For over 30 years, there has been a belief that hyperhomocysteinemia plays a role in atherothrombosis. However, not until recently has epidemiological evidence (over 100 case-control, cross-sectional, and prospective studies) shown an association between homocysteine levels and vascular disease. Regarding stroke risk, the evidence is still emerging. Trends for an association of the highest quartile of homocysteine and stroke have been seen in the Framingham Study as well as British Regional Heart Study. In the Northern Manhattan Study, elevation greater than 15 mg/dl was associated strongly with vascular death, combined vascular outcomes, and with ischemic stroke in a tri-ethnic population. The link between moderate homocysteine elevations (10-15 mol/l) and ischemic stroke were less dramatic than for vascular disease, the leap from association to causality has been difficult. Evidence from genetic conditions known to elevate hyperhomocysteinemia plays a role in atherothrombosis. Recognizing the preponderance of evidence from many epidemiologic, basic scientific, and genetic studies suggests that homocysteine is moderately associated with cardiovascular disease in those with genetic causes of marked hyperhomocysteinemia. Surrogate markers such as carotid plaque likewise show regression with homocysteine-lowering therapy. However, in a recent large international randomized trial among stroke survivors with moderate homocysteinemia, multivitamin therapy showed no reduction in the risk of stroke recurrence. Ongoing trials such as VITATOPS may help address the question regarding the benefits of homocysteine-lowering therapies.

For now, the preponderance of evidence from many epidemiologic, basic scientific, and genetic studies suggests that homocysteine is moderately associated with cardiovascular disease (stroke included). Given the safety and low cost of multivitamin therapy, recommendations suggest starting B₁₂, folate, and B₉ in those with elevated homocysteine and cardiovascular disease. Whether reducing homocysteine will translate into a reduction in vascular or stroke risk is still an area of uncertainty.

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References


Invited Comments

This study shows that hyperhomocysteinaemia is associated with an increased risk of stroke in the world. Elevated homocysteine is a risk factor for stroke both in the young[1] and in the elderly,[2] as well as for recurrent stroke.[3] Numerous studies have shown that supplementation with folate, vitamin B6, and B12 reduces the level of homocysteine. Intervention studies have so far been disappointing in being unable to show a reduced risk of stroke and cardiovascular events in vitamin B-treated groups,[4,5] however, the results of many ongoing randomized trials are awaited with great expectations.[6] In the meantime, however, it is tempting to recommend vitamin supplementation for patients with highly elevated homocysteine levels.

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