A review on association of serum homocysteine in diabetic neuropathy

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INTRODUCTION

Diabetes is a disease in which blood glucose or blood sugar levels are too high. Diabetic neuropathy is a type of nerve damage that can occur with diabetes. Symptoms such as pain, tingling, or numbness in the hands, arms, feet, and legs were noted in diabetic neuropathy patients. Roughly, 50% patients with diabetes suffer from diabetic neuropathy. Homocysteine is a non-protein forming sulfur amino acid. Homocysteine is a common amino acid in blood. Homocysteine is biosynthesized from methionine. Homocysteine levels are typically higher in men than women and increase with age. Elevated homocysteine levels can cause increased inflammation, irritation of the blood vessels, heart disease, neurological troubles, etc. Homocysteine levels are checked through blood tests. Homocysteine is a sensitive biomarker for both folate deficiency and cardiovascular disease. Hyperhomocysteinemia was an independent risk factor for the occurrence of diabetic neuropathy.

STRUCTURE OF HOMOCYSTEINE[6]

Chemical formula: C₄H₉NO₂S

Reference range:
The reference range of plasma homocysteine may vary with the technique used. Reference values by age are as follows:[7]

ABSTRACT

Diabetes is a disease in which blood glucose or blood sugar levels are too high. Diabetic neuropathy is a type of nerve damage that can occur with diabetes. Symptoms such as pain, tingling, or numbness in the hands, arms, feet, and legs. Roughly, 50% patients with diabetes suffer from diabetic neuropathy.[4] Homocysteine is a common amino acid in blood. Homocysteine receives another methyl group from either folic acid or Vitamin B-6 to regenerate methionine. Homocysteine levels are typically higher in men than women, and increase with age. Elevated homocysteine levels can cause increased inflammation, irritation of the blood vessels, heart disease, neurological troubles, etc. Homocysteine levels are checked through blood tests. Homocysteine is a sensitive biomarker for both folate deficiency and cardiovascular disease. Hyperhomocysteinemia was an independent risk factor for the occurrence of diabetic neuropathy.

Keywords: Diabetes, Diabetic neuropathy, Homocysteine, Hyperhomocysteinemia, Methionine

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• 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-h urine collection) varies with the technique used from 0 to 9 µmol/g creatinine.

Homocysteine levels are checked through blood tests. A normal homocysteine level is between 4.4 and 10.8 µmol per liter of blood. Abnormally high levels of homocysteine in the serum, above 15 µmol/L, are a medical condition called hyperhomocysteinemia.\(^8\) Plasma homocysteine levels are elevated in Vitamin B-12 deficiency, Vitamin B-6 deficiency, and in folic acid deficiency.\(^9\)

Elevation in plasma homocysteine is common in the general population, especially in the aged. A high level of homocysteine in the blood (hyperhomocysteinemia) makes a person more prone to endothelial cell injury, which leads to inflammation in the blood vessels, which in turn may lead to atherogenesis, which can result in ischemic injury. Elevation in plasma homocysteine is common in the general population, particularly in the elderly.\(^10\) Elevated levels of homocysteine in the blood appear to increase the risk of heart attack, stroke, peripheral vascular disease, and venous thromboembolism (blood clots in the veins).\(^11\)

Individuals with elevated levels of homocysteine have increased risk of cardiovascular disease (CVD) and arteriosclerosis.\(^12\) High level of homocysteine is also responsible for CVD in adolescents.\(^13\) High serum homocysteine (sr.hcy) developing vascular changes, especially in diabetes.\(^14\)

**METABOLISM OF HOMOCYSTEINE**

Homocysteine is a non-protein forming sulfur amino acid whose metabolism is at the intersection of two metabolic pathways: Remethylation and transsulfuration.\(^15\)

Figure 1 represents metabolism of homocysteine.\(^16\)

Homocysteine is not obtained from the diet. Instead, it is biosynthesized from methionine through a multistep process. Methionine is activated by ATP to S-adenosylmethionine (SAM), which serves a universal donor for methyl transfer reactions. S-adenosylhomocysteine (SAH) is produced as a product of methyl transfer reactions that utilize SAM as a methyl donor. L-Homocysteine is formed from the reversible hydrolysis of SAH. Levels of homocysteine are regulated by remethylation of homocysteine to methionine by the enzyme methionine synthase and transsulfuration of homocysteine to cystathionine by the enzyme cystathionine b-synthase.

Homocysteine remethylation requires Vitamin B-12 and 5,10-methyltetrahydrofolate, which is generated by 5,10-methylenetetrahydrofolate reductase (MTHFR). Homocysteine transsulfuration requires Vitamin B-6. In the liver and kidney, some homocysteine is remethylated to methionine through an alternative pathway catalyzed by betaine–homocysteine methyltransferase.\(^17\)

**Relation between Homocysteine and Diabetic neuropathy**

For the diabetic patients, serum levels of fasting blood sugar, post-prandial blood sugar, glycated hemoglobin (HbA1c), and associated blood parameters will be assessed.\(^18\) Dyslipidemia in DM poses a major threat of myocardial risk and heart attacks. As HbA1c is monitored every 3 months, we recommend the monitoring of lipid profile test also every 3 months. Regular monitoring of lipid profile is an important way to prevent silent heart attacks.\(^19\) Diabetic neuropathy will be confirmed using nerve conduction testing, electromyography, and quantitative sensory testing with clinically correlated. The sr.hcy levels will be quantified and correlated with other blood parameters. Monitoring sr.hcy concentration, as well as folate and Vitamin B-12 status in T2DM patients, could be used as an indicator for assessing microvascular risk in DM.\(^20\) Higher homocysteine levels are found in diabetics who have developed micro-/macro-vascular complications, and it is highly correlated with HbA1c and serum TG which are also indicators of poor diabetic control.\(^21\) sr.hcy independently can be used as predictive for cardiovascular risk events in T2DM patients.\(^22\) The data indicate that homocysteine is independently associated with the prevalence of diabetic neuropathy in a collective of type 2 diabetic patients. A larger, prospective study would be desirable to elucidate the function of homocysteine in the pathogenesis of diabetic neuropathy.\(^23\)

Elevated plasma homocysteine levels in type 2 diabetes are associated with a higher prevalence of
macroangiopathy and nephropathy.[24] Homocysteine is involved in the development of diabetic neuropathy in type 2 diabetic patients, and hyperhomocysteinemia is very potential to be associated with diabetic neuropathy.[25] Researchers conclude that homocysteine is up to 40 times more predictive than cholesterol in assessing CVD. Homocysteine is a sensitive biomarker for both flat deficiency and CVD.[26] Many studies concluded that the risk of atherosclerosis increases with the homocysteine level, regardless of whether cholesterol is normal or elevated.

In this study, plasma homocysteine and related factors influencing fasting homocysteine levels (Vitamin B-6, B-12, folate, and MTHFR polymorphism) were evaluated with regard to the prevalence of diabetic neuropathy. T2DM and metformin both can lower serum B12. Raised sr. hcy is considered as an early marker of B12 deficiency.[27]

**CONCLUSION**

Hyperhomocysteinemia was an independent risk factor for the occurrence of diabetic neuropathy. Treatment of existing hyperhomocysteinemia with folic acid and Vitamin B-12 may be useful in reducing the risk of microvascular complications in T2DM.

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**REFERENCES**


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