THE HOMING TRIAL: A RETROSPECTIVE PILOT STUDY ON THE EFFICACY OF PERSONALIZED BIOIDENTICAL HORMONE, DIETARY SUPPLEMENT AND NUTRITION CARE PLANS FOR AGE-RELATED MACULAR DEGENERATION (AMD)

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Abstract

The objective of the Hormones, Oxidative stress, Methylation, Inflammation and Gene expression (HOMING) trial was to assess the efficacy of personalized bio identical hormone, dietary supplement and nutritional care plans on dry and wet Age-related Macular Degeneration (AMD) outcomes. We evaluated 220 Age-related Macular Degeneration (AMD) patients that followed a personalized clinical care plan for up to 9 months. The care plans consisted of bio identical hormones, dietary supplements and nutrition recommendations with the objective to improve lab and clinical measurements linked to oxidative stress, inflammation and gene expression. Serum concentrations of CRP, HbA1c and homocysteine responded favorably to the HOMING protocol with full program compliance.

Sixty percent (42/70) of wet AMD patients reported improvement in visual acuity and/or a reduction in the frequency of anti-VEGF injections during the study period. Forty eight percent (44/92) of dry AMD patients reported improvement in visual acuity during the study period. Nine percent (4/45) patients reported improvement in visual acuity in the dry AMD control group and no (0/13) wet AMD patients in the control group reported improvement. Six percent (4/70) of wet AMD patients reported that their vision declined and/or that their F frequency increased during the study period. Five percent (4/92) of dry AMD patients reported that their vision was worse.

Keywords: Bio identical Hormones, Oxidative stress, Methylation, Inflammation, Gene Expression, Nutrition and AMD.

Introduction:

Age-related Macular Degeneration (AMD) is the leading cause of vision loss in the United States.[¹] The American Academy of Ophthalmology (AAO) classifies AMD as a disease of a region of the retina called the macula that is distinguished by well-defined clinical characteristics.[²]

The cells in the eye are dependent upon essential dietary nutrients for protection from oxidative damage, which can occur as a result of free radicals that are generated in the eye from sunlight and during normal metabolic processes. In AMD, the cells in the retina are damaged, which leads to a deterioration of vision and eye health. Numerous risk factors are linked to developing AMD, including dietary, lifestyle, race, environment, genetic and medical.[³,⁴,⁵,⁶] Multiple dietary nutrients are concentrated in the retina and are thought to play a protective roll against inflammation and oxidative injury.[⁷]

Zinc and the plant-derived carotenoids are concentrated in the eye in relatively high levels, however, there is a lack of consensus regarding the protective effects of recommended daily allowance (RDA) level nutrient intake.[⁸,⁹] Dietary consumption of carotenoids, antioxidants and zinc at intake levels at or below the recommended daily value are not associated with a reduction in risk for the development or progression of AMD, according to the data derived from large scale prospective studies.[¹⁰,¹¹,¹²,¹³] Conversely, other medium and large scale studies have shown a positive correlation at the highest levels of dietary intake for carotenoids, antioxidants and zinc in lowering the risk of progression to advanced AMD.[¹⁴,¹⁵,¹⁶,¹⁷] Numerous studies have also reported a reduction in risk for acquiring AMD associated with fish consumption (Twins Study, Age Related Eye Disease Study [AREDS], Blue Mountains Eye Study, Carotenoids in Age-Related Eye Disease Study, Nurse’s Health and Health Professionals Follow-Up Study).[¹³,¹⁶,¹⁷,¹⁸,¹⁹,²⁰] These reported findings are notable, particularly given that Omega-3 fatty acid intake from dietary supplements was not associated with an improvement in AMD outcomes in the second Age Related Eye Disease Study (AREDS II).[²¹]

Strict adherence to the Mediterranean diet has been shown to lower the risk of progression to advanced AMD by 26%.[²²] The Mediterranean diet is based on liberal consumption of plant derived foods, moderate fish consumption, low intake of meat and dairy and a preference towards mono-unsaturated fatty acids such as olive oil. A case controlled study evaluating the food consumption pattern for patients that participated in the AREDS study found that individuals following a typical Western diet were at increased risk for both early and advanced AMD, while individuals that consumed a traditional Asian diet were at lower risk for advancing to early or late AMD.[²³]
Food intake was assessed in the Melbourne Collaborative Cohort Study and relatively high dietary intake of fruits, vegetables, chicken, and nuts and low intake of red meat were associated with a lower rate of incidence of advanced AMD.\textsuperscript{xxviii} Consistent with the findings of these studies, the National Eye Institute (NEI) of the National Institutes of Health (NIH) recommends increased consumption of fish rich in omega-3 fatty acids and green leafy vegetables as a preventative measure in mitigating the risk of developing and/or progressing early and late AMD.\textsuperscript{xxix}

The nutrition-based AMD professional guidelines were developed from the two AREDS study reports, whose primary objectives were to evaluate the targeted use of high dose carotenoids, antioxidants, omega-3 fatty acids and mineral supplements on the risk of AMD development and progression. AREDS was undertaken to determine if daily intake of select vitamins and minerals could reduce the risk of cataract and AMD.

The AREDS I study participants were randomized to receive daily oral tablets containing one of the following preparations: 1. Antioxidants (500 mg vitamin C, 15 mg beta-carotene, and 400 IU of vitamin E), 2. 80 mg zinc oxide, 2 mg cupric oxide, 3. Antioxidants plus zinc and copper, or 4. Placebo. The first AREDS formulation reduced risk for progression from intermediate AMD to advanced AMD by 25% after 5 years.\textsuperscript{xxx} The authors of the AREDS I study concluded that persons older than 55 years should have eye exams to determine their risk of developing AMD. Individuals with intermediate or advanced AMD were encouraged to consider taking a supplement of antioxidants plus zinc comparable to the formulations used in the AREDS I study.\textsuperscript{30}

The AREDS II study was conducted to assess whether increased dietary intake of lutein plus zeaxanthin, omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] plus eicosapentaenoic acid [EPA]), or a combination of both may further lower the risk of developing advanced AMD. A separate arm of the trial also examined the use of a lower dose zinc preparation as compared to the AREDS I trial (25 mg vs 80 mg).\textsuperscript{xxx} The results of the Lutein Antioxidant Supplement Trial (LAST) provided clinical evidence to support the inclusion of lutein and zeaxanthin in the AREDS II study. The LAST study demonstrated that supplementing lutein and zeaxanthin plus a multi-vitamin resulted in improvements in macular pigment density, visual acuity, contrast sensitivity and AMD scoring compared to placebo.\textsuperscript{xxx, xxxii}

Our objective in conducting the Hormones, Oxidative stress, Methylation, Inflammation and Gene expression (HOMING) trial was to assess the efficacy of personalized bioidentical hormone, dietary supplement and nutritional care plans on dry and wet Age-related Macular Degeneration (AMD) outcomes. The protocol was comprised of bioidentical hormones, dietary supplements and nutrition recommendations with the objective to favorably shift lab and clinical measurements linked to oxidative stress, inflammation and gene expression.

Methods

The HOMING trial was a retrospective, 9 month study conducted using a telemedicine system from March to December of 2020. Two hundred and twenty patients with dry and wet AMD were evaluated for the study. Participants submitted responses to questionnaires through their private telemedicine portal account. The care plans were comprised of bioidentical hormones, dietary supplements and nutrition recommendations with the objective to improve laboratory measurements linked to oxidative stress, inflammation and gene expression (Table I).

<table>
<thead>
<tr>
<th>Table I. Laboratory Panel Tests</th>
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<tbody>
<tr>
<td><strong>1. Hormones</strong></td>
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<tr>
<td>a.  Pregnenolone</td>
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<tr>
<td>b.  DHEAS</td>
</tr>
<tr>
<td>c.  Estradiol</td>
</tr>
<tr>
<td>d.  Progesterone (Female Only)</td>
</tr>
<tr>
<td>e.  Free and Total Testosterone</td>
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<tr>
<td>f.  Vitamin D-25OH</td>
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<tr>
<td>g.  TSH</td>
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<tr>
<td>h.  T4</td>
</tr>
<tr>
<td>i.  FT3</td>
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<tr>
<td>j.  rT3</td>
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<tr>
<td><strong>1. Blood Chemistry Tests</strong></td>
</tr>
<tr>
<td>a.  Complete Blood Panel (CBC)</td>
</tr>
<tr>
<td>b.  Homocysteine</td>
</tr>
<tr>
<td>c.  HbA1c</td>
</tr>
<tr>
<td>d.  CRP</td>
</tr>
<tr>
<td>e.  Lipid Panel</td>
</tr>
<tr>
<td>f.  B12</td>
</tr>
<tr>
<td>g.  Ferritin</td>
</tr>
<tr>
<td>h.  PSA (Male Only)</td>
</tr>
<tr>
<td>i.  Fasting Blood Glucose (FBG)</td>
</tr>
<tr>
<td>j.  Insulin</td>
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<tr>
<td>k.  RBC Magnesium</td>
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</table>
Female patients completed laboratory testing for all hormone and blood chemistry tests with the exception of PSA. Male patients completed laboratory testing for all hormone and blood chemistry tests with the exception of progesterone. Ferritin, insulin and RBC magnesium testing was only completed by select patients and was only used for non AMD health concerns. Following the evaluation of their hormone and blood chemistry reports and health histories, patients received recommendations for hormones and dietary supplements based upon the results of laboratory blood testing and the answers to a self-reported health history questionnaire (Table II).

<table>
<thead>
<tr>
<th>Table II. Hormone and Dietary Supplement Formulary</th>
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### 1. Hormones

- a. Pregnenolone
- b. DHEA
- c. 7-Keto DHEA
- d. Estrogen (estradiol and/or estradiol)
- e. Vitamin D3
- f. Progesterone
- g. Thyroxine (T4)
- h. Triiodothyronine (T3)

### 2. Dietary Supplements

- a. Lutein
- b. Zeaxanthin
- c. Meso-Zeaxanthin
- d. Saffron
- e. Bilberry
- f. Black Currant Extract
- g. Zinc
- h. Vitamin C
- i. Vitamin E
- j. Beta Carotene
- k. Pterostilbene
- l. Triglyceride EPA/DHA
- m. Glutathione
- n. Curcumin
- o. N-Acetyl Cysteine (NAC)
- p. Astaxanthin
- q. Ubiquinol (CoQ10)
- r. Melatonin
- s. Quercetin
- t. Pycnogenol
- u. Citicoline
- v. Barberry
- w. Alpha Lipoic Acid (ALA)
- x. Milk Thistle (Silymarin)

Assessments of visual acuity were performed by the patient’s eye professional and via in-home assessment by the patient. Determinations on changes in injection frequency were made by the patient’s retina specialist. Characteristics potentially influencing changes in visual acuity were the patient’s comorbidities, medications, AMD baseline status and compliance with program recommendations.

Self-reported changes in visual acuity and injection frequency were obtained via an internal questionnaire feature in our telemedicine system. Patients were provided at least one week to respond to the initial questionnaire and a follow-up questionnaire. Patients that did not respond to the original and follow-up questionnaires were excluded from the study. Patients that reported declining visual acuity or an increase in injection frequency were contacted via telephone for additional follow-up to determine their level of compliance with program recommendations and whether there were potential mitigating factors influencing their reported AMD progression.

The individual components for each personalized protocol were selected based on the patient’s ocular and systemic history, current medications, current care plan and laboratory data (Table I). Supplements were procured from the health professional supplement company called Full Scripts. Compliance was voluntary and patients were encouraged to take their recommended supplements in the initial program delivery and in follow-up communications, both via telephone and text messaging through their patient portal in the health system. Patients that were deemed “non-compliant” were assigned to the control group for the data analysis.

Patients were provided with a self-guided Mediterranean style dietary protocol through the patient portal in the telehealth system that was created by a registered dietitian. While patients were encouraged to follow the Mediterranean style dietary protocol we did not have an effective means to track compliance and we relied exclusively on self-reporting to assess compliance. Dietary compliance was not used to assign patients to the experimental or control groups.

### Results

We evaluated 220 Age-related Macular Degeneration (AMD) patients that followed a personalized HOMING protocol for up to 9 months. The study population was comprised of patients with both dry and wet macular degeneration. The care plans consisted of bioidentical hormones, dietary supplements and nutrition recommendations with the objective to improve lab and clinical measurements linked to oxidative stress, inflammation and gene expression.

Sixty percent (42/70) of wet AMD patients reported improvement in visual acuity and/or a reduction in the
frequency of anti-VEGF injections during the study period. Forty eight percent (44/92) of dry AMD patients reported improvement in visual acuity during the study period. Nine percent (4/45) patients reported improvement in visual acuity in the dry AMD control group and no (0/13) wet AMD patients in the control group reported improvement. Six percent (4/70) of wet AMD patients reported that their vision declined and/or that their frequency increased during the study period. Five percent (4/92) of dry AMD patients reported that their vision was worse. The self-reported study data is presented in table III.

<table>
<thead>
<tr>
<th>Treatment Group (n = 162)</th>
<th>Control Group (n = 58)</th>
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<tbody>
<tr>
<td><strong>Wet (n = 70)</strong></td>
<td><strong>Dry (n = 92)</strong></td>
</tr>
<tr>
<td>Worse</td>
<td>Same</td>
</tr>
<tr>
<td>4 (6%)</td>
<td>25</td>
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<td>0%</td>
<td>9%</td>
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Baseline laboratory testing served as the foundation for each patient’s personalized HOMING protocol. Follow-up testing was requested at 3 months for each patient. The average improvement in CRP level from baseline to follow-up was 10.4%. The average improvement in HbA1c from baseline to follow-up was 5.1%. The average improvement in homocysteine (Hcy) from baseline to follow-up was 8.4%. The average for all three metrics improved in the study, despite each metric’s average value being within their respective reference range at baseline. The average baseline and follow-up laboratory data is presented in table IV.

<table>
<thead>
<tr>
<th>Table IV. Key Laboratory Measurements</th>
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<tr>
<td><strong>Baseline Avg.</strong></td>
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<tr>
<td>CRP (mg/L)</td>
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<td>2.22</td>
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Discussion

This retrospective study reports on the self-reported outcomes derived from a modality care plans (HOMING Protocol) comprised of the hormone and dietary supplement formulary presented in Table II. The literature shows a connection between HOMING and macular degeneration. We propose that the HOMING protocol favorably impacts RPE cell biochemistry, directly and via epigenetic mechanisms, and lowers VEGF levels. A TITLE search term to review this literature generated 155 references.[xxxvi] If we search TITLE and ABSTRACT we find 2243 references.[xxxvii] It is important to note that the literature search for each of the HOMING modalities is conducted independently. Our hypothesis is that adherence to a personalized care plan for a minimum of 6 months will aid in the return of visual function so long as damage to the retina and choroid is not irreversible.

The HOMING protocol has the potential to reverse cell dysfunction, which represents a significant paradigm shift relative to the current standard of care. We do not have any reason to believe that the HOMING method can reverse the damage caused by cell death or scarring. Therefore, it stands to reason that initiating the HOMING protocol as early as possible in a patient’s AMD disease progression would be more likely to lead to favorable AMD outcomes. Side effects of protocol components were self-limiting and readily addressed by dose adjustment or removal of the offending component from the patient’s protocol. The key areas of emphasis in the HOMING protocol are summarized in the sections that follow.

HOMING - Hormones

Our early work in AMD focused on the importance of steroidal hormones to the health of the macula. Since steroidal hormones are derivatives of cholesterol, we hypothesized that cholesterol accumulation in the macula was linked to low levels of steroidal hormones that typically accompanies aging.[xxxvii] This hypothesis is consistent with literature describing cholesterol in drusen.[xxxvii] Literature evidence also shows that deficiency of the steroidal hormone DHEA is associated with AMD risk[xxxviii] and that this effect may be mediated via IL-6.[xxxix]
In a landmark paper published in the Italian literature entitled “Neurosteroids in the Retina”, researchers clearly laid out the importance of steroid hormones in the macula.[xliv] Estrogens, androgens and progesterone receptors are present throughout the eye and are locally produced in ocular tissues. These hormones have a neuroprotective action on the retina and modulate ocular blood flow. As a result, exposure to hormone replacement therapy appears to protect AMD.[xlvi] Sex hormone replacement therapy is also associated with lower risk of all macular degeneration stages including neovascular, early or intermediate dry disease and geographic atrophy.[xlix]

Estrogens can benefit macular degeneration due to their anti-oxidative and anti-inflammatory effects in retinal cells[xlvi] and estrogens lower inflammation by way of TNF and NF kappa B.[xliv, xlv] The neuroactive steroids, 17beta-estradiol and dehydroepiandrosterone-sulfate, enhanced survival and protected DNA of human retinal pigment epithelial cells challenged by oxidative stress. The results of the study suggest that neuroactive steroids protect retinal cells from oxidative stress and that this effect is mediated by sigma 1 receptors.[xlii] Interestingly, Pregnenolone is a sigma 1 agonist and has been shown to lower IOP.[xlvi]

HOMING - Oxidative Stress

Oxidative stress is a significant driver in the pathogenesis of AMD. Oxidative stress can be thought of as the imbalance between the production of reactive oxygen species (ROS) and their elimination by protective mechanisms.[xliv] Oxidative stress causes mitochondrial damage and down regulates the NRF2 genes that regulate oxidation.[xli] Mitochondrial damage causes the reduction of ATP which is critical for the high metabolic activity of the RPE.[lv] The cell damage that results from oxidative stress triggers inflammation, which can exacerbate and accelerate the progression of AMD and other age-related, chronic diseases.

Oxidative stress is managed both directly and indirectly by way of epigenetic effects viadietary supplement, bioidentical hormone, lifestyle and dietary modifications. In particular, smoking cessation is known to be of great benefit to reduce the risk of macular degeneration, especially when combined with diet.[li,lii] Lifestyle and dietary approaches to oxidative stress management can be augmented with a diverse array of dietary supplements and hormones such as curcumin,[lv] pregnenolone by way of mitochondrial respiration [lv], b-vitamins [lv], resveratrol [lvii], melatonin [lviii], estrogens [li, lx] and progesterone.[lx]

HOMING - Methylation

Methylation or one carbon metabolism is a fundamental biochemical process that affects many biochemical pathways, notablyregulating the expression of genes (epigenetics) via DNA methylation. The biochemistry of methylation involves the formation of SAMe in the methionine cycle. This process is facilitated by the folate cycle end product methyl folate, which works with B12 in the methylation of homocysteine. Homocysteine methylation regenerates methionine, which interacts with ATP and generates SAMe.

Hypomethylation is a common finding that often precedes a significant number of disease states and is part of the pathogenesis of AMD.[liv] One of the hallmarks of hypomethylation is elevated homocysteine, which is a driver of inflammation via NF kappa beta.[lviii] MTHFR is a crucial gene linked to the methylation pathway and abnormal MTHFR genes have been linked to an increased risk of macular degeneration.[lx] Hypomethylation of NF-xB-mediated pathway genes causes the induction of cytokines/chemokines IL-8, MCP-1, IL-6 and CCL5 which further adds to the challenge of managing inflammation.[lxv]

HOMING - Inflammation

Inflammation is a complex area of biochemistry and involves immune system components like B cells, T cells, macrophages and leukocytes. Cytokines are the general class of molecules to which chemokines, interferons, interleukins and others belong. Interleukins are messenger molecules between immune cells they are typically denoted by IL + number. Inflammation is a significant part of the pathogenesis of macular degeneration. Degenerative changes in RPE cells initiates a cycle that promotes the development of chronic inflammation in the retina and the choroid. This is in conjunction with age-related changes in the immune system that contribute to this process by altering the functions of immune cells.

The transcription factor NF-xB regulates multiple aspects of innate and adaptive immune functions and serves as a pivotal mediator of inflammatory responses. NF-xB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation. It is one of the major signal-transduction pathways that are activated in response to oxidant stress. It also plays vital role in human lens epithelial cells (HLE) death after inducing oxidative stress.[lvii] The activation of NF-xB has been linked with AMD.[lviii, lx] Activation of NF-xB is one of the important activation pathways for macrophage migration in AMD and the mechanism of protection against inflammation in AMD involves inhibition of nuclear translocation NF-xB along with degradation of NF-xB inhibitor alpha.[lxv]

TNF-Alpha has been shown to play a prime role in coordinating the cytokine cascade in many inflammatory diseases and because of its role as a “master-regulator” of inflammatory cytokine production, it has been proposed as a therapeutic target for multiple diseases.[lxii] Humira (adalimumab), a tumor necrosis factor antagonist, has been shown to benefit neovascular AMD in treatment failures of anti-VEGF therapy.[lxii]
CRP plays important roles in inflammatory processes and host responses to infection including the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, particularly interleukin-6 and tumor necrosis factor-α. In terms of pro-inflammatory cytokine production, mCRP increases interleukin-8 and monocyte chemoattractant protein-1 production, whereas nCRP has no detectable effect on their levels.[lxxxiv] This is important with regard to AMD because eyes homozygous for the high-risk CFH (Y402H) allele had elevated monomeric CRP (mCRP) within the choriocapillaris and Bruch's membrane, compared to those with the low-risk genotype. Individuals carrying the high risk polymorphism of the H gene that normally blocks excessive complement activity have been shown to be at greater risk for acquiring AMD.

The impairment of the hemo-ophthalmic barrier caused by the defeat of RPE makes antigens of the outer layers of the retina accessible leading to an autoimmune reaction.[lxxxv] Moreover, pro-inflammatory mCRP significantly affects endothelial cell phenotypes in vitro and ex vivo, suggesting a role for mCRP in choroidal vascular dysfunction in AMD.[lxxvi] Individuals with neovascular AMD also have significantly higher plasma levels of IL-1β, IL-6, IL-10 and CRP and lower levels of DHEA.[lxxvii lxxviii lxxix] Numerous supplements and hormones included in HOMING protocol have been shown favorably impact inflammatory markers. Curcumin significantly inhibited the release of pro-inflammatory cytokines and has shown promise as a therapeutic for major retinal pathologies.[lxxx] Estrogen receptor activation can counteract endothelial dysfunction induced by TNF-alpha.[lxxxi] Progesterone can also inhibit TNF-alpha.[lxxii] Milk thistle (Milk Thistle) Silymarin supplementation significantly increased superoxide dismutase (SOD), glutathione peroxidase (GPX) activity and total antioxidant capacity (TAC) compared to patients taking the placebo, and a significant reduction in CRP.[lxxiii]

HOMING - Nutrition

Nutrition plays a central role in the prevention and management of AMD. Antioxidants (Beta carotene, vitamin C, vitamin E), Carotenoids (lutein and zeaxanthin) and zinc, and omega-3 poly unsaturated fatty acids have been investigated for their benefit in AMD.[lxxxvii] Macular pigment density can be modulated with the dietary intake of key nutrients. Dietary carotenoids (lutein, zeaxanthin and beta-carotene) intake was assessed for 13 subjects in a 15 week trial. Improvements in macular pigment density were achieved at 4 weeks for most subjects and remained elevated after resuming an unmodified diet. Another study result demonstrated that increasing dietary intake of retinal carotenoids from carotenoid rich foods such as spinach can help augment macular pigments for most people.[lxxvii]

An 18-week RCT consisting of 33 participants evaluated the effect of consuming 1 egg per day on serum lutein and zeaxanthin levels in blood serum. Blood concentrations of both carotenoids increased with consumption of one egg per day, while concentrations of lipids were not affected. Consumption of one egg per day increases serum lutein and zeaxanthin concentrations in older adults without altering serum lipid and lipoprotein cholesterol concentrations.[lxxxv]

A study involving 184 older adult subjects evaluated associations between MPOD, plasma lutein and zeaxanthin concentrations as a function of cognitive performance. The study data suggested that both higher MPOD and lutein + zeaxanthin concentrations were significantly associated with higher cognitive performance. Plasma Concentrations of Lutein and Zeaxanthin, Macular Pigment Optical Density, and Their Associations With Cognitive Performances Among Older Adults.[lxxxvi]

The Mediterranean diet reduces markers of inflammation and oxidative stress and reduce the risk of macular degeneration by 41% in studies that have spanned decades. [lxxxvii lxxxviii] Weight loss and decreased red meat consumption can also contribute to a lower incidence of AMD. [lxxxvii] Omega 3 fatty acid intake from fish was associated with a reduction in AMD risk. [lxxxv] A medium scale study involving 261 participants age 60 and older with early or intermediate AMD had a reduction in risk of progression of AMD when consuming higher levels of fish and nuts when compared to high levels of animal fat and/or linoleic acid consumption.

Dietary polyphenols lower oxidative stress via Nrf2, Phase II enzymes, inhibition of A2E photo-oxidation and regulation of IL-6.[lxxxv] Resveratrol is an antioxidant polyphenol that has been shown to convey protective effects against hydrogen peroxide induced oxidative damage to RPE as well as increase superoxide dismutase, glutathione peroxidase, catalase and glutathione levels.[lxxxv] Pterostilbene, a stilbenoidchemically related to resveratrol, conveys a protective effective on retinal pigment epithelial (RPE) cells in a high glucose environment via antioxidant effects. Pterostilbene has also been shown to decrease the expression of inflammatory mediators TNF alpha and IL-1Beta, inhibits NFkBeta protein expression, reduces ROS production and increases SOD activity.[lxxxv]

Bilberry extract has been shown to prevent macular degeneration and cataracts in rats fed bilberry extract and visual impairment in the lenses and retina were ameliorated in the experimental group.[lxxvii] Anthocyanin enriched bilberry extracts upregulate oxidative stress associated defense enzymes Heme Oxygenase-1 and Glutathione S-Transferase and modulate hydrogen peroxide induced free radicals in RPE cells. The findings of this study have implications for the prevention and management of AMD and similar retinal diseases.[lxxxv]

HOMING - Gene Expression and VEGF

Vascular endothelial growth factor (VEGF) is the major driver of neo-vascular AMD. The expression of VEGF is
regulated by DNA methylation.[\textsuperscript{cxi}] DNA hypomethylation correlated with vascular endothelial growth factor-C (VEGF-C) expression and the methyl donor SAMe downregulates VEGF.\textsuperscript{[cxi]} Lowering of homocysteine with B-vitamins and folic acid resulted in substantial reduction of plasma levels of VEGF.\textsuperscript{[cxi]} Hyperhomocysteinemia-induced oxidative stress activates retinal glial cells and increases VEGF expression in the rat retina, consistent with human clinical studies that have shown an association between poorly regulated homocysteine and oxidative stress induced tissue damage.\textsuperscript{[cxi]}

Expression of the pro-antigenic factor VEGF is increased by homocysteine and other thiol-containing reductive compounds via ATF4-dependent activation of VEGF transcription. The study findings have implications for the development and progression of diabetic retinopathy and AMD. Oxidative stress induces RPE senescence which increases the proinflammatory cytokines IL-6 and IL-8 and vascular endothelial growth factor (VEGF) and simultaneously down regulates complement factor H (CFH) expression. Reducing oxidative stress lowers proinflammatory cytokine levels, reduces VEGF and up regulates CFH.\textsuperscript{[2]}

The ARMS2 gene interacts with hormone replacement therapy (HRT) to modulate AMD risk. This finding is consistent with previous reports demonstrating a protective relationship between exogenous estrogen use and neovascular AMD.\textsuperscript{[c]i} Curcumin is an inhibitor of VEGF and has been shown to have therapeutic potential in the management of AMD. Curcumin has also been shown to inhibit the expression of COX-2 and blocking the MAPK signaling pathway, which have potential implications in risk mitigation for inflammatory disorders, cancer and retinal diseases such as AMD.\textsuperscript{[c]i}

Resveratrol has been shown to suppress VEGF secretion induced by inflammatory cytokines, TGF-Beta and hypoxia. Under pathological conditions, over expression of VEGF is known to worsen AMD. Therefore, resveratrol may be useful as dietary supplement in controlling pathological choroidal neovascularization processes in AMD and other retinal disorders.\textsuperscript{[c]i} Oral administration of the plant polyphenol resveratrol was shown to be protective against neovascular lesions in mice by inhibiting VEGF expression and angiogenic activation of retinal endothelial cells.\textsuperscript{[c]i}

An intervention study involving Omega 3 fatty acid supplementation afforded significantly lower levels of VEGF-A when used in combination with anti-VEGF treatment (eye injections) as compared to controls for patients with wet AMD.\textsuperscript{[c]i} A small-scale study evaluated the Mediterranean diet for modulating AMD linked blood chemistry risk factors. Concentrations of lipids and fatty acids, hs CRP, and IL-6 and VEGF were tracked. The Mediterranean diet has been shown to lower serum VEGF concentrations in healthy subjects by lowering the ratio of proinflammatory O6FA’s relative to the anti-inflammatory O3FA’s.\textsuperscript{[c]i}

**Conclusions**

The impressive self-reported and laboratory outcomes are consistent with literature evidence that serves as the foundation for the HOMING protocol. Sixty percent (42/70) of wet AMD patients reported improvement in visual acuity and/or a reduction in the frequency of anti-VEGF injections during the study period. Forty eight percent (44/92) of dry AMD patients reported improvement in visual acuity during the study period. Nine percent (4/45) patients reported improvement in visual acuity in the dry AMD control group and no (0/13) wet AMD patients in the control group reported improvement. Six percent (4/70) of wet AMD patients reported that their vision declined and/or that their frequency increased during the study period. Five percent (4/92) of dry AMD patients reported that their vision was worse.

Baseline laboratory testing served as the foundation for each patient’s personalized HOMING protocol. Follow-up testing was requested at 3 months for each patient. The average improvement in CRP level from baseline to follow-up was 10.4%. The average improvement in HbA1c from baseline to follow-up was 5.1%. The average improvement in homocysteine (Hcy) from baseline to follow-up was 8.4%. While many patients were able to complete follow-up testing in 3 month intervals, some individuals were unable to complete their follow-up testing at three months and were required to wait until the 6 month follow-up interval to complete their repeat lab testing.

Limitations with the study included limited oversight over dietary compliance and poor compliance with supplement and hormone recommendations due to their relatively high average monthly cost. Additionally, many patients were not able to use hormones or some supplements that impacted clotting risk to due to a personal or family history of cancer and/or use of blood thinning medications. There were a significant number of patients that also reported that they were unable to swallow capsules, which challenged our efforts to create and maintain the dietary supplement protocols for some individuals.

Further study is warranted to establish baseline levels for BCVA and OCT in dry AMD. Contrast sensitivity would also be advantageous to help explain the perception of patients should BCVA be unchanged. In patients with wet disease, BCVA should be assessed dynamically given the variability of fluid accumulation. The most convenient and reproducible times to measure BCVA include before an intravitreal injection or 2 weeks after an injection, assuming that vision at 2 weeks would be maximal before fluid re-accumulation. OCT should be assessed at reproducible times, which includes during visits to the retina specialist for scheduled anti-VEGF injections. Central retina thickness and MPOD should also be tracked in the clinic.
In summary, it is critical that future studies involve the patient’s optometrist, ophthalmologist and/or retina specialist to help promote a greater level of program compliance and to help track objective progress while the patient is following a HOMING protocol. The dynamic nature of the protocol and the unique and changing needs of the patient’s physiology over time necessitates the support of a collaborative care team in order to maximize the results and efficacy of the HOMING protocol. Future studies will ideally involve multiple, independent eye centers for data collection and evaluation.

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