

# Nutrition and Behavior as it Applies to Systemic and Ocular Disease<sup>2009</sup>

## Specific Nutrients and Their Relevance to Disease

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### Introduction

While arguable by some, the supplementation of the average diet has considerable support in the refereed medical literature. The following will address the specific supplements and how those supplements may be of benefit to the system. This discussion is not prescriptive, but rather descriptive, attempting to report fact.

### Attention to Behavior Modification, Proper Nutrition

Possible positive actions of behavior modification, proper nutrition and exercise in minimizing the risk for the development or progression of ganglion cell and nerve fiber damage in glaucoma and other ocular disease conditions include:

- Normalizing ocular collagen and protecting ocular tissue against the neurotoxicity of glutamate.
- Increasing ocular antioxidant defenses and scavenging harmful free radical molecules.
- Increasing the ocular level of glutathione to improve outflow and minimize antioxidant activity
- Preventing inappropriate release

and actions of nitric oxide (NO) and vasoconstrictors from vascular endothelium.

- Improving ocular blood flow
- Minimizing inflammation and modulating the immune system
- Protecting the mitochondria before the process of apoptosis is unstoppable

The primary activity of non-pharmaceutical and traditional medical systems is in modulating the immune system, providing neuroprotection and improving cardiovascular function through action on the mitochondria, the bioenergy center of the cells. That being said, no supplement is of value without a proper diet and exercise to enhance the effect. While genetics impacts on every situation, the switch for the DNA is still subject to outside forces and sources. Studies keep piling up substantiating the importance of a good workout on a regular basis. The latest study points to the fact that increased fitness is associated with 50% to 70% reductions in all-cause mortality.<sup>81</sup> Another new report states that adoption of four healthy lifestyle habits including exercise, eating a diet high in fruits and vegetables, maintaining a healthy weight, and not smoking, in middle

age is associated with a 40% reduction in all-cause mortality and 35% reduction in CVD events within 4 years.<sup>82</sup> To carry this a bit further another report suggests that adherence to a prudent diet of vegetables, whole grains, fruit, legumes, fish, and poultry is associated with lower rates of mortality from cardiovascular disease, other causes, and total mortality in female nurses. To contrast, adherence to a Western dietary pattern with high intake of red and processed meats, sweets and desserts, and french fries is associated with higher rates of cardiovascular disease, cancer, and all-cause mortality.<sup>83</sup> More than 60% of the US population is overweight according to the latest National Health and Nutrition Examination Survey (NHANES).<sup>84</sup>

### Constituents of a Diet that Support Healthy Systemic and Ocular Function

#### Vitamin A

Vitamin A is a generic term referring to a number of related compounds. It is available in a preformed variation called retinol found in many animal products. Preformed retinol has been reported as toxic at levels above 10,000 IU. The other form is

natural beta-carotene (carotenoid), which is found in fruits and vegetables and is used to form its own vitamin A.

Carotenoids comprise a class of natural fat-soluble pigments, which are found in numerous fruits and vegetables and are purported to have the characteristic of minimizing photo-oxidative damage to tissue. Retinol is an alcohol and retinal is an aldehyde, both referred to as preformed vitamin A. Retinol, retinal, and retinoic acid are retinoids. Beta-carotene and other carotenoids, that can be converted by the body into retinol, are provitamin A variations. Not all carotenoids synthesized by plants are provitamin A carotenoids.

Retinol reaches the eye through the circulatory system, ultimately accumulating in the retinal pigment epithelium in the form of a retinyl ester. The esters may isomerize to form 11-cis-retinol which can be oxidized to form 11-cis-retinal and transferred to the photoreceptor matrix of the rod where it binds with opsin to form rhodopsin. Absorption of light catalyzes the 11-cis-retinal to all-trans retinal triggering a cascade leading to the electrical signal that is sent through the retinal nerve fibers.

Additionally vitamin A is responsible for the normal functioning of the immune system<sup>85</sup> especially in the skin and mucosal cells.<sup>86</sup> The initial protective system from infection in the body is the mucosal system, specifically immunoglobulin A. Likewise the differentiation of white blood cells is dependant on vitamin A and retinoic acid.<sup>87</sup> Stem

cells are also dependent on retinoids for differentiation into red blood cells.<sup>88</sup> Absence of vitamin A from the diet significantly impacts on tear quality and is responsible for the genesis of Bitot's spots associated with severe dry eye. Vitamin A deficiency among children continues to be a leading cause of preventable blindness.<sup>89</sup> Vitamin A deficiency is considered by some to be a nutritionally-acquired immunodeficiency disease because of the importance of vitamin A to the immune system function.<sup>90</sup>

Conflict reigns in the discussion of the benefits of antioxidants and ocular disease. One study reports no strong associations between antioxidant consumption and the risk of primary open-angle glaucoma.<sup>91</sup> Another report suggests that higher intakes of protein, vitamin A, niacin, thiamin, and riboflavin (i.e. vitamin B-complex) are associated with reduced prevalence of nuclear cataract.<sup>92</sup> Intervention trials with large doses of beta-carotene found an adverse effect on the incidence of lung cancer in smokers and workers exposed to asbestos.<sup>93</sup> The results of the Beta-Carotene And Retinol Efficacy Trial (CARET) suggest that high-dose supplementation of vitamin A and beta-carotene should be avoided in people at high risk of lung cancer.<sup>94</sup>

Uses of large dosages of Vitamin A are not without risk and should be approached cautiously. Utilization in the management of retinitis pigmentosa demonstrated that with common forms of retinitis pigmentosa that supplementation

with 4,500 mcg (15,000 IU)/day of preformed vitamin A (retinol) significantly slowed the loss of retinal function over a period of 4-6 years. In contrast, supplementation with 400 IU/day of vitamin E increased the loss of retinal function by a small but significant amount, suggesting that patients with common forms of retinitis pigmentosa may benefit from long-term vitamin A supplementation but should avoid vitamin E supplementation at levels higher than those found in a typical multivitamin.<sup>95-96</sup> Both vitamin A serum levels and a fasting lipid profile should be obtained prior to initiation of therapy in all RP patients as there are often liver function issues creating hyperlipidemia issues in these patients.

Hypervitaminosis A is caused by over-consumption of preformed vitamin A, not carotenoids. Preformed vitamin A is rapidly absorbed and slowly cleared from the body. Therefore, toxicity from preformed vitamin A may result acutely from high-dose exposure over a short period of time or chronically from a much lower intake.<sup>97</sup> Hypervitaminosis A is characterized by dry skin, loss of appetite, headache, cerebral and optic disc edema, and bone and joint pain. In January 2001, the Food and Nutrition Board (FNB) of the Institute of Medicine set the tolerable upper level of vitamin A intake for adults at 3,000 mcg (10,000 IU)/day of preformed vitamin A for persons over age 19 but lower dosages are recommended for children.<sup>98</sup> Results of some studies indicate that vitamin A intake is not

associated with detrimental effects on bone mineral density (BMD) or create an increased risk for fracture<sup>99-101</sup> while other studies report the opposite.<sup>102-103</sup>

A safe recommendation would be that combined multivitamin supplements should provide no more than 2,500 IU of vitamin A or 5,000 IU of vitamin A, of which at least 50% comes from beta-carotene.

### Lycopene

Lycopene is a carotenoid in the same family as beta-carotene. Lycopene gives a tomato and several other fruits, their deep red color. Lycopene is one of the major carotenoids in the diet of North Americans and accounts for close to 50% of the carotenoid distribution found in blood. One study provides the experimental evidence for protective effects of dietary tomatoes rich in carotenoids on oxidative stress in the retinal pigment epithelium.<sup>104</sup> Lutein and lycopene, two prevalent carotenoids in the human diet have become increasingly popular ingredients in dietary supplements. A large body of human and animal research suggests that oral forms of these carotenoids may provide benefits in the areas of eye, prostate, skin and cardiovascular health. The evidence of safety is strong at intakes up to 20mg/d for lutein, and 75 mg/d for lycopene.<sup>105</sup> One study suggests that lycopene protects against experimental cataract development by virtue of its antioxidant properties, and it may be useful for prophylaxis or therapy against cataracts.<sup>106</sup>

Cooking and processing of tomato products makes lycopene more readily available to the body, indicating that there may be an added health benefit to eating processed tomato foods like tomato soup, pasta sauce and vegetable juices. In humans, the bioavailability of lycopene is greater from tomato paste than from fresh tomatoes.<sup>107</sup>

### Vitamin B1-Thiamin

Thiamine is a water soluble complex also recognized as vitamin B1. It occurs as free thiamin and in phosphorylated forms. It is required in conjunction with a number of other nutrients within the processing of enzymes. Beriberi is the result of severe thiamin deficiency appearing in three forms, wet affecting the cardiovascular system, cerebral affecting the nervous system, and dry affecting the muscular systems.<sup>108</sup> Cerebral beriberi can develop into Wernicke's encephalopathy with associated eye movement disorders and vision loss and Korsakoff's psychosis in alcohol abuse.<sup>109-110</sup> Thiamin deficiency may result from both inadequate consumption of thiamin as well as excessive loss of thiamin through the kidneys via disease or diuretic use.<sup>111-113</sup>

Dietary consumption of thiamin has been reported with the development of cataracts. Higher consumption of thiamin reportedly minimizes the risk for cataract development.<sup>113-115</sup> There is also a reported relationship to dementias but the implication is associated more with the enzymatic variations of thiamin rather than pure free

thiamin. There is no strong evidence to recommend thiamin supplementation in dementias.<sup>116-120</sup>

Whole grain cereals, legumes, nuts, lean pork and yeast are good sources of thiamin. Most processed foods lose thiamin and must be fortified. There are no established upper levels for toxicity and the FDA recommends about 1.1 to 1.2 mg/day for most individuals.<sup>118</sup>

### Vitamin B2-Riboflavin

Riboflavin is a water soluble vitamin also known as B2. Riboflavin is an essential component of coenzymes (flavoenzymes) functioning in the oxidation-reduction process. Flavoenzymes are critical in the metabolism of vitamin B6, Niacin and Folic Acid and can thus be instrumental in issues such as hyperhomocysteinemia.<sup>121-123</sup> Riboflavin is also involved in iron metabolism critical to red blood cell formation.<sup>124</sup>

There are suggestions that riboflavin deficiency may precipitate age-related cataracts yet controversy exists in this arena as well.<sup>125-129</sup> There has also been the suggestion that there is a relationship with migraine headaches and riboflavin. The association is purportedly via the mitochondrial oxygen metabolism but success with supplementation is limited by absorption of only 25 mg per day when given orally.<sup>130-134</sup>

New interest has arisen with the suggestion that cross-linking riboflavin and UVA irradiation may be efficacious in the inhibition of progression of keratoconus and the management of microbial keratitis.<sup>135-137</sup>

Cereals, milk, cheese, eggs, almonds and meats are good natural sources and many foods are fortified with riboflavin. There is no upper level of toxic intake of riboflavin and the primary side effect of excesses is flavinuria. The RDA for riboflavin is 1.1 to 1.3 mg per day.

### Vitamin B3-Niacin

Niacin is a water-soluble vitamin that is referred to as vitamin B3 or nicotinic acid. Nicotinamide is a derivative used to form coenzymes that function in the oxidation-reduction reactions in the body. The coenzymes include nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which function in carbohydrate, fat, protein and alcohol catabolism, and synthesis of fatty acids and cholesterol. There is also evidence that NAD functions in cell signaling, transcription, and cell differentiation.<sup>138-140</sup> NAD can be synthesized from tryptophan in conjunction with vitamin B6, riboflavin and iron.

Pellagra is the condition associated with severe niacin deficiency. Pellagra is associated with corn consumption as the primary source of nutrition. Corn contains niacin but in a bound form that is released by heating it in an alkaline solution. Many cultures prepare corn in this manner limiting the occurrence of niacin deficiency. Pellagra manifests as dermatitis, dementia, diarrhea and death as well as accelerated cataract formation.<sup>141-142</sup>

Because of the activity of NAD on cell signaling, there are suggestions that consumption of niacin will decrease the risk of cancers. The research is currently very sketchy but offers some promise in the area of oral cancers.<sup>143-145</sup> Niacin also has implications in conditions like Type 1 diabetes because of the association with the reactive oxygen species (ROS) pathway and relationships to inflammation. While there appears to be some effect with supplementation on Beta Cells of the pancreas, the research is not definitive.<sup>146-148</sup>

The fame of niacin lies in the relationship to cardiovascular disorders and the reported ability to alter blood lipids. Nicotinic acid reduces serum cholesterol and has been shown to reduce triglycerides, recurrent nonfatal myocardial infarction and stroke while increasing HDL when given at three grams per day. This effect is enhanced at lower doses of niacin when combined with statins.<sup>149-153</sup> The effect is dampened by the concurrent use of antioxidants.<sup>154</sup> Additionally, it has been suggested that the use of oral niacin does produce retinal vasodilation and may be of benefit in both ARMD and retinal ischemic disorders<sup>155</sup> but the long term effect on choroidal circulation is questionable.<sup>156</sup>

Food sources of niacin include meat, poultry, red fish, fortified cereals, and legumes. The RDA for niacin is 12 to 16 Niacin Equivalents (NE) per day. 1 mg of NE is equal to 60 mg of tryptophan

which equals 1 mg of niacin.

Toxicity is rare from food consumption of niacin but supplementation with nicotinic acid can create flushing, gastrointestinal problems, itching, liver damage, altered glucose tolerance, arrhythmia, and migraine.<sup>157-158</sup> Nicotinamide is better tolerated but still has associations with reactions. The upper tolerable level of niacin consumption is set by the Food and Nutrition Board at 35 mg/day.<sup>159</sup> It has also been reported that oral nicotinic acid may cause a spiking of intraocular pressure<sup>160</sup> as well as cystoid macular edema (niacin maculopathy) at 3 grams per day.<sup>161-162</sup> It has likewise been suggested that ocular surface disorders, discoloration of the peri-orbital area and loss of eyebrows and lashes may occur with niacin use.<sup>163</sup>

### Biotin

Biotin is a water-soluble material that is usually classified as a B vitamin and is required in the body but can only be synthesized by bacteria, molds, algae, yeasts and some plants. It is attached to 5 enzymes-carboxylases. These carboxylases function in metabolic reactions including: synthesis of fatty acids and regulation of mitochondrial fatty acid oxidation, gluconeogenesis, catabolism of leucine (amino acid), and metabolism of some amino acids, cholesterol and fatty acids.<sup>164</sup> Under most circumstances dietary deficiency of biotin does not occur. Raw egg whites and prolonged IV feeding



may create deficiency that manifests as hair loss and rash with facial fat deposition, depression, lethargy and numbness.<sup>165</sup> Biotin depletion also occurs naturally in pregnancy.<sup>166</sup> While there have been suggestions that biotin supplementation (even with chromium picolinate) may be beneficial in diabetes especially with hypertriglyceridemia, there is no strong indication for recommendation.<sup>167-171</sup> Profound biotinidase deficiency (PBD) is an autosomal recessively inherited disorder that can create optic neuropathy.<sup>172-173</sup> Biotin is obviously critical in the body but it appears to be provided for in the diet in most developed countries.

Food sources of biotin include egg yolk, liver, yeast and pork. The adequate intake level for biotin established by the Food and Nutrition Board of the Institute of Medicine is in the 35 to 60 mcg/day range. There is no established upper level of tolerance for biotin.

### Vitamin B5-Pantothenic Acid

Pantothenic acid is found in cells in the form of coenzyme A and is critical to a number of functions. Coenzyme A (CoA) is instrumental in the synthesis of essential fats, acetylcholine, heme and melatonin. Cell signaling (DNA, gene expression and transcription of mRNA) depends on acetylation reactions that are likewise dependant on CoA.<sup>174-175</sup>

Deficiency of pantothenic acid is rare in the typical diet. Bacteria residing in the colon are capable of producing their own pantothenic acid but the research indicates that this form may not be used by the

host. Malnutrition may create the deficiency of pantothenic acid if severe. Most research work in B5 is in the area of animals. Food sources abound for pantothenic acid and are highest in fish, chicken and eggs. An adequate intake level appears to be about 5 mg/day for most adults. There is no established upper level of intake.<sup>176-177</sup>

### Vitamin B6 – Pyridoxamine, Pyridoxine, Pyridoxal

Vitamin B6 – pyridoxamine – is a water-soluble vitamin discovered in 1930 during nutrition studies on rats. It must be obtained from the diet or from supplements because humans cannot synthesize Vitamin B6. It is critical in the function of many enzymes and the genesis of hemoglobin as well as interacting with gene expression influencing platelet aggregation. Vitamin B6 is critical in maintenance of the thymus and thus the integrity of the immune system. Magnesium is a cofactor necessary in the proper absorption of vitamin B6. More than 100 enzymatic functions depend on the adequate presence of vitamin B6.

An added note is that coincidental supplementation with folic acid reduces the risk of hyperhomocystenemia and thus cardiovascular disease in prone individuals.<sup>178</sup> Most individuals employ two different pathways to metabolize homocysteine. One converts homocysteine back to methionine and is dependent on folic acid and vitamin B12. The other pathway converts excess homocysteine to the amino acid

cysteine, which the kidneys flush from the body. This metabolism requires three B vitamin-dependent enzymes, made up of B6, B12 and folate. It has been suggested that the B vitamin, choline and its metabolite, betaine, are also players in this sophisticated metabolic process.<sup>179-186</sup> One study reports reduced oscillatory potentials suggesting microvascular damage to the retina through homocysteine. Decreased photoreceptor function as well as ganglion cell loss as indicated by pathological flash VEPs may reflect a cytotoxic impact of homocysteine on neurons of the visual pathway.<sup>187</sup>

The phosphate ester derivative pyridoxal 5-phosphate (PLP) is the principal coenzyme form of vitamin B6 and has the most importance in human metabolism.<sup>188</sup> Vitamin B6 deficiency has been associated with impaired immune function, especially in the elderly, because production of immune system white blood cells called lymphocytes, and an anti-inflammatory protein called interleukin-2 (IL-2) are dependent on vitamin B6 intake.

In the brain, the synthesis of the neurotransmitter, serotonin, from the amino acid, tryptophan, is catalyzed by a PLP-dependent enzyme. Other neurotransmitters, such as dopamine, norepinephrine and gamma-aminobutyric acid (GABA), are also synthesized using PLP-dependent enzymes.<sup>189</sup>

Gyrate atrophy of the retina and choroid is a rare autosomal recessive inherited disease, characterized by progressive chorioretinal atrophy

that results in progressive deterioration of peripheral and night vision. Ultimately the condition leads to blindness and is related to hyperornithemia. The exact mechanism of chorioretinal atrophy in hyperornithinemia is not known and a small percentage of the affected people respond to Vitamin B6 supplementation.<sup>190</sup>

It is also recognized that Vitamin B6 is an important co-factor in stimulating the neurotransmitters associated with the blink response and the tear production as well as being a major co-factor in both Omega-6 and Omega-3 fatty acid metabolism. As such, B6 plays a role in maintenance of a healthy tear system.

Vitamin B6 also affects steroid hormones by binding to receptors and inhibiting inappropriate signaling of steroid hormones. There are suggestions that B6 deficiency may be implicated in breast cancer and prostate cancer.<sup>191</sup> Recent studies suggest that women who take birth control pills are almost always deficient in vitamin B6.<sup>192</sup>

Deficiency of vitamin B6 is rare but may occur in conditions related to alcohol excesses. Baked potatoes with skin, bananas, salmon, chicken with no skin, spinach, and avocado all are excellent food sources for vitamin B6. The RDA for adults is about 1.5 to 1.7 mg per day. High doses of pyridoxine (1000 mg/day) may create sensory neuropathy involving pain and numbness in the extremities. The tolerable upper intake level is set at 100 mg/day for adults.<sup>193-194</sup>

### Folic Acid

Folic acid and folate both describe the water-soluble B complex vitamin. Folic acid is the more stable form that occurs only rarely in foods or in the body. Folate is the form usually found in foods and the human body.<sup>195</sup> Folate coenzymes mediate the transfer of one-carbon units in a number of reactions critical to the metabolism of nucleic acids and amino acids and play a vital role in DNA metabolism through two different pathways. Those pathways are: 1.) the synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes; 2.) the synthesis of methionine, and methionine is required for the synthesis of S-adenosylmethionine (SAM).<sup>196</sup> The synthesis of methionine from homocysteine re-

quires the folate coenzyme as well as a vitamin B12-dependent enzyme and as such is intimately involved in hyperhomocysteinemia.

Folate deficiency can result in decreased synthesis of methionine and a buildup of homocysteine. Folic Acid is related to homocysteine levels and elevated homocysteine levels and decreased folic acid levels are related to a number of conditions including dementia. Deficiencies may triple the risk of dementia in the elderly.<sup>197</sup> Vascular disease and elevated homocysteine increase risk for both late-onset depression and Alzheimer's disease and may partly mediate their relationship.<sup>198</sup> Several investigators have described associations between decreased folate levels and cognitive impairment in the elderly.<sup>199-202</sup> In a sample of 1,092

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men and women without dementia followed for an average of ten years, those with higher plasma homocysteine levels at baseline had a significantly higher risk of developing Alzheimer's disease and other types of dementia. Those with plasma homocysteine levels greater than 14 micromoles/liter had nearly twice the risk of developing Alzheimer's disease.<sup>203</sup>

The most well-recognized complication of folate deficiency are neural tube defects, anencephaly or spina bifida, in pregnancy. Randomized trials demonstrated 60% to 100% reductions in neural tube defects when women consumed folic acid supplements in the peri-conceptional period. In 1998 there was even FDA legislation mandating folate fortification of all enriched grain products. Unfortunately, compliance is less than ideal resulting in a continuation of a preventable disorder.<sup>204</sup>

Observational studies have found that relatively low folate intake and high alcohol intake are associated with increased incidence of colorectal cancer.<sup>205-206</sup> While dietary folate may be protective against colorectal cancer, high doses may actually accelerate tumor growth in cancer patients with colorectal adenoma.<sup>207</sup> Obviously more research must be performed in this area with better controls for collateral factors. One study reported that women consuming at least one alcoholic drink per day, with folic acid intake of at least 600 mcg daily had about half the risk of breast cancer compared with women who consumed less

that 300 mcg of folic acid daily.<sup>208</sup>

Folate deficiency is usually related to dietary insufficiency which may be also associated with mal-absorption issues. Drug interactions may also contribute to deficiencies. NSAIDs in therapeutic dosages may interfere with folate metabolism. Long-term use of anticonvulsants, phenytoin, phenobarbital, and primidone inhibits absorption.<sup>209</sup> Anti-cholesterol agents may also decrease absorption of folate.<sup>210</sup> Methotrexate is a folic acid antagonist which simulates folate deficiency and there is a report of presumed methotrexate induced optic neuropathy reversed with folate supplementation.<sup>211</sup> Trimethoprim, pyrimetamine, triamterene and sulfasalazine may likewise affect absorption.<sup>209</sup>

It is recommended that adults take a 400 mcg supplement of folic acid daily with the tolerable upper limit set at 1000 mcg/day. A supplement regimen of 400 mcg of folic acid, 2 mg of vitamin B6, and 6 mcg of vitamin B12 has been advocated by the American Heart Association if an initial trial of a folate-rich diet is not successful in adequately lowering homocysteine levels.<sup>212</sup> Maximum dosages should not exceed 1 mg/day and all folic acid should be consumed with B12 and B6 to maximize effect and minimize toxicity.

Natural sources of folate include green leafy vegetables (spinach, asparagus), citrus fruit juices, legumes, fortified cereals and grain products. Recently the Food and Nutrition Board of the Institute of Medicine set the new dietary recommendation for folate, introducing a new

unit, the Dietary Folate Equivalent (DFE). Implementation of the DFE reflects the higher bioavailability of synthetic folic acid found in supplements and fortified foods compared to that of naturally occurring food folates.<sup>213</sup> For example: 1 microgram (mcg) of food folate provides 1 mcg of DFE, while 1 mcg of folic acid taken with meals or as fortified food provides 1.7 mcg of DFE and 1 mcg of folic acid (supplement) taken on an empty stomach provides 2 mcg of DFE.

## Vitamin B12

Vitamin B12 is water-soluble with a very complex chemical structure containing a metal ion, cobalt and as such cobalamin is the term used to refer to compounds having vitamin B12 activity.<sup>214</sup> Methylcobalamin is necessary for the function of the folate-dependent enzyme, methionine synthase and as such is very involved in the homocysteinemia issue. This enzyme is required for the synthesis of the amino acid, methionine, from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA.<sup>215</sup>

Vitamin B12 deficiency is estimated to affect 10%-15% of individuals over the age of 60. Associations with vitamin B12 deficiency are: 1.) an autoimmune condition known as pernicious anemia and; 2.) food-bound vitamin B<sub>12</sub> mal-absorption. Although both causes become more

common with increasing age, they are separate conditions.<sup>216</sup> Absorption of vitamin B12 from food requires normal function of the stomach, pancreas, and small intestine. Malabsorption may be associated with issues such as alcoholism and even bariatric surgery. While most address the necessity of avoidance of oral treatment of pernicious anemia, high-dose oral therapy is considered to be as effective as intramuscular injection.<sup>217-220</sup>

Although vitamin B12 deficiency is known to damage the myelin sheath covering cranial, spinal, and peripheral nerves, the biochemical processes leading to neurological damage in B12 deficiency are not well understood. Individuals with Alzheimer's disease often have low blood levels of vitamin B12. One study found lower vitamin B12 levels in the cerebrospinal fluid of patients with Alzheimer's disease than in patients with other types of dementia, though blood levels of vitamin B12 did not differ.<sup>221</sup> Vitamin B12 has demonstrated value in improving retinal function in POAG. Vitamin B12 exerts protective action on glutamate-induced neurotoxicity at the site of the retinal neurons. The signs of nitric oxide neurotoxicity are similar to the nerve impairment and symptoms of a vitamin B12 deficiency that include retinal degeneration and visual loss.<sup>222-227</sup> There are many neurological manifestations of vitamin B12 deficiency. Optic neuropathy is a rare, but important, manifestation of vitamin B12 deficiency that should be suspected in patients with risk factors

for malnutrition. Vitamin B12 optic neuropathy is a reversible, treatable cause of vision loss and may be a harbinger for other manifestations of the disease.<sup>228</sup>

The RDA for vitamin B12 is approximately 2.4 mcg/day for adults. No tolerable upper level is set. B12 is synthesized by bacteria present in animal products therefore vegetarians must supplement. Clams, mussels, crab, salmon, rockfish are excellent sources of B12 with beef, chicken, turkey, egg and milk products providing a source as well.

Certain drugs reduce the absorption of B12 and include proton pump inhibitors, gastric acid inhibitors, cholestyramine, chloramphenicol, colchicines and metformin.<sup>229-231</sup> Because vitamin B12 malabsorption and vitamin B12 deficiency are more common in older adults, some respected nutritionists recommend that adults older than 50 years take up to 100 to 400 mcg/day of supplemental vitamin B12, an amount provided by a number of vitamin B-complex supplements.

### Special Topic: Hyperhomocysteinemia as a Systemic and Ocular Risk Factor

Recent studies point to the fact that there is a newly recognized risk factor implicated in systemic vascular disease. This risk factor is homocysteine (Hcy), an amino acid and a basic unit of protein.<sup>232-236</sup> Homocysteine is formed during the metabolism of methionine, an essential amino acid derived from the diet. Mild hyperhomocysteinemia occurs in

approximately 5 to 7% of the population who remain asymptomatic until the third or fourth decade when premature coronary artery disease and arterial and venous thrombosis may develop. In the elderly population, hyperhomocysteinemia may be as high as 30 to 40%. A landmark study in 1992 of over 14,000 male physicians found that those with the highest levels of homocysteine had more than three times the risk for heart disease.<sup>237</sup> It has been estimated that hyperhomocysteinemia may be responsible for up to 10% of coronary artery disease (CAD). One study concludes that hyperhomocysteinemia is an independent risk factor for Coronary Artery Disease (CAD) in young patients (below 45 years old) – especially in men – and vitamin B12 deficiency is a preventable cause of hyperhomocysteinemia.<sup>238</sup> Hyperhomocysteinemia, known to be an important risk factor in endothelial dysfunction, seems to be an important determinant in erectile dysfunction (ED). In one study data suggests that slightly elevated homocysteine levels are significantly related with arterial and probably endothelial dysfunction in patients with ED.<sup>239</sup>

Compared with healthy women, those women with rheumatoid arthritis are deficient in vitamin B6 and have elevated levels of homocysteine. This may contribute to the increased risk of cardiovascular events seen with RA. A decrease in RBC folate levels was noted but not plasma levels in RA patients.<sup>240</sup> There is also the link of hyperho-



homocysteinemia to an increase for the risk of hip fracture.<sup>241</sup>

Elevations in homocysteine levels typically are caused by genetic defects in the enzymes involved in homocysteine metabolism or by nutritional defects in vitamin co-factors. Homocystinuria and severe hyperhomocysteinemia are caused by rare inborn errors of metabolism resulting in marked elevations while vitamin deficiencies can raise levels exceeding 100 mmol/L. Homocystinuria is very rare and creates an entirely different clinical picture than hyperhomocysteinemia characterized by mental retardation, skeletal deformities and bilateral lens subluxation.

It is estimated that vitamin deficiency contributes to a considerable number of cases of hyperhomocysteinemia. While there is not definitive evidence whether hyperhomocysteinemia is the cause of complications or if hyperhomocysteinemia is a marker for critical vitamin levels involved in metabolism, current knowledge supports the link to increased vascular risk. Several therapeutic drugs including methotrexate, theophylline, cyclosporine and anticonvulsants also may precipitate hyperhomocysteinemia.

Typically foods rich in Vitamin B12 (Cobalamin), B6 (Pyridoxine) and Folate (Folic Acid) work to keep homocysteine at relatively safe levels. Conversely, low levels of these vitamins correlate to elevated homocysteine levels or hyperhomocysteinemia. Folate seems to be the most effective of the group of three to create a lowering of the homo-

cysteine levels, but synergism with the B vitamin group is critical.

Research in the area of hyperhomocysteinemia suggests that a minimum of 400 mcg of folate in women of childbearing age helps prevent neural tube defects such as spinal bifida and anencephaly in newborns. There is a corollary in vascular disease suggesting that 400 mcg of folate per day is likewise necessary to decrease the levels of homocysteine.<sup>212</sup>

### Naturally Occurring Folate

Folate occurs naturally in legumes, leafy green vegetables, liver, some fruits, enriched breakfast cereals, whole grain products, and enriched grain foods. Retention of folate during preparation of foods is critical with freshly prepared foods. Canned foods do not contain similar beneficial levels. The following guidelines should be used in the preparation of foods rich in folate to get the maximum nutritional effect:

- Avoid cutting foods into small pieces
- Cook al dente
- Cook with a minimal amount of water
- Eat foods raw when possible

### Hyperhomocysteinemia and Systemic Disease

Elevated homocysteine has been detected in 30% of individuals with coronary vascular disease, 42% of patients with cerebrovascular disease and 28% with peripheral vascular disease.<sup>242-243</sup> Homocysteine has been found to be up to 40 times more predictive than cholesterol in assess-

ing cardiovascular disease risk.<sup>244-245</sup> Damage to blood vessels associated with hyperhomocysteinemia includes injury to arterial endothelial cells and promotion of smooth muscle growth which result in plaque. Hyperhomocysteinemia also disrupts normal blood clotting increasing the risk of thrombi. The strongest links between hyperhomocysteinemia and systemic disease involve the association to vascular occlusive events but other relationships are being discovered. Reports link elevated homocysteine levels to all of the following systemic conditions:<sup>246</sup>

- Increased cardiovascular morbidity and mortality
- 15-30% of patients with premature vascular disease<sup>237</sup>
- 25% of non-diabetic patients under age 55 with heart attacks or stroke have hyperhomocysteinemia versus 5% of those without
- Increased risk of cancer deaths<sup>237</sup>
- Increasing the risk of Alzheimer's disease<sup>247</sup>
- Chronic gastrointestinal disease – irritative bowel disease<sup>248</sup>
- Collagen disorders and osteoporosis<sup>249</sup>
- Chronic renal insufficiency<sup>250</sup>
- Relationship to depression<sup>251-252</sup>

Homocysteine levels should be evaluated in patients with premature atherosclerotic disease and a strong family history of:

- Myocardial infarction
- Peripheral vascular disease
- Stroke
- Recurrent pulmonary embolism
- Venous thrombosis

- Renal failure
- Cardiac or renal transplant

## Hyperhomocysteinemia and Ocular Disease

Any ocular disease with a relationship to a compromise or alteration of the vascular system could be implicated in hyperhomocysteinemia. Reports link elevated homocysteine levels to all of the following ocular conditions:

- Primary Open Angle Glaucoma<sup>253</sup>
- Pseudoexfoliation and pseudoexfoliative glaucoma<sup>254</sup> and risk of thromboembolic events in these patients<sup>255</sup>
- Non-arteritic ischemic optic neuropathy especially in younger patients<sup>256-260</sup>
- Neovascular glaucoma in patients with diabetes<sup>261</sup>
- Exudative age related macular degeneration<sup>262-265</sup>
- Retinal vaso-occlusive disease independent of other risk factors especially in younger patients<sup>258, 266-267</sup>
- Retinal emboli<sup>257</sup>
- Behcet's disease<sup>268-273</sup>
- Diabetic retinopathy,<sup>274-276</sup> especially macular edema<sup>277</sup>

## Testing for Hyperhomocysteinemia

While some screening tests are available typically the Hcy levels are tested in a fasting plasma situation. After an over-night fast plasma homocysteine levels are measured on a morning specimen collected in a lavender (EDTA) tube. Testing should be done immediately as the blood cells continue to release ho-

mocysteine. Enzyme immunoassay is rapid and results in excellent analysis. A methionine load challenge may be administered as well in patients suspected of hyperhomocysteinemia but with normal fasting levels.

Optimal levels are considered <10mmol/L but normals usually are considered in the 5 to 15 mmol/L range. Levels over 100 mmol/L are considered severe. Levels tend to increase with age.

Results of a large population-based study have suggested that inflammatory markers are the major determinants of Hcy and vitamin B(6) concentrations.<sup>278</sup>

## Recommendations

As a primary eye care practitioner you should be aware of the systemic and ocular health risks of hyperhomocysteinemia. Be aware of the benefits of supplementation and behavioral modification to reduce the health risks associated with the condition. If you as a clinician shy away from recommending vitamin supplements for macular degeneration or are hesitant about recommending lifestyle changes, the work on hyperhomocysteinemia should change your opinion about folate, vitamin B12 and vitamin B6 supplementation. Likewise vitamins E and C are known to work synergistically to facilitate the **folate anti-homocysteine cocktail**. If you do nothing else but recommend foods high in the complex supplemented by not more than 400 to 1000 mcg of folic acid per day, 10 to 50 mg of vitamin B6, and 50-300 mcg of vitamin B12 per day, you may impact soundly

on ocular and systemic morbidity and mortality in your patients. You should also be aware of the ocular and systemic associations to hyperhomocysteinemia and order blood work on patients with those presentations. In one study folic acid and **N-acetylcysteine** lowered plasma homocysteine levels and improved endothelial function.<sup>279</sup>

It has also been suggested that should folic acid, B12 and B6 not lower homocysteine levels, that 1500 mg of betaine or 2000 mg of choline per day may be of benefit. In a subset of patients, vitamin B2 (riboflavin) was also beneficial in lowering the homocysteine levels.

Along with vitamin supplementation, persons with elevated homocysteine levels should adopt a heart healthy diet and lifestyle including low saturated fat diets, diets low in methionine (meats and eggs), and exercise. Smoking and excessive alcohol consumption may likewise impact negatively on both hyperhomocysteinemia and cardiovascular risk.

[Part 3 of this series will be a continuation of the discussion of the specific supplements and their benefits in the management of diseases and disorders.](#)

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