

## Review

# Homocysteine-A potent modulator

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Homocysteine is an amino acid and is an intermediate metabolite of methionine metabolism. It is metabolized by two pathways, the trans-methylation and trans-sulphuration. These processes rely on an adequate supply of vitamin B<sub>12</sub> and B<sub>6</sub> and folic acid. Deficiency of vitamin B<sub>12</sub>, B<sub>6</sub> and folic acid can build up homocysteine level in blood stream. High homocysteine levels has been implicated in a variety of clinical conditions and is widely accepted, alongside smoking, obesity, hypertension and dyslipidemia as being an independent risk factor for cardiovascular disease. Homocysteine promotes artery problems in more than one way. Homocysteine got a bad rap from its cozy relationship with heart attacks and stroke. Researchers have repeatedly demonstrated that if they give a person a drink containing methionine, homocysteine will shoot up, and blood flow will shrink up. If they give the person a gram of vitamin C before they give the methionine, blood flow will be maintained. This indicates that antioxidant (vitamin C) prevents the formation of free radicals from homocysteine, which interferes with the ability of the blood vessels and causes cardio vascular diseases. Hence, further research is required to confirm whether antioxidant rich diet can prevent the homocysteine formation in the body or not.

**Key words:** Homocysteine, vitamins, methonine, disease.

## INTRODUCTION

More over than cholesterol, there is a new molecule in the list. Last 10 years, there has been an explosion of interest. A sulfur containing amino acid that occupies a central location in the metabolic pathways—its homocysteine a major risk factor in hyperhomocysteinemia. Homocysteine is not found in our diet, and thus the answer to why it represents such a problem lies in examining how it is produced in our body. Homocysteine is formed in methionine metabolism and the imbalance between the rate of production of homocysteine through methylation, remethylation reactions in methionine metabolism can result in increase in the release of homocysteine to the extracellular medium and ultimately the plasma and urine. High levels of homocysteine have been linked to cardiovascular disease. Recent research shows that elevated levels of homocysteine is one of the risk factor for many vascular diseases, neurodegenerative diseases like Alzheimer's

and congenital heart defects.

In this article we review the various biochemical and genetic link of homocysteine and its associated risk factors and also emphasizing on the simple ways to prevent the elevation of homocysteine which may aid in the prevention of many disorders associated with it.

## HISTORY OF HOMOCYSTEINE

The importance of homocysteine to human health first came to light in the 1960's by Kilmer McCully who was interested in homocystinuria, a rare disease that results in high homocysteine levels in the blood. It turned out that people with this condition often suffered from heart disease and strokes, even at a very young age. Several children with homocystinuria had died of heart attacks, despite their age and lack of fat deposits. Dr. McCully noticed that they had blood vessels damaged by atherosclerotic plaques. He suggested that maybe the homocysteine had something to do with how these cholesterol deposits were formed inside the arteries. He

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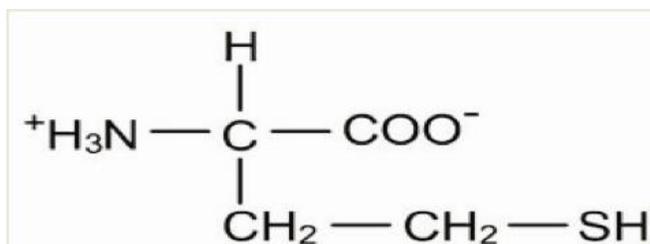


Figure 1. Structure of homocysteine.

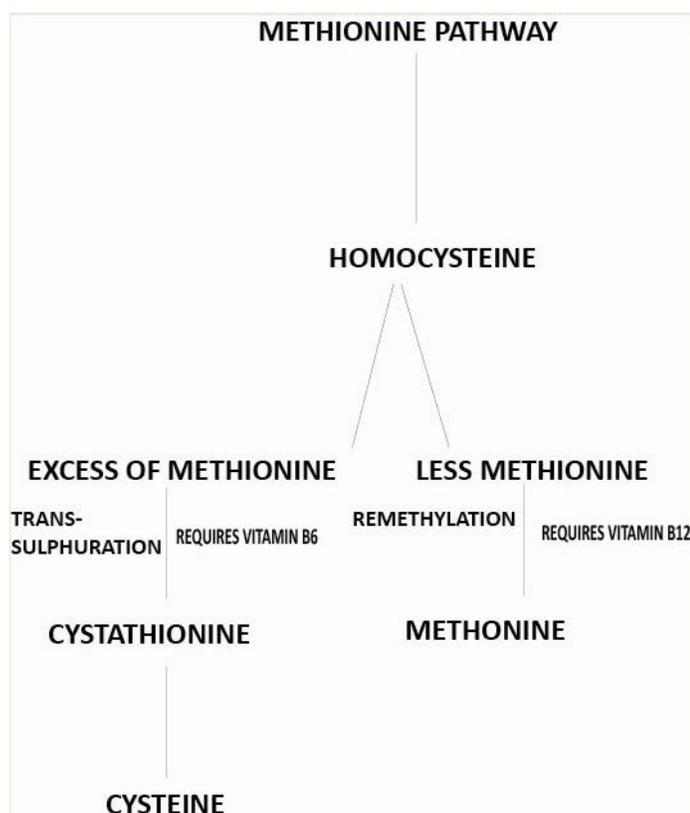


Figure 2. Homocysteine metabolism.

suggested that maybe the homocysteine had something to do with how these cholesterol deposits were formed inside the arteries (McCully, 1969), however whether to take homocysteine levels as a clinical determinant for heart disease or as other researches suggest while to take it as a marker rather than a cause is still controversial. However now researchers have also discovered that homocysteine plays a part in much more diverse health concerns like osteoporosis, depression, Alzheimer's and some conditions in pregnancy. To understand how one molecule can have influence in so many diseases, we need to take a closer look at this compound and its metabolic pathway.

## Homocysteine metabolism

Homocysteine is non-protein sulphur containing amino acid and a normal intermediate in methionine metabolism (Figure 1). Proteins are metabolized, broken down into individual amino acid, including the sulfur-containing amino acid Methionine. Homocysteine formed during the methionine metabolism can be removed from the system only by two ways: when there is excess methionine, it will be converted into cysteine by transsulphuration reaction (Figure 2).

Secondly when there is low level of methionine it will be remade into methionine by remethylation both the reaction requires vitamins and folic acid as a major cofactor. Thus if a person ingests lots of protein, and there is not enough folic acid, B<sub>6</sub> and B<sub>12</sub> available to help digest it, homocysteine levels can build up in the blood stream. Indeed, studies have shown that oral folic acid supplements are effective in bringing homocysteine levels down. In a seesaw effect, as folic acid levels rise in the blood stream, levels of homocysteine drop (Stam et al., 2005).

## Genetic link

Severe homocysteinemia with homocystinuria was first identified in cases of rare inborn errors of metabolism characterized by marked elevations of plasma and urine homocysteine concentrations. The most common of these is the deficiency of CBS, the homozygous form of which occurs in approximately 1 in 2, 00,000 live births. Associated with fasting plasma homocysteine concentrations of up to 200 mol/L. Clinical manifestations include:

- 1) Mental retardation
- 2) Thromboembolism
- 3) Seizures
- 4) Premature atherosclerosis
- 5) Skeletal deformities

The heterozygote state is estimated to occur in 1 to 2% of the population of 3 lakhs. These patients have mild elevations of fasting homocysteine. Recent epidemiologic studies suggest that they are at increased risk for premature atherosclerosis. Homozygous deficiency of N<sub>5</sub>, N<sub>10</sub> methylenetetrahydrofolate reductase (MTHFR) is rare and results in severe hyper homocysteinemia and early death, which is mainly due to the transition in the MTHFR Gene in the 677 codon with a change in the amino acid from valine to alanine (C677T).

Patients homozygous for the C677T mutation have slight elevations in homocysteine levels and are at increased risk for premature vascular disease. Recent observations suggest that patients with the MTHFR genotype have higher folate requirements than individuals with a normal genotype.

## HOMOCYSTEINE AND VARIOUS HEALTH DISORDERS

### Cardiovascular diseases

Homocysteine is believed to have a causal influence on the development of cardiovascular disease. It damages the walls of the arteries. As a result they become clogged, thickened and less flexible. The blood clots more easily so it is more likely to form a blockage and cause a heart attack. Epidemiological evidence now exists to conclude that moderately elevated homocysteine increases the risk of cardiovascular events (Lievers et al., 2003).

### Artherosclerosis and stroke

Strokes affect the arteries leading to and from the brain and can be caused by either a blood clot or a blood vessel rupturing. As cerebrovascular events are similar in many ways to cardiovascular events, it should not be surprising that homocysteine is also an independent risk factor for ischemic stroke.

### Alzheimer's diseases

Alzheimer's diseases destroys brain cells, causing problems with memory, thinking and behavior severe enough to affect work, lifelong hobbies or social life. Gets worse over time, and it is fatal. Today it is the seventh-leading cause of death. Recently the New England journal of medicine suggest that elevated homocysteine levels could be a strong risk factor associated with poor cognition and dementia.

### Renal disorders

Normal kidney metabolism and filtration plays a prominent role in removing homocysteine from the blood interestingly patients with renal disease have unusually high rate of cardiovascular morbidity and death. Likewise, renal transplant recipients typically have elevated homocysteine levels (Friedman et al., 2001).

### Other complications related to elevated homocysteine level

High homocysteine level during maternity will increase the chance of miscarriage and serious pregnancy complications, which will be fatal for both mother and the child. Moreover homocysteine seems to be inappropriately stimulate some nerve cell receptors,

which can interfere brain function.it is also been proposed that homocysteine maybe a causative agent got osteoporosis condition which weakens the bone (Bostom et al., 1999b).

### Factors that cause elevated levels of homocysteine

#### *Lifestyle factors*

- a) Smoking
- b) High consumption of coffee
- c) Alcohol consumption (moderate beer intake may be beneficial)

#### *Diet*

- a) Low consumption of fruits and vegetables
- b) No consumption of multivitamins
- c) Low intake of folic acid, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>
- d) High intake of methionine-containing proteins

#### *Diseases or inherited causes*

- a) Cystathionine beta-synthase deficiency
- b) 5MTHFR errors
- c) Methionine synthase deficiencies
- d) Chronic renal failure

#### *Drugs that increase homocysteine*

- a) Some antiepileptic drugs (phenobarbital, valproate, phenytoin etc.)
- b) Diuretic therapy
- c) Methotrexate
- d) Nitrous oxide
- e) Estrogen-containing oral contraceptives
- f) Metformin
- g) Niacin

## VITAMIN AND HOMOCYSTEINE METABOLISM

It is evident from homocysteine metabolism that folic acid vitamin B<sub>6</sub> and vitamin B<sub>12</sub> are important cofactors, which metabolizes homocysteine into methionine and cysteine. Based on this fact several researchers suggest that vitamin supplementation can lower the homocysteine levels in turn the related complications. It is also been proposed that vitamin therapy with folic acid alone or complemented with vitamin B<sub>6</sub> and B<sub>12</sub> with cereal grain products contain folate can lower plasma homocysteine (Bostom et al., 1999a). According to WHO report vitamin supplementation during pregnancy can prevent birth

defects and miscarriages. Furthermore, increased dietary intake of folic acid and vitamin B<sub>12</sub> (but not B<sub>6</sub>) is inversely related to reduction in stroke risk.

### How to reduce the level of homocysteine or how to keep it under control?

There are 10 commandments to lower your homocysteine levels namely:

- 1) Eat less fatty meat, more fish and vegetable protein
- 2) Eat your greens
- 3) Have a clove of garlic a day
- 4) Do not add salt to your food
- 5) Cut back on tea and coffee
- 6) Limit your alcohol
- 7) Reduce your stress
- 8) Stop smoking
- 9) Supplement a high-strength multivitamin
- 10) Proper well balanced diet with more intake of water

### CONCLUSION

Because folic acid supplements do significantly lower homocysteine levels in the blood stream, such proposals to add folic acid to foods have been made. Proponents note that the addition of vitamin B<sub>6</sub> to the food supply has resulted in a gradual drop in death from cardiovascular causes since the 1960s. However, such plans are controversial, for one because folic acid supplements can mask the symptoms of pernicious anemia, a vitamin B<sub>12</sub> deficiency that hampers the bone marrow's ability to make blood, which can cause irreversible nerve damage.

Thankfully, in the absence of metabolic defects that keep homocysteine levels abnormally high, all the risks associated with high homocysteine levels seem to be avoidable with good nutrition. Leafy green vegetables, orange juice and beans are good sources of folic acid. Vitamin B<sub>6</sub> is found in starchy foods such as whole grains, potatoes, bananas, as well as turkey and tuna, and vitamin B<sub>12</sub> is found in meat, seafood and dairy products. While high homocysteine levels are found in tandem with many ailments, proving a real biochemical connection between homocysteine and disease is important before serious recommendations can be made about diet and vitamin supplementation.

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