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Betaine - *also known as glycine betaine, trimethylglycine, and betaine HCl (salt form)*

Common Indications:

- Hyperhomocysteinemia
- Cardiovascular Health
- Fatty Liver Disease, Alcoholic and Non-Alcoholic
- Hepatoprotection
- Neuroprotection, Alzheimer's disease
- Repletion of Carnitine Stores
- Improving Exercise Performance
- Gastric Re-acidification
- Breast Protection

General Comments:

Betaine is derived from sugar beets (*Beta vulgaris*) for use as a supplement. Betaine is a methyl donor for the conversion of homocysteine to methionine and without this natural conversion homocysteine levels rise and become problematic. Betaine can be bound to hydrochloric acid and serve as an aid to digestion, stimulating digestive enzyme production in the small intestine. It also serves to stimulate hepatic function and carnitine production.

Benefits & Mechanism of Action:

Hyperhomocysteinemia

Betaine is an essential part of betaine homocysteine methyltransferase (BHMT). BHMT converts homocysteine to methionine in the liver while folate-dependent remethylation of homocysteine takes place in the cells.[1] Betaine exhibits a strong reduction of plasma homocysteine levels when there is also a folic acid deficiency. When folate levels are high, there is a weaker effect.[2] Doses up to 6g per day of betaine have been shown to decrease homocysteine levels by 50%, even in instances where folic acid supplementation had no effect.[3] Additional studies show that smaller amounts of betaine, obtained through diet, are sufficient enough to lower homocysteine levels significantly.[4,5,6] Betaine is also successful in lowering homocysteine levels in patients who are deficient in

vitamin B6 or who have hyperhomocysteinemia that is non-responsive to vitamin B6.[7,8]

Cardiovascular Health

Betaine is involved in the methylation reaction that regulates homocysteine levels in the body.[9] The serum levels of betain correlate with serum folate, plasma S-adenosyl-methionine and S-adenosyl-homocysteine. Two past studies have rasied concern that long term use at high doses of betaine and choline may be associated with increasing lipid levels and increasing inflammatory mediators, including C-reactive protein (CRP), IL-6 and TNF- alpha so monitoring is needed.[3,10]

Fatty Liver Disease, Alcoholic and Non-Alcoholic

Betaine is reported to increase generation of hepatic S-adenosyl-methionine (SAM) and reduce hepatic insulin resistance.[11] Increasing levels of SAM is correlated with reducing nonalcoholic steatohepatitis.[12,13] Betaine supplementation also positively affects liver function in the presence of alcohol damage. supplementing betaine helps the liver overcome the impaired methionine synthetase pathway by boosting the betaine homocysteine methyltransferase (BHMT) pathway.[14,15,16,17] All of these studies show a decrease in liver impairment in the presence of alcohol damage and suggest that betaine be considered an approach to prevent alcoholic liver disease.

Hepatoprotection

Hepatotoxicity from exposure to carbon tetrachloride is widely documented. It has been removed from use in pesticides and household products but is still available for scientific research. It is still used to evaluate hepatoprotective agents and to act as a solvent in infrared spectroscopy and for halogens. Betaine exhibited protective effects and a significant effect in recovering a carbon tetrachloride injured liver when given both orally and intraperitoneally.[18] A 2014 study looked at the effect of betaine supplementation on hepatopathy associated with short bowel syndrome (SBS). Patients showed a decrease in hepatic fat and was considered a potential agent for treatment for SBS.[19]

Neuroprotection, Alzheimer's disease

There is an association between elevated levels of homocysteine and the formation of beta-amyloid plaque and tau hyperphosphorylation, markers of Alzheimer's disease.[20] Betaine supplementation demonstrated amelioration of hyperhomocysteinemia-induced memory deficits, an enhancing of long-term potentiation, and increasing dendritic branches numbers and density of dendritic

spines.[21] The same study also showed an up-regulation of NR1, NR2A, synaptotagmin, synaptophysin, and phosphorylated synapsin 1 protein levels.[21] Betaine also reduced tau hyperphosphorylation at multiple sites in the brain by activating protein phosphatase-2A and decreasing demethylated PP2A(C) at Leu309 and phosphorylated PP2A(C) at Tyr307.[21]

Repletion of Carnitine Stores

A deficiency in carnitine is associated with diabetes, hemodialysis, trauma, malnutrition, cardiomyopathy, obesity, fasting, drug interactions, and endocrine imbalances.[22] An animal study looked at the supplementation of betaine in a methionine deficient diet and found that there was increased carnitine synthesis and free carnitine in the liver.[23]

Improving Exercise Performance

Betaine supplementation has been shown to improve performance in activities that require muscle endurance.[24] However, the same study and an additional one found no effect on muscle force and power.[24,25]

Gastric Re-acidification

Betaine has been used as a digestive aid in persons with high stomach pH, including those on a proton-pump inhibitor.[26] Supplementation increases overall gut digestive function and allows for better absorption of medications that require an acidic pH for optimal solubility.

Breast Protection

A 2013 study in China reported a significant inverse association between betaine supplementation and breast cancer risk.[27] Betaine supplementation was also shown to reduce all-cause and cancer specific mortality in a population based study.[28] Both studies suggest that betaine plays an important role in the prevention of and increased survival after diagnosis of breast cancer.

Dose:

Hyperhomocysteinemia, Cardiovascular Health, Fatty Liver Disease, Repletion of Carnitine Stores

- Up to 6g per day in divided doses

Hepatoprotective, carbon tetrachloride toxicity

- Oral 15mg/kg body weight
- Intraperitoneal 3mg/kg body weight

Hepatoprotective, Short Bowel Syndrome

- 10g per day in two divided doses, for 3 months

Neuroprotection

- Prevention of dementia: 0.5-1g daily
- Treatment of dementia: 1-3g daily[20] or 12.5mg/kg/day[21]

Improving exercise performance

- Human studies used 2.5g/day

Gastric Re-acidification

- Studies used up to 1.5g/day

Breast Protection

- Study participants had 126-400 mg/day

Cautions and Side Effects:

Betaine is reported safe in recommended dosages. Betaine HCl should be used with close monitoring from a knowledgeable physician to prevent stomach upset from improper dosing or food/medication combinations.

Symptoms of Deficiency:

Low levels of betaine are associated with increased levels of homocysteine but there is no specific "deficiency" reportable.

Food Sources:

Food sources of betaine include beets, broccoli, grains, wheat, shellfish, and spinach. Refining whole wheat to white flour removes 54% of the betaine content. [29]

References:

Hyperhomocysteinemia

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Cardiovascular Health

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Fatty Liver Disease, Alcoholic and Non-Alcoholic

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Hepatoprotection

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Neuroprotection, Alzheimer's disease

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Repletion of Carnitine Stores

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Improving Exercise Performance

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Gastric Re-acidification

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Breast Protection

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