ROLE OF HOMOCYSTEINE IN THE DEVELOPMENT OF CARDIOVASCULAR DISEASE

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Introduction:

Homocysteine has been under a lot of speculation since its discovery in 1932. Recent years have shown a dramatic increase in research towards the better understanding of the notoriety of this amino acid of interest.

Homocysteine is an amino acid and breakdown product of protein metabolism that, when present in high concentrations, has been linked to an increased risk of heart attacks and strokes. Elevated homocysteine levels are thought to contribute to plaque formation by damaging arterial walls.

Homocysteine, a sulfhydryl-containing amino acid, is an intermediate product in the normal biosynthesis of the amino acids methionine and cysteine. It is an amino acid produced via demethylation of dietary methionine, which is abundant in animal protein. It is present in plasma in four different forms: around 1% circulates as free thiol, 70–80% remains disulphide-bound to plasma proteins, mainly albumin and 20–30% combines with itself to form the dimer homocysteine or with other thiols . Homocysteine is a key determinant of the methylation cycle.

High homocysteine levels in the blood can damage the lining of the arteries. In addition, high homocysteine levels may make blood clot more easily than it should. This can increase the risk of blood vessel blockages. A clot inside the blood vessel is called a thrombus. A thrombus can travel in the bloodstream and get stuck in lungs (called a pulmonary embolism), in brain (which can cause a stroke) or in heart (which can cause a heart attack) People who have very high levels of homocysteine are at an increased risk for coronary artery disease.

Causes of high homocysteine level:

Homocysteine is normally changed into other amino acids for use by the body. If the homocysteine level is too high, one may not be getting enough B vitamins to help the body use the homocysteine.

Most people who have a high homocysteine level don't get enough folate (also called folic acid), vitamin B6 or vitamin B12 in their diet. Replacing these vitamins often helps return the homocysteine level to normal. Other possible causes of a high homocysteine level include low levels of thyroid hormone, kidney disease, psoriasis, some medicines or when the condition runs in your family. Homocysteine levels increase in the body when the metabolism to cysteine of methionine to cysteine is impaired. This may be due to dietary deficiencies in vitamin B6, vitamin B12, and folic acid.

The Risk Factors for Elevated Homocysteine Levels:

Elevated homocysteine levels in the body do not cause any symptoms. However, elevated levels of it in the blood increases the risk factors for certain diseases and conditions; for example:

- Elevated homocysteine levels affect the interior lining of blood vessels in the body, increasing the risk of atherosclerosis or narrowing of blood vessels. This can result in early heart attack and stroke.
- There is a relationship between the levels of homocysteine in the body and the size of the carotid arteries that supply the brain with blood; the higher homocysteine level, the narrower (stenosed) the carotid artery becomes.
- The risk of deep vein thrombosis (DVT) and pulmonary embolism may be linked to elevated homocysteine levels.
- There may be a relationship between elevated homocysteine levels and broken bones, especially in the elderly.
- Alzheimer's disease and other types of dementia may be more frequently seen in patients with increased or elevated levels of the amino acid in the blood.
- In infants who have the genetic condition homocystinuria, the inherited abnormalities affect the body's metabolism of homocysteine to cysteine. This may result in dislocation of the lens in the eye, sunken chest, Marfan-type appearance (long thin body type), mental retardation, and seizures. Neonatal strokes may also be seen with high homocysteine levels.
- In pregnancy, homocysteine levels tend to decrease. Elevated homocysteine levels may be associated with some fetal abnormalities and with potential blood vessel problems in the placenta, causing abruption. There may also be an association with pre-eclampsia.

Reference Range of homocysteine level:

Plasma and urine homocysteine tests are indicated in the screening and diagnosis of different types of homocystinuria.

The reference range of plasma homocysteine may vary with the technique used. Reference values by age are as follows:

- Age 0-30 years: 4.6-8.1 µmol/L
- Age 30-59 years: 6.3-11.2 µmol/L (males); 4-5-7.9 µmol/L (females)
- Age >59 years: 5.8-11.9 µmol/L

The reference range of urine homocysteine (24-hour urine collection) varies with the technique used, from 0-9 µmol/g creatinine.

Homocysteine and cardiovascular disease:

Cardiovascular diseases (CVD) as the name suggests, comprise of diseases of the heart and blood vessels. Cardiovascular disease is believed to account for one third of all deaths worldwide, and the prevalence is still on the rise. CVD is among the diseases with multiple contributing factors, hence making it difficult to pinpoint a particular factor alone. The main factor that is of relevance to this study is homocysteine. Coronary artery disease is the narrowing or blockage of the arteries and vessels that supply oxygen and nutrients to the heart. Homocysteine has been recognized as a risk factor as early as 1990s, for the

presence of atherosclerotic vascular disease and hypercoagulability states. Subgroup analyses conducted in a study also showed that elevated homocysteine was associated with higher risk of coronary artery disease in patients with chronic renal dysfunction .Researchers have long debated the extent to which homocysteine should be considered as a risk factor for cardiovascular diseases, since according to some, only 50% of CVD can be explained by "classical" risk factors, and they say that "new" risk factors could significantly boost the CVD predictive power.

Homocysteine is known as an independent risk factor for atherosclerosis. Arteriosclerosis is defined as a continuous inflammatory damage to the arterial intima with increased permeability to plasma, deposition of plasma lipids in plaques and fibrosis and calcification of plaques. Several cross-sectional and case control studies have pointed towards a clear correlation between total serum homocysteine and the incidence of coronary, carotid, and peripheral vascular disease. Homocysteine can mediate the formation of cardiovascular disease by several different mechanisms such as its adverse effects on vascular endothelium and smooth muscle cells with resultant alterations in subclinical arterial structure and function.

Investigators have reported a significant association of serum homocysteine concentration with different indices of arterial stiffness such as pulse pressure and aortic stiffness as assessed by carotid-femoral Pulse Wave Velocity (PWV) in the general population. The carotid-femoral PWV was found to be significantly higher in the high homocysteine group than in the normal homocysteine group ($P = 0.01$), however there was no difference in carotid-radial PWV between the high homocysteine group and the normal homocysteine group. In an experimental study on mini pigs, mild hyperhomocysteinemia was found to cause an arterial, site-dependent deterioration of the elastic structure involving metalloproteinase- related elastolysis.

A separate study involving the analysis of men aged 65 years or older, carotid RI (Resistive Index) has shown a significant degree of association with homocysteine. The data utilised carotid RI as a surrogate marker of cerebral peripheral artery resistance and pointed out a significant association between the index and homocysteine levels in elderly male patients with essential hypertension. This indicates that increased serum homocysteine may be a marker of an increase in RI particularly in elderly patients with a greater risk of stroke. Despite these evidences the fact that the subjects of this research were aged 65 and older, should be taken under consideration during speculation in terms of age related factor.

Although it may be of lesser significance, we cannot completely overshadow this factor. Apart from being part of the antioxidant defence system, some vitamins also play a role as enzyme cofactors. Vitamin B_6, B_{12} and folic acid are essential cofactors in homocysteine-methionine metabolism. Therefore low vitamin B availability (B_6, B_{12} and folic acid) leads to impaired re-methylation of homocysteine to methionine and thus to homocysteine

accumulation. Increased homocysteine levels were found to be associated with arteriosclerotic outcomes and risk of stroke in elderly individuals, and are considered as an independent risk marker for cardiovascular diseases.

However, lowering homocysteine levels by B-vitamin supplementation failed to demonstrate beneficial effects in cardiovascular diseases and this has been proven to be true in many other research works. In addition, B vitamins were shown to reduce homocysteine without improving endothelial dysfunction or hypercoagulability. Recent data also seem to indicate that homocysteine accumulates secondary to heightened oxidative stress associated with immune activation. The association between cardiovascular diseases and homocysteine may result from deficiency of B vitamins or it may only alter vascular reactivity when folate is simultaneously low. On the contrary, folate is associated with alteration in vascular reactivity without homocysteine concentration changes. Homocysteine has been positively associated with both diastolic and systolic blood pressure. In case of homocysteine concentration increase of 5 μmol/L (about 1 SD), diastolic and systolic blood pressure in men increased by 0.5 and 0.7 mmHg, respectively. In case of women, the correlation of homocysteine and blood pressure was stronger, with 0.7 and 1.2 mmHg increase in diastolic and systolic blood pressure, respectively.

Conclusion:

Homocysteine is an independent cardiovascular disease risk factor modifiable by nutrition and exercise. However, it is now widely accepted that food sources alone cannot consistently supply the levels of nutrients necessary to sustain optimal homocysteine metabolism. In fact, emerging studies are uncovering novel nutritional strategies for lowering high homocysteine levels offering new possibilities for preventing cardiovascular disease. This field definitely needs more research input until a definitive proof is available to cast off any shadow of doubt regarding the correlation between homocysteine and cardiovascular disease.

Reference:

1. Venes D, Clarence WT. In: Taber's Cyclopedic Medical Dictionary. 21. Venes D, editor. Philadelphia: F.A. Davis; 2005. p. 1089.

2. Faeh D, Chiolero A, Paccaud F. Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about it? Swiss Med Wkly. 2006; 136:745–56.

3. Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. Lancet. 1999; 354:407–13. doi: 10.1016/S0140-6736(98)11058-9.

4.Veeranna V, Zalawadiya SK, Niraj A, Pradhan J, Ference B, Burack RC, et al. Homocysteine and reclassification of cardiovascular disease risk. J Am Coll Cardiol. 2011;58:1025–33. doi: 10.1016/j.jacc.2011.05.028.

5. Mangge H, Becker K, Fuchs D, Gostner JM. Antioxidants, inflammation and cardiovascular disease. World J Cardiol. 2014;6(6):462–77. doi: 10.4330/wjc.v6.i6.462.