Folic acid and biotin:
Growing evidence that their levels are far more important than we knew them to be

BIOTINIDASE DEFICIENCY
Biotinidase is the enzyme responsible for the recycling of the vitamin biotin. Biotinidase acts as a hydrolase by cleaving biocytin and biotinyl-peptides, thereby liberating biotin for reutilization. Biotinidase is also important for making biotin bioavailable from bound dietary sources. The interest in this enzyme has been increased by the discovery of biotinidase deficiency, an inherited biotin-responsive disorder that can result in neurological and cutaneous abnormalities.

Recent reports have stressed the need to screen children with early onset of seizures, encephalopathy, neurodevelopmental delay, skin rash and alopecia. Enzyme estimation remains the conclusive test. The clinician should be alert to simple clinical pointers which aid in early diagnosis of these disorders.¹

CAUSES OF BIOTIN DEFICIENCY
• A diet that contains raw egg whites quickly and almost invariably leads to biotin deficiency.
• Several cases of biotin deficiency in patients receiving prolonged total parenteral nutrition (TPN) therapy without added biotin have been reported. Therefore, all patients receiving TPN must also receive biotin at the recommended daily dose, especially if TPN therapy is expected to last more than 1 week. All hospital pharmacies currently include biotin in TPN preparations.
• Prolonged use of certain drugs, especially phenytoin, primidone, and carbamazepine, may lead to biotin deficiency. Therefore, supplemental biotin, in addition to the usual minimum daily requirements, has been suggested for patients who are treated with anticonvulsants that have been linked to biotin deficiency.
• Alterations in the intestinal flora caused by the prolonged administration of antibiotics are presumed to be the basis for biotin deficiency.

BIOTIN DEFICIENCY UP-REGULATES TNF-ALPHA PRODUCTION
Biotin, a water-soluble vitamin of the B complex, functions as a cofactor of carboxylases that catalyze an indispensable cellular metabolism. Although significant decreases in serum biotin levels have been reported in patients with chronic inflammatory diseases. In a study, experts investigated the effects of biotin deficiency on TNF-alpha production. The results indicated that biotin deficiency may up-regulate TNF-alpha production or that biotin excess down-regulates TNF-alpha production, suggesting that biotin status may influence inflammatory diseases.²

BIOTIN IN TYPE 2 DIABETIC PATIENTS AND IN NONDIABETICS WITH HYPERTRIGLYCERIDEMIA
Biotin is a water-soluble vitamin that acts as a prosthetic group of carboxylases. Several studies have reported a relationship between biotin and blood lipids. In the present work experts investigated the effect of biotin administration on the concentration of plasma lipids, as well as glucose and insulin in type 2 diabetic and...
nondiabetic subjects. They found that the vitamin significantly reduced (P=0.005) plasma triacylglycerol and VLDL concentrations.

Biotin produced the following changes (mean of absolute differences between 0 and 28 day treatment ± S.E.M.): a) triacylglycerol -0.55 ± 0.2 in the diabetic group and -0.92 ± 0.36 in the nondiabetic group; b) VLDL: -0.11 ± 0.04 in the diabetic group and -0.18 ± 0.07 in the nondiabetic group. It was concluded that pharmacological doses of biotin decrease hypertriglyceridemia.

**BIOTIN SUPPLEMENT DURING PREGNANCY**

A deficiency of biotin may occur in as many as 50% of pregnant women, and this deficiency may increase the risk of birth defects, according to a report in the American Journal of Clinical Nutrition (2002;75:295–9). In this study, laboratory evidence of biotin deficiency was found both in the early (first trimester) and late (third trimester) stages of pregnancy, and was corrected by supplementation.

Prior to this study, it had been generally believed that biotin deficiency is rare, because biotin is found in a wide variety of foods and is also manufactured by intestinal bacteria. This new study indicates that a more subtle form of biotin deficiency occurs during pregnancy, possibly as a result of the increased demand for nutrients placed on the mother by the growing fetus.

Researchers have recommended that pregnant women use a prenatal multiple vitamin-and-mineral formula that contains biotin. Taking a biotin-containing prenatal formula seems a reasonable step for pregnant women, since the vitamin is considered safe and has not been associated with adverse side effects. At least 25 countries have included biotinidase deficiency in their screening programs for neonatal disease.

Biotin supplements have also been used for several other health conditions. Preliminary studies have suggested that biotin in large amounts (such as 5 to 16 mg per day) can help control blood sugar levels or improve nerve damage in diabetics.

**MARGINAL BIOTIN DEFICIENCY IS TERATOGENIC**

Studies of biotin status during pregnancy provide evidence that a marginal degree of biotin develops in a substantial proportion of women during normal pregnancy. Several lines of evidence suggest that, although the degree of biotin deficiency is not severe enough to produce the classic cutaneous and behavioral manifestations of biotin deficiency, the deficiency is severe enough to produce metabolic derangements in women and that characteristic fetal malformations occur at a high rate.

Moreover, analysis of data from a published multivitamin supplementation study provide significant albeit indirect evidence that the marginal degree of biotin deficiency that occurs spontaneously in normal human gestation is teratogenic.

Reduced activity of the biotin-dependent enzymes acetyl-CoA carboxylase and propionyl-CoA carboxylase can cause alterations of lipid metabolism and might theoretically lead to alterations of polyunsaturated fatty acid and prostaglandin metabolism that derange normal skeletal development.4

**SPINAL CORD DEMYELINATION WITH BIOTINIDASE DEFICIENCY**

Biotinidase deficiency is a treatable cause of severe neurological disorders and skin problems. Spinal cord impairment is a rare complication of this disease and is commonly unrecognized. Findings indicate that biotinidase deficiency should be considered in the differential diagnosis of unexplained spinal cord demyelination because prompt diagnosis and treatment with biotin may enable an excellent recovery.5

**LOW SERUM BIOTINIDASE ACTIVITY IN CHILDREN WITH VALPROIC ACID**

Valproic acid (VPA) is an effective antiepileptic drug (AED), which is associated with dose-related adverse reactions such as skin rash, hair loss (alopecia), etc. Profound as well as partial biotinidase deficiency causes dermatologic manifestations similar these.

Therefore, it was of interest to evaluate serum biotinidase activity in patients receiving VPA monotherapy. It is suggested that VPA impairs the liver mitochondrial function, resulting in a low biotinidase activity and or biotin deficiency. Biotin supplementation could restore some of the side effects of the drug.6

**ROLE OF FOLIC ACID IN LOWERING CVD**

The B vitamins are water-soluble vitamins that are required as coenzymes for reactions essential for cellular function. Plasma homocysteine (tHcy) is very responsive to intervention with the B-vitamins required for its metabolism, in particular folic acid. Supplementation with oral folate and vitamins B6 and B12 (mainly folate) reduce plasma homocysteine levels to a significant degree. Thus, although primarily aimed at reducing neural-tube defects, folic acid fortification may have an important role in the primary prevention of cardiovascular diseases (CVD) via tHcy lowering. During the last years, many epidemiologic studies have identified homocysteine as an independent risk factor for cardiovascular diseases like coronary events, stroke, and venous thromboembolism.

Recent trials showed that vitamin supplementation leads to slower progression or even regression of atherosclerotic lesions in the carotid arteries, as confirmed by ultrasonographic measurement of carotid intima media thickness. In fact, a recent meta-analysis of clinical trials has confirmed that folic acid supplementation reduces the risk of stroke, particularly in individuals without a history of stroke.

Evidence supporting a causal relationship between elevated tHcy and heart disease also comes from genetic studies. The most important genetic determinant of tHcy in the general population is the common C677T variant in methylenetetrahydrofolate reductase (MTHFR) that results in higher tHcy. Individuals with the homozygous mutant (TT) genotype have a significantly higher (14-21%) risk of heart disease.7

**FOLIC ACID DEFICIENCY CAUSES NEUROLOGICAL AND PSYCHIATRIC DISEASES**

Hyperhomocysteinemia (HHcy) is also related to central nervous system diseases. Epidemiological studies show a positive, dose-
dependent relationship between plasma total homocysteine (tHcy) concentration and neurodegenerative disease risk. tHcy is a marker of B-vitamin folate, B12, B6 status. Hypomethylation, caused by low B-vitamin status and HHcy, is linked to key pathomechanisms of dementia; B-vitamin supplementation could potentially reduce neurological damage.

In retrospective studies, the association between tHcy and cognition is impressive; there is also evidence that tHcy-lowering treatment could be effective in primary and secondary stroke prevention. Increased tHcy and low serum folate occur in patients with Parkinson’s disease, especially those receiving L-dopa. There is also an association between HHcy and multiple sclerosis, and between B-vitamin status and depression.

Studies also confirm a causal role for tHcy in epilepsy, and certain anti-epileptics enhance HHcy. B-vitamin status should be optimized by ensuring sufficient intake in patients with neuropsychiatric diseases. HHcy occurs commonly in the elderly and can contribute to age-related neurodegeneration. Treatment with folic acid, B12, and B6 lowers tHcy. For secondary and primary prevention from several neuropsychiatric disorders, it seems prudent to actively identify deficient subjects and ensure sufficient vitamin intake.

The aim of this study was to determine whether hyperhomocysteinemia caused by levodopa used in idiopathic Parkinson’s disease (IPD) is associated with cognitive or physical impairments. The conclusion that was arrived at was that in those patients with IPD who are detected to have hyperhomocysteinemia, the assessment of the cognitive performance, folic acid and vitamin B12 levels and the supplementation of folic acid and vitamin B12 to the treatment regimen might be appropriate.

**REFERENCES**

Avoid Marginal, Asymptomatic Biotin Deficiency & Prevent Foetal Birth Defects

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Biotin 5mg. + Folic Acid 5mg. Tablet

Advantage
✓ Works in unison
✓ Supports optimize physiological functions
✓ Useful In Biotinidase Deficiency

Biotin
✓ Maintains healthy hair, skin and muscle tissue
✓ Essential for fat and carbohydrate metabolism
✓ Water-soluble vitamin & required by our bodies

Folic Acid
✓ Cell development
✓ Essential in amino acid & DNA synthesis
✓ Helps in RBC maturation & prevents anaemia

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