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Ocular Vascular Health and Disease

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ABSTRACT

Background: One-carbon metabolism integrates the folate and methionine cycles to direct single-carbon units into nucleotide synthesis, redox balance, and S-adenosylmethionine-dependent methylation reactions that are essential for retinal development, maintenance, and repair. Given the eye's exceptionally high metabolic demand, perturbations in these pathways may contribute to age-related macular degeneration, glaucoma, and diabetic retinopathy, the three leading causes of irreversible blindness worldwide.

Aim: This review provides an overview of the role of one-carbon metabolism in retinal diseases and evaluate use of homocysteine as a biomarker of pathway dysfuction to identify patients who may benefit from adjunctive nutrient-based treatment.

Methods: We synthesize current evidence on the biochemical architecture of folate-mediated one-carbon metabolism in the eye that support DNA repair, mitochondrial RNA formylation, and homocysteine remethylation.

Results: Across preclinical and clinical studies, altered one-carbon metabolism is associated with hyperhomocysteinemia, oxidative stress, mitochondrial dysfunction, and microvascular injury. These mechanisms converge to cause photoreceptor damage, retinal neurodegeneration and vascular complications in macular degeneration, glaucoma and diabetic retinopathy. Preclinical and clinical studies show that replenishing folate and other vitamins that support one-carbon metabolism normalizes homocysteine and mitigates neurovascular injury, improving ocular and systemic outcomes. Clinical evidence reveals slowed glaucoma progression, reduced risk or severity of diabetic retinopathy, and protection against retinal vascular damage.

Conclusion: Thus, elevated homocysteine may identify patients for whom vitamin replenishment may provide a useful adjunct to standard care. One-carbon metabolism may represent a unifying biochemical framework across major retinal diseases of aging, and homocysteine may function as a practical biomarker to guide intervention alongside standard ophthalmological therapy, with further randomised trials needed to refine its clinical utility.

1. Introduction

One-carbon (1C) metabolism has emerged as a unifying biochemical axis linking systemic nutritional status to retinal integrity and the pathogenesis of major blinding diseases of aging. This network integrates the folate and methionine cycles to traffic single-carbon units from amino acid donors into nucleotide biosynthesis and S-adenosylmethionine (SAM)–dependent methylation reactions, thereby coupling amino acid metabolism, DNA/RNA synthesis, and epigenetic regulation. Within the eye, an organ with exceptionally high metabolic and repair demands, 1C metabolism is particularly critical, as it supports continuous photoreceptor renewal, maintains retinal vascular homeostasis, and constrains oxidative stress through efficient homocysteine recycling. Dysregulation of this pathway, often driven by deficiencies in B vitamins and related cofactors, leads to hyperhomocysteinemia, impaired nucleotide synthesis, and disturbed methylation capacity, changes that are increasingly recognized as early drivers of retinal degeneration rather than mere epiphenomena.[1,2]

Converging evidence now implicates disturbed 1C metabolism in each of the three most prevalent causes of irreversible vision loss worldwide: age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy. Elevated homocysteine, a hallmark of impaired 1C flux, has been associated with microvascular dysfunction, blood–retinal barrier breakdown, and increased risk of diabetic retinopathy and AMD, positioning 1C metabolites as both biomarkers and mechanistic contributors to disease. In glaucoma, metabolomic and genetic data indicate that 1C pathways are dysregulated, and experimental models demonstrate that correcting these defects can attenuate retinal ganglion cell loss and optic nerve damage. Collectively, these observations support a model in which defects in folate-mediated and methionine cycle–dependent reactions converge on oxidative injury, mitochondrial stress, and neurovascular instability across these seemingly distinct diseases.[1–5]

Importantly, the nutrient-dependence of 1C metabolism renders it a modifiable therapeutic target. Folate (vitamin B9), vitamins B6 and B12, and choline are indispensable cofactors for homocysteine remethylation and transsulfuration, and their deficiency is a leading cause of elevated homocysteine and impaired methylation capacity. Experimental supplementation with these vitamins in animal models of glaucoma normalizes 1C flux, reduces homocysteine, and preserves retinal structure and optic nerve function, while B vitamin repletion in hyperhomocysteinemic models of retinal vascular disease improves barrier integrity and mitigates neurovascular damage. Observational and interventional data in humans further suggest that higher intakes or supplementation of B vitamins, including folate, may reduce the risk or slow progression of diabetic retinopathy, AMD, and glaucoma, though definitive randomized evidence is still emerging. Against this backdrop, the present work focuses on the role of nutrients that fuel 1C metabolism in ocular health, exploring how restoring or optimizing these vitamin-dependent pathways might offer a low-cost, broadly accessible strategy to prevent or attenuate the major retinal diseases of aging.[2–6]

2. Nutrients in One-Carbon Metabolism and Ocular Health

One-carbon (1C) metabolism is a sophisticated and intricate biochemical network within living organisms, responsible for the transfer and utilization of one-carbon units. The 1C metabolic network primarily comprises two interlocking cycles: the Folate Cycle and the Methionine Cycle. The former manages the mobilization of 1C units from donors such as serine and formate, while the latter utilizes these units to generate S-adenosylmethionine (SAM)-the universal methyl donor for cellular utilization. This metabolic pathway serves as a vital bridge connecting amino acid metabolism, nucleotide synthesis, and epigenetic modifications (namely methylation).[7] Recent evidence has suggested restoring 1C metabolism when there is a B vitamin deficiency may be neuroprotective of the retina, particularly under glaucomatous conditions.[8] This is being tested in a trial currently ongoing.[9]

1C metabolism involves various enzymes and is highly dependent on the availability of multiple vitamins and nutrients.[7] Although the eye is a compact organ, it possesses an exceptionally high energy demand.[10] Dysregulation of 1C metabolism due to nutrient deficiency often manifests first in the eyes, such as elevated homocysteine level causing increasing oxidative stress, serving as an early signal that may eventually progress into chronic ocular diseases and other systematic health issues.[11–13]

2.1 FOLATE-MEDIATED ONE-CARBON METABOLISM

Folate, also known as vitamin B9, is a transporter of methyl groups by accepting them from serine to ultimately form methionine by recycling homocysteine. Driven by serine hydroxymethyltransferase (SHMT) and the cofactor vitamin B6, tetrahydrofolate (THF) obtains a one-carbon unit from serine to form 5,10-methylenetetrahydrofolate (5,10-methylene-THF).[14] A portion of this 5,10-methylene-THF is directly consumed as a substrate for dTMP synthesis or is oxidized to 10-formyltetrahydrofolate (10-formyl-THF), which is the only donor for purine synthesis. The remaining portion continues through the folate cycle, where it is converted into 5-methyltetrahydrofolate (5-mTHF) by methylenetetrahydrofolate reductase (MTHFR).[15,16] 5-mTHF serves as the primary methyl donor for the remethylation of homocysteine and thereby determines the status of SAM. While the methionine cycle governs epigenetic regulation, the folate-mediated production of 10-formyl-THF is equally critical for the eye, as it sustains the pool of nucleotides required for the vigorous DNA repair activities in photoreceptors. A deficiency in 10-formyl-THF leads to the impairment of nucleotide synthesis, thereby compromising the cellular repair capacity.

THF-mediated 1C metabolism is compartmentalized in the cytoplasm, mitochondria, and nucleus and the metabolic pathways are interdependent. [7] 1C metabolism in the cytoplasm is required for the synthesis

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of purines and thymidylate and the remethylation of homocysteine to methionine. In the mitochondria where occurs the interconversion of serine and glycine, 1C metabolism is required for the synthesis of formylated mtRNA; Mitochondria are also the primary source of 1C units for cytoplasmic metabolism by releasing formates into cytoplasm.

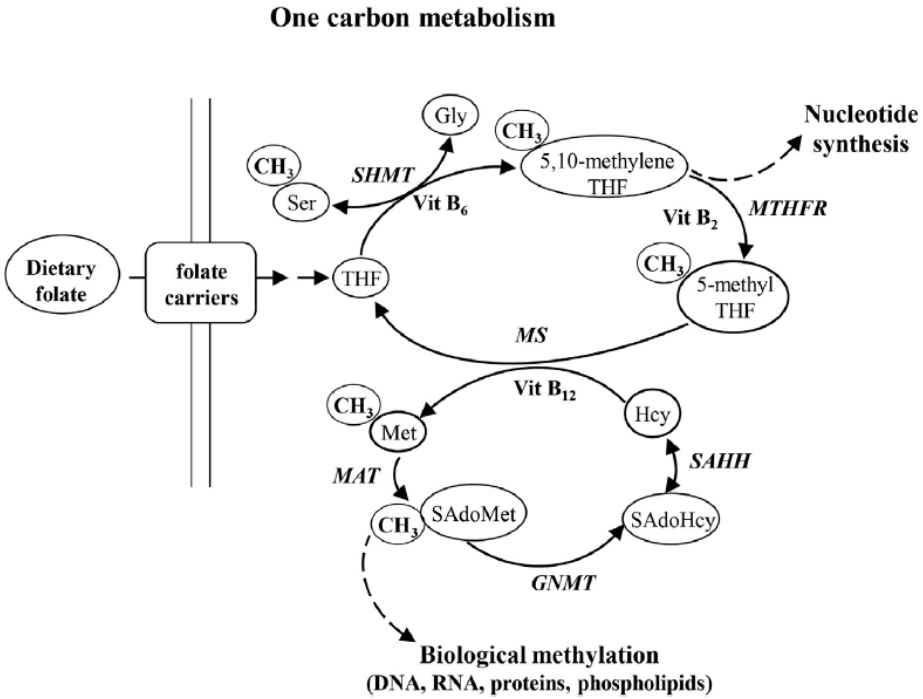

Fig 1. Nutrients involved in one-carbon metabolism.[7]

2.2 OTHER B-VITAMINS IN ONE-CARBON METABOLISM

B-Vitamins are essential water-soluble cofactors for maintaining the functional integrity of 1C metabolism.[17] Genetic polymorphisms (such as those affecting MTHFR) combined with B-vitamin deficiencies can disrupt 1C metabolic homeostasis, leading to an excessive accumulation of toxic homocysteine. This accumulation, in turn, compromises the structural and functional integrity of vascular endothelial cells and blood-retinal barrier.[18]

Vitamin B2 (riboflavin) serves as a critical cofactor for the synthesis of 5-mTHF from 5,10-methylene-THF. The functional integrity of MTHFR is intrinsically linked to riboflavin status. As a precursor to flavin adenine dinucleotide (FAD), riboflavin provides the prosthetic group that stabilizes the MTHFR enzyme and facilitates the hydride transfer necessary for 5-mTHF production. Consequently, B2 deficiency can impair the remethylation of homocysteine, contributing to the pathogenesis of vascular-related ocular conditions.[18,19]

Vitamin B6 is a vital cofactor for the SHMT in folate cycle, facilitating the initial mobilization of 1C units from serine to THF. It exists in several natural forms, primarily pyridoxal, pyridoxine, and pyridoxamine, with pyridoxal-5'-phosphate (PLP) being the active coenzyme form. PLP is essential for the catalytic activity of SHMT, enabling THF to acquire a 1C unit from serine to generate 5,10-methylene-THF. Beyond its direct involvement in 1C unit mobilization, B6 is also the key enzyme cofactor in the transsulfuration pathway, where homocysteine is metabolized into cystathionine-a critical precursor for the synthesis of the potent antioxidant glutathione. Consequently, a deficiency in Vitamin B6 not only restricts the synthesis of the methyl donor 5-mTHF but also impairs transsulfuration efficiency, leading to the pathological accumulation of homocysteine.[21,22]

Vitamin B12 (cobalamin), acting as an essential coenzyme for methionine synthase (MTR), facilitates the transfer of the methyl group from 5-mTHF to homocysteine, converting it back into methionine. This step is critical for maintaining the SAM/SAH ratio; an efficient remethylation ensures the provision of SAM while preventing the accumulation of S-adenosylhomocysteine (SAH), a potent inhibitor of cellular methylation. When B12 is deficient, this remethylation process is stalled, triggering the "Methyl Trap" phenomenon. In this state, folate becomes metabolically sequestered as 5-mTHF, which cannot be converted back into other functional folate derivatives. This secondary folate deficiency occurs despite adequate total folate levels, ultimately impairing nucleotide synthesis and cellular methylation.[23,24] Megaloblastic anemia is a direct consequence of Vitamin B12 deficiency, as the depletion of B12 disrupts the folate pool, cutting off the supply of 10-formyl-THF and 5,10-methylene-THF required for DNA synthesis.[25] Beyond its role as a coenzyme in one-carbon metabolism, B12 exists in another active form, adenosylcobalamin, which serves as a coenzyme for methylmalonyl-CoA mutase within the mitochondria. Consequently, a B12 deficiency leads to the accumulation of methylmalonic acid (MMA)-a neurotoxic metabolite that can directly damage retinal ganglion cells (RGCs).[26]

2.3 CHOLINE AND METHYLATION

Choline is essential for the synthesis of phospholipids such as phosphatidylcholine and is, therefore, involved in

neurodevelopment. In 1C metabolism network, its metabolite betaine is another major methyl donor via betaine-homocysteine S-methyltransferase (BHMT) pathway, which serves as a tissue-specific compensatory route, particularly in the liver and kidneys, to recycle homocysteine when folate-dependent pathway is compromised.[27] The metabolic synergy between choline and folate extends beyond the BHMT pathway. The catabolism of dimethylglycine (DMG), the product of betaine after giving away a methyl group, to sarcosine, and subsequently to glycine, occurs within the mitochondria via DMG dehydrogenase and sarcosine dehydrogenase. The subsequent mobilization of methyl groups from DMG and sarcosine is folate-dependent, as it requires available THF to capture 1C unit within the mitochondria. Consequently, under conditions of severe folate deficiency, the 'recharging' effect of DMG and sarcosine on the 5-mTHF pool is significantly attenuated, highlighting that choline functions as a synergistic partner rather than a complete substitute for folate.[28]

3. Folate Sources, Absorption and Bioavailability

Vitamin B9, commonly known as folate, is an essential water-soluble B vitamin required for DNA synthesis, amino acid metabolism, and key methylation reactions. Folate exists both as naturally occurring reduced vitamers in foods and as the synthetic oxidized compound folic acid used in supplements and food fortification, the latter being highly stable during processing and storage. Understanding natural and synthetic sources, comparative bioavailability, and the influence of genetic variation on folate metabolism is critical for optimizing health and preventing deficiency-related conditions.[29–32]

3.1 FOLATE FROM FOODS

Folate occurs naturally in a wide range of foods, with the highest concentrations typically found in certain vegetables, legumes, and organ meats. Among these, spinach, liver, asparagus, and Brussels sprouts are particularly folate-rich and contribute substantially to dietary intake when consumed regularly.[32,33]

In most foods, folate is present predominantly as polyglutamated tetrahydrofolate derivatives (such as L-methylfolate), which are the physiologically relevant forms for one-carbon metabolism. In the intestinal lumen, γ-glutamyl hydrolases remove the additional glutamate residues, converting polyglutamated forms to monoglutamate L-methylfolate that can be absorbed and subsequently utilized by cells.[34]

Table 1. Key food sources of folate

Food Product	Example Foods
Dark green leafy vegetables	Spinach, kale, collard greens, and romaine lettuce
Legumes	Beans, lentils, peas
Fruits	Oranges, avocados, bananas, and melons
Nuts and seeds	Peanuts, sunflower seeds
Other vegetables	Asparagus, Brussels sprouts, broccoli, beets
Animal products	Liver and eggs (liver being especially high)
Whole grains	Fortified and unfortified whole grain products

Sources: [29,31–33]

3.2 SYNTHETIC FOLIC ACID AND NATURAL FOLATE USED IN MEDICAL FOODS

Folic acid, used in fortified foods and dietary supplements, is a fully oxidized, monoglutamate form that is chemically distinct from naturally occurring food folates. Unlike polyglutamated food folates, folic acid does not require deconjugation or release from plant matrices before absorption, contributing to its high and consistent bioavailability.[30,35,36]

Food fortification programs and folic acid–containing supplements provide a reliable source of folate intake, compensating for instability and losses of natural food folate during harvesting, storage, and cooking, and have been associated with reduced rates of folate deficiency and related disorders in many populations. Folic acid is most commonly delivered through fortified cereal grains and dedicated vitamin preparations.

In addition, certain medical foods provide L-methylfolate (L-5-methyltetrahydrofolate), a bioactive folate form that can be used directly in one-carbon transfer reactions and is employed in specific clinical contexts. Leucovorin and levoleucovorin, reduced folate drugs, are used therapeutically to replenish folate stores depleted by chemotherapy and have also been used to improve communication symptoms in some individuals with autism spectrum disorder.[37] Both L-methylfolate and levoleucovorin are now available as pure L-isomers, whereas earlier formulations were often racemic mixtures of L- and D-isomers in which only approximately 50% of the dose was biologically usable, necessitating higher total doses to achieve equivalent pharmacologic effects.

3.3. BIOAVAILABILITY AND ABSORPTION

The bioavailability of naturally occurring folate is variable and generally lower than that of synthetic folic acid. Estimates indicate that food-derived folate provides approximately 50–60% of the bioavailability of folic acid consumed with a meal.[30,38,39]

Several factors contribute to this reduced bioavailability. First, folate in plant-based foods may be tightly bound within cellular structures, limiting its release during digestion. Second, natural folate predominantly exists in the polyglutamate form, which must undergo enzymatic deconjugation to monoglutamate before absorption in the small intestine. Third, folate is chemically labile and readily degraded by heat, light, and oxidation, leading to additional losses during food processing and storage.[30,38,39]

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Recent studies indicate that the bioavailability of natural folate can range from approximately 44% to 80%, depending on the specific food matrix and preparation method, with a median value around 65% compared to synthetic folic acid.[30,39,40] To address these differences, food labeling employs dietary folate equivalents (DFE), wherein 1 DFE is defined as 0.6 µg of folic acid or L-methylfolate. Variability in folate release and stability, compounded by the limited absorption efficiency of natural dietary sources, underpins the rationale for mandatory folic acid fortification programs. Such initiatives have demonstrably improved population folate status and substantially reduced the incidence of neural tube defects.[32,38]

3.4. GENETIC INFLUENCES ON FOLATE METABOLISM

Several common genetic polymorphisms influence folate absorption, metabolism, and the body's overall methylation capacity. MTHFR (methylenetetrahydrofolate reductase) C677T and A1298C variants alter the conversion of folic acid and food-derived folates to the bioactive L-methylfolate form, thereby affecting homocysteine concentrations and modulating susceptibility to neural tube defects and autism spectrum disorder (ASD) in certain populations.[41–44] Individuals carrying these polymorphisms may exhibit higher homocysteine levels and may preferentially benefit from L-methylfolate rather than folic acid supplementation.[45–47]

Polymorphisms in additional folate-related genes, including MTR, MTRR, FOLH1, RFC1, and SHMT, can modify intestinal absorption, tissue distribution, and intracellular utilization of folate, with downstream consequences for DNA methylation and associated health outcomes.[41–44] Variants in DHFR (dihydrofolate reductase) influence the reduction of folic acid to tetrahydrofolate and thus determine how efficiently synthetic folic acid is metabolized, with the potential for unmetabolized folic acid to accumulate in individuals with relatively low DHFR activity.[48]

3.5. FOLATE TRANSPORT INTO THE BRAIN AND EYE

Folate must cross the blood–brain barrier (BBB) and the blood-retina barrier (BRB) to support normal neurological function and neurodevelopment. This process is mediated by at least two major transport systems that together maintain folate homeostasis within the central nervous system.

Folate receptor alpha (FRα), expressed at the choroid plexus, is essential for high-affinity transport of folate from the circulation into the cerebrospinal fluid (CSF) and brain parenchyma. Pathogenic variants in the FOLR1 gene, which encodes FRα, can lead to cerebral folate deficiency (CFD), a syndrome characterized by low CSF folate and prominent neurological manifestations despite normal or near-normal systemic folate levels.[49]

The reduced folate carrier (RFC, SLC19A1) provides an additional route for folate entry into multiple tissues, including the brain, but as a facilitative (non–energy-dependent) transporter it can only equilibrate, rather than concentrate, folate relative to plasma. In contrast, FRα-mediated mechanisms allow cerebral folate concentrations to exceed those in blood, with brain folate levels typically 2–5 times higher than plasma, reaching approximately five-fold higher in early childhood and gradually declining to about two-fold higher through later childhood and adolescence. Genetic variation in SLC19A1 can modulate the efficiency of this transport and thereby influence folate delivery to the central nervous system.[50,51]

Emerging data also implicate the vitamin D receptor (VDR) in regulating components of folate transport across the BBB and BRB, particularly in the context of certain neurological diseases, suggesting potential crosstalk between vitamin D signaling and folate homeostasis in the brain. Disruption of folate transport, through FOLR1 or SLC19A1 mutations, autoantibodies directed against FRα, or other disease-related mechanisms, can produce cerebral folate deficiency, with low brain folate despite adequate or even normal circulating folate status.[51]

Pharmacologic doses of reduced folate preparations such as leucovorin/levoleucovorin can, in some cases, bypass these transport defects and restore CSF and brain folate levels, leading to clinical improvement in affected individuals. These genetic and immunologic factors help explain inter-individual differences in folate requirements, variable responses to supplementation, and differential risk for conditions associated with systemic and cerebral folate deficiency, including neural tube defects, cardiovascular disease, and autism spectrum disorder. Ongoing research into the interaction of genetic variation, environmental exposures, and folate-dependent pathways is expected to support more personalized recommendations for folate intake and targeted use of specific folate forms in clinical practice.[41–44,52]

4. Retinal Vascularization and Retinal Disease

Folate deficiency leads to hyperhomocysteinemia, which in turn damages retinal vascular endothelial cells through oxidative stress, inflammation, and disruption of barrier function. Adequate folate status and effective folate transport are therefore essential for homocysteine detoxification, endothelial protection, and preservation of retinal vascular integrity in eye diseases such as diabetic retinopathy, retinal vascular occlusions, glaucoma, and age-related macular degeneration (AMD). In all four of these disorders, retinal capillaries are particularly sensitive to hyperhomocysteinemia, leading to reduced vascular perfusion and elevated retinal venous pressure.[45,47,53]

4.1 RETINAL HYPERHOMOCYSTEINE AND VASCULAR DYSFUNCTION

Folate is a key dietary determinant of plasma homocysteine concentrations, as it supports the remethylation of homocysteine to methionine and thereby helps maintain low circulating homocysteine levels. Folate deficiency is the most common cause of hyperhomocysteinemia in the general population.[11,54,55]

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Elevated homocysteine exerts direct toxic effects on retinal vascular endothelial cells and contributes to the pathogenesis of retinal vascular diseases, including retinal vascular occlusions, diabetic retinopathy, glaucoma, and AMD. Mechanistically, homocysteine impairs endothelial function by inducing oxidative stress, downregulating tight junction proteins, increasing vascular permeability, and promoting inflammatory signaling, which together compromise the blood–retinal barrier (BRB)and weaken retinal vascular integrity.[11,55,56] In another study, Samra et al. reported a novel mechanism linking hyperhomocysteinemia to AMD. Hyperhomocysteinemia alters mitochondrial glucose metabolism, shifting the primary pathway from the tricarboxylic acid (TCA) cycle to glycolysis. The resulting acidic environment, characterized by a high lactate/pyruvate ratio, triggers the growth of neovascularization and disrupts the structure of the retinal pigment epithelium barrier.[57]

Experimental models demonstrate that high homocysteine levels lead to loss of retinal ganglion cells and thinning of retinal layers, changes that can be partially reversed by folate supplementation.[55] These findings suggest that folate's protective actions extend beyond homocysteine lowering and may also involve direct support of endothelial cell health and enhancement of antioxidant capacity.

The efficacy of folate in protecting the retinal vasculature depends on its uptake into retinal cells, predominantly as L-methylfolate. Efficient folate transport is crucial for maintaining the integrity of the inner blood–retinal barrier and for protecting against ischemic injury, whereas impaired transport or localized retinal folate deficiency can arise even when serum folate levels are normal, leading to elevated intra-retinal homocysteine and vascular dysfunction.[54,58] Folate, particularly L-methylfolate, also supports nitric oxide (NO) production, a vasodilator that maintains retinal blood flow; impaired folate availability may therefore promote vasoconstriction and exacerbate ischemia within the retina.[54]

4.2. RETINAL OXIDATIVE STRESS AND ANTIOXIDANTS

Oxidative stress is a central mechanism by which elevated homocysteine (hyperhomocysteinemia) promotes retinal injury. High homocysteine levels increase the generation of reactive oxygen species (ROS) in retinal endothelial and glial cells, overwhelming intrinsic antioxidant defenses and precipitating cellular dysfunction and tissue damage.[56,59,60]

Homocysteine-induced oxidative stress downregulates tight junction proteins in retinal endothelial cells, thereby increasing vascular permeability and contributing to BRB, a key feature of vision-threatening disorders such as diabetic retinopathy and age-related macular degeneration. Excess ROS also activate inflammatory signaling cascades and induce apoptosis of retinal neurons, including retinal ganglion cells, further compromising retinal architecture and visual function.[56,61] Elevated homocysteine decreased retinal light response and microglial activation, while reducing retinal blood flow.[62]

In addition to directly generating ROS, elevated homocysteine impairs the retina's antioxidant capacity, as reflected by reduced levels of protective enzymes (e.g., superoxide dismutase, glutathione peroxidase) and diminished total antioxidant capacity in both clinical cohorts and experimental models. The resulting pro-oxidant milieu promotes endothelial toxicity, enhances hypercoagulability, and increases susceptibility to retinal vascular occlusive events such as central retinal vein occlusion.[6,60]

Experimental data indicate that antioxidant therapies can at least partially reverse these deleterious effects, reducing ROS formation and restoring barrier integrity in homocysteine-exposed retinal cells.[56] Collectively, these findings underscore oxidative stress as a pivotal mediator of homocysteine-induced retinal damage, integrating vascular dysfunction, BRB breakdown, inflammation, and neuronal loss across diverse retinal disease states.[56,59,63]

4.3. EVIDENCE FROM VITAMIN TREATMENT

Emerging clinical evidence supports the use of medical food–level B vitamins, specifically formulations containing L-methylfolate, to treat elevated homocysteine in patients with retinal disease. Across several studies, the medical food Ocufolin, a formulation that provides varying doses of the AREDS2 regimen for dry AMD, combined with L-methylfolate, vitamin B12, and additional B vitamins to support endothelial health, was used as the therapeutic intervention (a formulation that may ultimately be conceptualized as an "AREDS3" approach due to its added vascular support). In each study, this therapy lowered homocysteine levels and improved retinal perfusion, with associated improvements in clinical outcomes across multiple retinal conditions.

In diabetic retinopathy, L-methylfolate–based therapy reduced homocysteine concentrations and enhanced retinal perfusion, while also lowering stroke risk, leading to recommendations to use retinal imaging to evaluate patients for central nervous system microangiopathy.[64] In a small case series of glaucoma, similar vitamin therapy was associated with alleviation of glaucomatous changes. Retinal venous pressure was elevated in both high-tension and normal-tension glaucoma and decreased following medical food treatment, paralleling improvements in retinal perfusion and patient outcomes.[46,47] These findings suggest that normal-tension glaucoma, traditionally difficult to manage, is characterized by elevated retinal venous pressure and may respond favorably to this vitamin-based vascular support strategy. Retinal venous pressure appears to more accurately reflect intraocular vascular conditions that compromise perfusion and contribute to disorders such as glaucoma.[53]

AMD patients treated with Ocufolin were likewise evaluated for retinal venous pressure and homocysteine levels and showed reductions in both parameters. The standard clinical treatment for neovascular AMD involves anti-VEGF injections to suppress the growth of abnormal, leaky blood vessels. However, this intervention inadvertently reinstates a hypoxic state within the ocular

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vasculature. As a result, many nAMD patients require frequent injections to manage recurrent neovascularization and retinal edema. In a specific study, researchers observed that when patients received an oral nutritional supplement called Ocufolin in conjunction with standard anti-VEGF therapy, they experienced a 25% greater reduction in retinal edema after four months compared to the group receiving anti-VEGF treatment alone.[65]

In neovascular AMD, this oral vitamin therapy was associated with a reduced need for anti-VEGF intravitreal injections, with some evidence of stronger clinical outcomes when vitamin therapy was combined with anti-VEGF. These preliminary data support the concept that concomitant lowering of homocysteine and retinal venous pressure may enhance the efficacy of anti-VEGF therapy in neovascular AMD. Another study measured retinal venous pressure (RVP) and compared the effectiveness of anti-VEGF injections to treat AMD in 31 patients. They found that patients with lower RVP had more favorable outcomes including superior visual function, which would indicate a likely reduction in needed injection frequency.[66]

Since the medical vitamin treatment was documented to reduce RVP,[65] these two studies appear to be supportive of the same finding, that lower RVP decreases the anti-VEGF injection frequency. Given the absence of reported adverse effects, these findings justify further, larger-scale trials to evaluate B-vitamin–based medical foods as adjunctive therapy and to determine whether such regimens should be incorporated into standard care, potentially allowing longer intervals between anti-VEGF injections under close monitoring.

Future work should prioritize rigorously designed randomized controlled trials testing homocysteine-guided vitamin supplementation across major ocular diseases, longitudinal studies validating homocysteine and related metabolites as predictive biomarkers, and mechanistic investigations that clarify how genetic variation in one-carbon enzymes shapes retinal vulnerability. Such efforts will be essential to determine whether systematic assessment of one-carbon metabolism, coupled with targeted nutrient repletion, can be incorporated into routine ophthalmic practice to prevent or slow vision loss in at-risk populations.[1,4,5,11,67,68,70,71]

5. Conclusion

One-carbon metabolism has emerged as a central, nutrient-dependent pathway linking systemic metabolic status with retinal neuronal and vascular integrity, providing a mechanistic framework that unites age-related macular degeneration, glaucoma, and diabetic retinopathy under a common biochemical axis. Across these conditions, disturbances in folate- and methionine-cycle flux, often driven by inadequate availability of folate, vitamins B6 and B12, and related cofactors, are associated with elevated homocysteine, impaired nucleotide synthesis, oxidative stress, and microvascular dysfunction, all of which can accelerate retinal injury. At the same time, converging experimental and clinical data indicate that restoring one-carbon metabolism with targeted vitamin repletion can normalize homocysteine, stabilize retinal structure, and slow neurovascular damage, including in glaucomatous models now being translated into clinical trials.[1,4,11,67]

Within this framework, homocysteine represents a pragmatic, widely available biomarker of one-carbon pathway insufficiency that may help identify patients whose ocular disease is driven, in part, by correctable metabolic deviations. Elevated homocysteine has been consistently linked with increased risk and severity of diabetic retinopathy and other retinal vascular complications, and even modest elevations may signal the need for intensified risk-factor management. Although homocysteine may be more pathogenic than causative in glaucoma, raised levels still reflect dysfunction in one-carbon metabolism and the handling of key cofactors, supporting its use as a metabolic marker for considering adjunctive vitamin-based interventions. Accordingly, routine monitoring of homocysteine in patients with AMD, glaucoma, diabetic retinopathy, and other retinal vascular diseases could guide adjunct care applying folate, B6, B12, and choline supplementation aimed at restoring normative one-carbon metabolism.[1,4,5,11,67–71]

We thus propose that optimizing one-carbon metabolism with appropriate vitamin therapy should be explored as an adjunctive strategy alongside standard-of-care treatments such as intraocular pressure lowering, anti-VEGF injections, and glycemic and blood pressure control.

The authors have no conflicts of interest to declare.

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