}$, extensive soft intermediate drusen (63-142 um) or nonsubfoveal GA
- Advanced/stage 4 = vision loss due to neovascular AMD or subfoveal GA in one eye
- AREDS formulation: VitC (500 mg), vitE (400 IU), betacarotene (15 mg), zinc (80 mg)
- Findings:
 - Intermediate or advanced AMD had 25% risk reduction for progression to more advanced stage of AMD and 19% reduction in mod vision loss (≥ 3 lines) at 5 years
 - 23% reduction in progressing to advanced AMD at 10 years
 - No benefit for no AMD or early stage, no increased mortality

8

AREDS2

- Objective: Replaced beta carotene with lutein (10mg) and zeaxanthin (2 mg) and added omega 3
- AREDS2: vitC, vitE, lutein, zeaxanthin, zinc; no betacarotene
- Findings
 - Similar visual outcomes as AREDS
 - Less risk of lung cancer in current and former smokers (beta carotene)

9

AMD Prognosis

- Risk of developing advanced AMD in one eye at 5 or 10 years
 - Presence of 1 or more large drusen ($\geq 125\text{um}$) (1 point)
 - Presence of pigment abnormalities (1 point)
 - If no large drusen; presence of bilateral intermediate drusen ($63\text{-}124\text{um}$)
 - Presence of neovascular AMD (2 points)**

Table 4-1 Five- and 10-Year Risks^a of Advanced AMD in 1 Eye

Number of Risk Factor Points	5-Year Risk, %	10-Year Risk, %
0	0.5	1
1	3	7
2	12	22
3	25	50
4	50	67

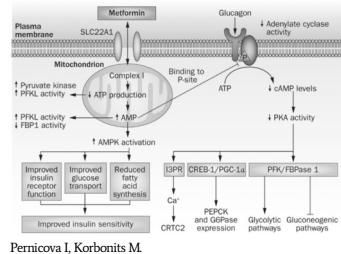
AMD = age-related macular degeneration.

^a Risks are based on the number of Age-Related Eye Disease Study (AREDS) risk factors (see text).

10

Metformin Mechanism of Action

- Primary site of action: mitochondria
- Inhibit hepatic gluconeogenesis
- Opposing glucagon mediated signaling in the liver
- Minor: increase glucose uptake in skeletal muscle



11

Metformin Indications

- Diabetes mellitus type 2

12

Metformin Adverse Effects

- Nausea/vomiting
- GI upset
- Diarrhea
- Weakness
- Metallic taste
- Lactic acidosis (rare, most severe)

13

AMD and Metformin Studies

- Blitzer et al. JAMA Ophthalmol. 2021 Mar.
- Objective: Determine whether metformin use is associated with reduced odds of developing of AMD
- Methods
 - Case-control study
 - 55 years or older with new diagnosed AMD (cases) matched with control subjects
 - Exposure: dosage of metformin
- Results
 - Metformin associated with reduced odds of developing AMD (OR 0.94, 95% CI, 0.92-0.96)
 - Dose dependent: low to moderate doses of metformin showed the greatest potential benefit
 - Doses of more than 1080 g of metformin over 2 years did not have reduced odds of developing AMD
- Conclusions
 - Metformin may be useful as a preventive therapy for AMD and provides the basis for potential prospective clinical trials

14

AMD and Metformin Studies

- Romdhoniyyah et al. Ophthalmol Ther. 2021 Jun.
- Objective: Systemic review and meta analysis to review beneficial associations between metformin and AMD
- Methods
 - Systemic search of several databases for clinical studies between metformin and AMD (5 retrospective studies)
- Results
 - Pts taking metformin were less likely to have AMD although statistical significance was not met (pooled adjusted OR = 0.80, 95% CI 0.54-1.05, I² = 98.8%)
- Conclusions
 - Metformin may be associated with decreased risk of any AMD (although should be interpreted with caution because of the failure to meet statistical significance)
 - Limitations: small number of studies limited routine record data

15

AMD and Metformin Studies

- Stewart et al. Ophthalmol Retina, 2020 Nov.
- Objectives: Evaluate the development of AMD in those taking metformin vs not taking the drug
- Methods
 - Cross sectional retrospective study
 - N = 3120 diabetic pts >60 years old
- Results
 - Those taking metformin were less likely to have age-related macular degeneration compared with those not taking the drug (OR 0.70, 95%CI 0.55-0.88)

16

AMD and Metformin Studies

- Chen et al. J Ophthalmol. Oct 2019.
- Objectives: whether metformin is associated with a lower risk of subsequent AMD in patients with type 2 diabetes
- Methods
 - Retrospective cohort study
 - Type 2 diabetics using metformin (N=45,524) vs type 2 diabetics not using metformin (N = 22,681)
- Results
 - Metformin group had a significantly lower risk of AMD (adjusted HR = 0.54; 95% confidence interval [CI], 0.50-0.58)
- Conclusions
 - Among patients with type 2 diabetes, those who use metformin are at a significantly lower risk of developing AMD relative to individuals who do not use metformin
 - Significantly lower AMD risk was found with a higher dose of metformin

17

AMD and Metformin Current Clinical Trials

- Title: Metformin for the minimization of Geographic Atrophy Progression in Patients with AMD
- Objectives: The purpose of this study is to determine whether **metformin**, an FDA-approved drug for the treatment of type II diabetes, is a safe and effective treatment to decrease the progression of geographic atrophy in non-diabetic patients with Age-related Macular Degeneration (AMD).
- Treatment vs observation groups
 - Treatment group: Metformin daily for 18 months + standard ophthalmic care over 24 months
 - Observation group: standard ophthalmic care over 24months
 - Testing: fundus photos, autofluorescence, OCT
- Outcomes
 - Rate of change in area of geographic atrophy on imaging
 - BCVA
 - Systemic safety of metformin use (monitoring for adverse effects)

18

Conclusions

- AMD is a chronic progressive degenerative disorder of the macula due to age related changes leading to loss of central vision
- AREDS2 supplementation has been shown in clinical trials to decrease the risk of progression from nonexudative to exudative AMD
- Metformin is a widely used oral medication for the management of diabetes mellitus type 2
- Metformin use may be associated with a decreased risk of developing AMD
- Further studies are required to evaluate the efficacy of metformin use and the development of AMD

19

References

1. Gheorghe A, Mabdi I, Musat O AGE-RELATED MACULAR DEGENERATION. *Rom J Ophthalmol*. 2015;59(2):74-77.
2. Stali A. The Diagnosis and Treatment of Age-Related Macular Degeneration. *Dtsch Arztebl Int*. 2020;117(29-30):513-520. doi:10.3238/arztebl.2020.0513
3. Persechino I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol*. 2010;14:145-156 (2014). PMID: 24300000 PMCID: PMC3021325
4. Blitzer AL, Han SA, Colby KA, Skondra D. Association of Metformin Use With Age-Related Macular Degeneration: A Case-Control Study. *JAMA Ophthalmol*. 2021 Mar;139(3):302-309. doi: 10.1001/jamaophthalmol.2020.331. PMID: 33475969 PMCID: PMC821082
5. Romdhoniyah DF, Harding SP, Cheyne CP, Beare NAV. Metformin: A Potential Role in Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis. *Ophthalmol Ther*. 2021 Jun;10(2):245-260. doi: 10.1007/s40123-021-00344-3. Epub 2021 Apr 12. PMID: 33846058 PMCID: PMC8079568
6. Dang KR, Wu T, Hui YN, Du HJ. Newly-found functions of metformin for the prevention and treatment of age-related macular degeneration. *Int J Ophthalmol*. 2021 Aug;18(14):1274-1280. doi: 10.18240/ijoo.2021.08.20. PMID: 34414094 PMCID: PMC8942286
7. Stewart JA, Lamy R, Wu F, Keenan JD. Relationship between Oral Metformin Use and Age-Related Macular Degeneration. *Ophthalmic Retina*. 2020 Nov;4(11):1118-1119. doi: 10.1007/s40603-020-00603. Epub 2020 Jun 7. PMID: 32529055 PMCID: PMC699665
8. Chen YY, Shen YC, Lai YJ, Wang CY, Lin KH, Feng SC, Liang CY, Wei LC, Chou P. Association between Metformin and a Lower Risk of Age-Related Macular Degeneration in Patients with Type 2 Diabetes. *J Ophthalmol*. 2019 Oct 31;2019:1649156. doi: 10.1155/2019/1649156. PMID: 31781371 PMCID: PMC6875398

20

Thank you!

Questions/comments?

21