

INFLUENCE OF MEDITERRANEAN-STYLE DIET ON AMD

Our findings suggest certain dietary and lifestyle habits may confer long-term protective benefits.

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AMD is a progressive, multifactorial cause of vision loss, especially in Western countries. While early stages may be only mildly symptomatic, advanced AMD, whether geographic atrophy or neovascular disease, can significantly affect a patient's independence and quality of life.

Among the identified risk factors—age, genetics, smoking, race, hypertension, diet—few are readily modifiable, which, given the noncurative nature of currently available therapies, places great emphasis on those that are adjustable.

Epidemiological research has demonstrated an association between diet and the risk of AMD development or progression. Diets rich in saturated fats, refined grains, and red meats, reflective of a typical Western diet, are linked to increased AMD risk.¹ In contrast, a Mediterranean diet, characterized by high levels of fruits, vegetables, whole grains, and fish, is associated with slower disease progression.² Despite these findings, a definitive causal link has not been established, and the biological mechanisms underlying this apparent gut-eye connection remain poorly understood.

Thus, gut microbiome has gained attention as a promising area of investigation with significant mechanistic and therapeutic implications. The gut microbiome is a complex ecosystem of microbes within the gastrointestinal tract that is heavily influenced by host intake and exerts systemic effects on host immune function and metabolism. Beyond its immediate effect on the gut, alterations in the gut microbiome have been implicated in a wide array of systemic diseases, ranging from Alzheimer

disease to diabetes.³ Gut dysbiosis, or an imbalance in the composition of the gut microbiome, has been identified in patients with AMD, pointing toward a potential role of the microbiome in disease progression.¹

Using a laser-induced choroidal neovascularization (CNV) mouse model of wet AMD, our team demonstrated that dietary changes may induce gut dysbiosis and modify susceptibility to neovascularization.

THE MEDITERRANEAN DIET PROTECTS AGAINST CNV

In our study, mice were fed one of three diets: a Mediterranean-style diet (MED) rich in olive oil, fish protein, and egg whites to replicate a human Mediterranean diet; a Western style diet (WD) with predominantly simple sugars

KEY TAKEAWAYS

- ▶ Gut dysbiosis, or an imbalance in the composition of the gut microbiome, has been identified in patients with AMD, pointing toward a potential role of the microbiome in disease progression.
- ▶ In our study, mice were fed three diets: a Mediterranean diet, a Western diet, and a low fat, high fiber mouse diet rich in wheat and corn that is standard for laboratory mice.
- ▶ Compared with the Western diet, the Mediterranean diet was protective against wet AMD and was associated with a decrease in proinflammatory gut bacteria.

DIETS RICH IN SATURATED FATS, REFINED GRAINS, AND RED MEATS, REFLECTIVE OF A TYPICAL WESTERN DIET, ARE LINKED TO INCREASED AMD RISK.

and butter-based fats to mimic a typical human Western diet; and a low fat, high fiber mouse diet (LFHFB) rich in wheat and corn that is standard for laboratory mice. The MED and WD contained similar amounts of carbohydrates, proteins, and fats but differed in the sources of these macronutrients. The mice were fed their assigned diets for 6 months, a duration considered to represent long-term dietary exposure in murine models.

Afterward, all mice underwent laser-induced CNV, and 1 week later, the eyes were assessed for lesion size and subretinal microglia/macrophage infiltration. We found that the WD mice had significantly increased angiogenic and local inflammatory response, while the MED mice had suppressed lesion size and microglia/macrophage recruitment, reinforcing our current understanding of diet as an AMD risk factor in humans.

MICROBIAL DYSBIOSIS MEDIATES INFLAMMATORY SUSCEPTIBILITY

To investigate the role of the gut microbiome in driving these findings, we investigated the makeup of the gut microbiome from each group using 16s sequencing of the bacterial DNA from their stool. This revealed distinct microbial signatures between the MED-, LFHFB-, and WD-fed mice. Although each group displayed a dominance of Firmicutes at the phylum level, clear compositional divergence emerged when comparing MED mice with WD mice. Proinflammatory bacteria such as *Lactococcus*, *Eubacterium*, and *Romboutsia* were higher in WD mice, yet were almost absent with the MED and LFHFB mice.

When the gut microbiome is altered as such, the integrity of the intestinal wall can be compromised, allowing absorption of bacterial toxins into the blood and promotion of a low-grade systemic inflammation.⁴ Downstream signaling pathways can subsequently activate choroidal angiogenesis via increased production of interleukin-1-beta and VEGF.⁵ Mamun et al showed increased *Lactococcus* abundance in high-fat or metabolic disease states in mice and humans.⁶ *Eubacterium ventriosum* has also been found to be enriched in patients with AMD compared with controls, which has been associated with elevated levels of proinflammatory cytokines.^{7,8} These taxa have been linked to gut barrier dysfunction, increased endotoxin release, and systemic inflammatory priming, processes known to propagate complement factor H activation and angiogenic signaling in the retina.¹ Therefore, these diet-induced alterations could

contribute to susceptibility to AMD and neovascularization.

After identifying these compositional differences, we performed mass spectrometry to assess levels of bacterially produced metabolites. This revealed increased levels of antiinflammatory metabolites, including isobutyrate, propionate, and valerate, in MED mice compared with WD mice. Isobutyrate is a branched chain fatty acid derived from dietary protein, while propionate and valerate are short chain fatty acids derived from fiber. They play active roles both locally in the gut and systemically. At the gut wall, they promote integrity of the intestinal wall barrier, preventing absorption of bacterial toxins and associated low-grade inflammation. Impairments in this process have been previously associated with ocular diseases, such as diabetic retinopathy and uveitis, in addition to AMD.⁴ Short chain fatty acids can also be absorbed and delivered to the eye, where they mitigate the proinflammatory response by reducing cytokine production and limiting immune cell migration, which could explain our observed microglia results.⁹

THE GUT MICROBIOME DRIVES THE CONNECTION

To determine whether the observed dietary effects on wet AMD features were truly driven by the microbiome changes, we conducted fecal transplants from MED and WD mice to germ-free mice, which lack their own innate gut microbiome. The germ-free mice were kept on the standard LFHFB diet and underwent the same laser-induced CNV. The fecal transplants replicated the original diet-induced phenotypes seen in the donors. Fecal transplants from MED mice led to decreased CNV and immune cell infiltration, while transplants from WD mice were associated with greater angiogenic response. This finding suggests diet-driven microbial communities can shape host susceptibility to CNV, even in the absence of direct dietary exposure. Moreover, reduced microglial and macrophage infiltration in MED transplant recipients further supports the notion that gut-derived signals influence retinal immune tone, possibly by limiting proinflammatory or proangiogenic pathways that exacerbate lesion expansion and severity.

These results reinforce the emerging concept of a gut-retina axis and indicate that MED-associated microbiota may confer resilience against CNV by attenuating both angiogenic and inflammatory responses. As such, our study raises the possibility that targeting the gut microbial composition—either through dietary interventions, probiotic/prebiotic

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supplements, or human fecal transplants from healthy donors—could offer a novel strategy to either directly mitigate CNV in wet AMD or to be used as an adjunctive therapy with current treatment standards.

NEW TREATMENT POSSIBILITIES

Although additional studies are warranted to further delineate the underlying pathways and mechanisms involved, the gut microbiome may represent a promising new avenue for approaching AMD treatment. ■

Acknowledgements: Funding was provided by the Edward N. & Della L. Thome Memorial Foundation; the Bright Focus Foundation; the Illinois Society for the Prevention of Blindness; FORE-I Foundation; The University of Chicago Women's Board; the Institute for Translational Medicine; the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; Genentech ARVO Foundation AMD Translational Awards; and the Bucksbaum Foundation.

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