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Hyperhomocystenemia: Current status

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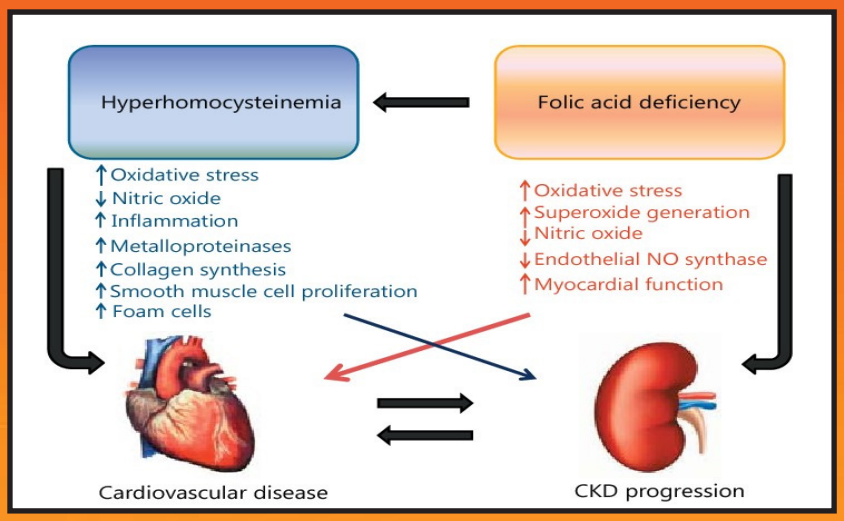
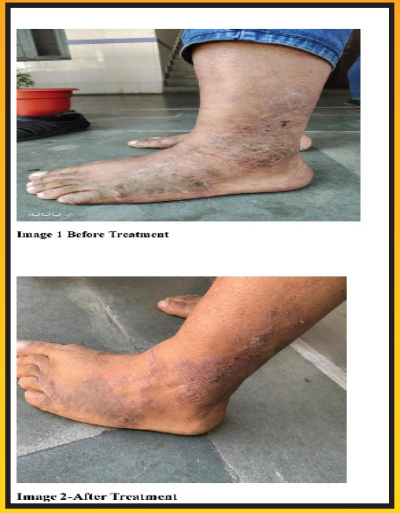


Efficacy of Virechana Karma in Vicharchika - Case Study



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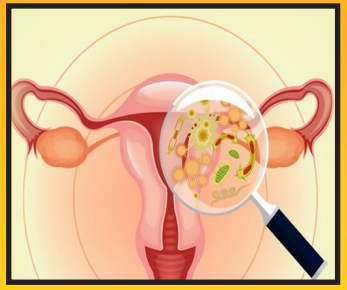
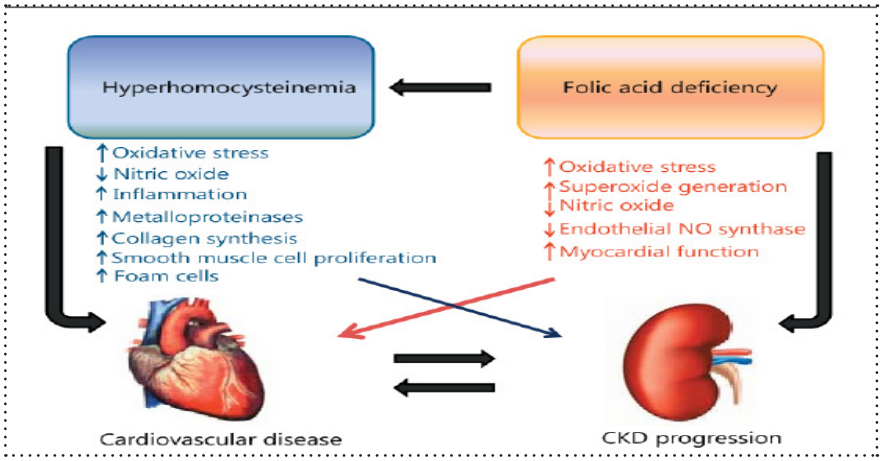


Role of Probiotics in Treatment Among Women with Symptomatic White Discharge

GENERAL

Hyperhomocystenemia: Current status

SANJAY AGRAWAL



INTRODUCTION

Homocysteine (Hcy) is a sulphur-containing amino acid produced during the metabolism of methionine. Homocysteine is metabolized through two vitamin-dependent pathways viz. remethylation (requiring folate and vitamin B12), which converts homocysteine back to methionine, and transsulfuration (pathway requiring vitamin B12), which converts homocysteine to cysteine and taurine and a second remethylation pathway in the liver and kidney utilizes betaine instead of folate (folate independent) (Ref.1)

Hyperhomocystenemia refers to the condition where there is greater than 15 micromole/L of homocysteine in the blood. Normal total Hcy levels range between 5 and 15 µmol/l , with elevations of 16 to 30 mmol/l, 31 to 100 mmol/l, and >100 mmol/l classified as mild, moderate, and severe hyperhomocystenemia, respectively. Several genetic defects (Genetic enzyme polymorphisms MTHFR, methionine synthase, cystathionine β synthase), nutritional deficiencies (dietary deficiency of folic acid, vitamin B12, vitamin B6, methionine), lifestyle factors(chronic alcohol intake, smoking, high coffee intake)and other aetiologies can cause elevations in homocysteine levels (renal failure, diabetes, systemic lupus erythematosus, hyperproliferative disorders, medications (methotrexate, sulphonamides, antacids).

Elevated levels of homocysteine have been associated with increased cardiovascular, cerebrovascular, and thromboembolic diseases. (Ref.2). There is also an increased risk for osteoporosis, schizophrenia, and brain atrophy in specific populations with hyperhomocystenemia (Ref.3). Elevated levels of homocysteine can increase the risk of atherosclerosis by causing endothelial injury, promoting inflammation, and increasing oxidative stress (Ref.4). However, the exact mechanism is still unknown, and more research needs to be done to identify the pathophysiology.

While there are clear associations between homocysteine and cerebrovascular disease, the evaluation and treatment remain controversial as studies have shown conflicting results in its effect in lowering risks for cardiovascular and cerebrovascular disease.

HOMOCYSTEINE: AN INDEPENDENT RISK FACTOR

Many investigators have proposed that homocysteine should be considered a risk factor for CVD and CAD, since only 50% of these diseases can be explained by the classical Framingham Risk Factors (FRFs- dyslipidaemia, hypertension, DM, and smoking), and they suggest that additional risk factors should be added to FRFs to boost their predictive value (Ref.5). In this regard, Vereenna et al (Ref.6) prospectively validated the incremental value of homocysteine level in predicting adverse CV events beyond the FRFs, and stated that homocysteine fulfils the criteria to be considered a novel marker for CAD and be added to FRFs.

A number of retrospective (case-control and observational) and prospective studies carried out over the past three decades indicate that homocysteine is a graded, independent risk factor for myocardial infarction, stroke, and venous thromboembolism. (Ref.7).

Like LDL-C and C-reactive protein, homocysteine should be considered as a graded risk factor for cardiovascular disease. (Ref.8). A meta-analysis found that for every 2.5 mmol/L increase in plasma total homocysteine, the risk of myocardial infarction increases by about 10% and the risk of stroke increases by about 20%. (Ref.9).

It has not been established whether homocysteine is a consequence, a cause, or a marker of cardiovascular

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disease. Evidence that elevated homocysteine may be a consequence of vascular disease is that the relative risk associated with mild homocysteine elevation has tended to be higher in retrospective studies (in which homocysteine was measured after a vascular event) than in prospective studies (in which it was measured before an event). However, when analysis is limited to prospective data and adjusted for other risk factors, hyperhomocystenemia still emerges as a modest but significant risk factor for cardiovascular events. Elevated total homocysteine is also a strong predictor of mortality in patients with pre-existing cardiovascular disease or other risk factors.

HOMOCYSTEINE-LOWERING THERAPY

Homocysteine-lowering therapy is life-saving for patients with severe hyperhomocysteinemia due to autosomal-recessive deficiency of cystathionine beta-synthase. Approximately 50% of patients respond to treatment with vitamin B6 in pharmacological doses. Its adjunctive therapy may include methionine restriction, cysteine supplementation, betaine, vitamin B12 and folic acid. (Ref.10).

In individuals with mild or moderate hyperhomocysteinemia, B vitamins are highly effective in lowering homocysteine. A meta-analysis of 12 randomized trials found that treatment with folic acid 0.5 to 5 mg/day decreased homocysteine levels by 25%, and that the addition of vitamin B12 0.5 mg/day decreased homocysteine by another 7%. (Ref.11).

HOMOCYSTEINE LOWERING FOR PRIMARY PREVENTION

Several prospective case control, randomized, placebo-controlled trials, reviews and meta-analyses of prospective, randomized control trials (RCTs) have demonstrated an association of hyperhomocystenemia with an increased incidence of CAD and stroke and that treatment with homocysteine lowering vitamins (folic acid ± B vitamins) reduces CV events and mortality (Ref.12).

HOMOCYSTEINE LOWERING FOR SECONDARY PREVENTION

Park et al (Ref.13) analysed the secondary protective effects of folic acid plus B vitamins on CAD and stroke prevention in three RCTs including 4643 high-risk patients. The Vitamin Intervention for Stroke Prevention (VISP) trial assessed the preventive effects of homocysteine lowering with folic acid plus B6 and B12 vitamins against stroke in 1773 individuals after 2 years of follow-up. The VITAmins TO Prevent Stroke (VITATORS) trial assessed the preventive effects of folic acid plus B vitamins on the incidence of stroke, myocardial infarction (MI), or vascular death in 1,463 patients with a recent stroke or transient ischemic attack (TIA) after 3 years of follow up compared to placebo. The HOPE-2 trial, evaluated whether folic acid, B6, and B12 vitamins reduced the risk of death from CV causes, MI, or stroke among 1407 patients with pre-existing CAD, cerebrovascular disease, or peripheral vascular disease. In all the three studies, the treated group had lower incidence of recurrent stroke than the control group, HR 0.86 (95% CI 0.62–1.19) for VISP, HR 0.65 (95% CI 0.46–0.91) for VITATORS, and HR 0.60 (95% CI 0.39–0.92) for HOPE-2 trial, with an overall risk reduction of 29%.

In another meta-analysis of 11 RCTs involving 65,790 patients with CAD (age 50–69 years), Tan et al (Ref. 14) examined the effects of folic acid ± B vitamin supplementation on stroke prevention. After a follow-up ranging from 1 to 7 years, the incidence of stroke was significantly reduced in patients with pre-existing CAD, RR 0.90 (95% CI 0.84–0.97, p = 0.005), and lowering of homocysteine levels by 25% or more produced greater reduction.

In contrast to the above mentioned studies, other similar studies have found no such association of treatment of homocysteine with the incidence of CAD and stroke. In a RCT of 12,064 survivors of MI, effects of homocysteine reduction with folic acid plus B vitamins on vascular and nonvascular outcomes was studied. Treatment with folic acid 2 mg/day +B12 1 mg/day resulted in 3.8 µmol (28%) reduction of homocysteine compared to placebo, but resulted in no significant difference in vascular events (25.5%) compared to (24.8%) for placebo after 6.7 years of follow-up.(Ref.15).

The Norwegian Vitamin Trial and the Western Norway B Vitamin Intervention Trial involving 6,837 subjects reported that Folic acid plus vitamin B12 supplementation lowered the homocysteine levels by 25%, but did not affect the MACE incidence or the CV mortality during a follow-up of 3.3 years. In a meta-analysis of 24 RCTs involving 57,952 patients (age: 48–69), Zhang et al (Ref.16) observed that supplementation with folic acid + B vitamin had no effect on MACE, total mortality, CV mortality, MI or stroke, after a mean follow-up of 3.2 years.

CONCLUSION

At present, there is no consensus regarding the association of homocysteine with the incidence of CAD and stoke, or whether this association is casual (Ref.17). However, some studies have shown an association of homocysteine with atherosclerosis and CAD and others have shown a benefit of treatment of hyperhomocystenemia with folic acid ± B vitamins on primary and secondary prevention of CAD and stroke. While other studies have shown no benefit of treatment of hyperhomocystenemia on the secondary prevention of CAD, except a modest 10% reduction in risk of stroke.

The American Heart Association (AHA) (Ref.18) and a European expert panel (Ref. 19) advise against general screening for hyperhomocystenemia. The US Preventive Services Task Force has also concluded that evidence is insufficient to recommend vitamin supplements to prevent cardiovascular disease (Ref.20).

At present, routine screening of all patients for elevated homocysteine is not yet recommended. However, screening and treatment with homocysteine lowering vitamins may be advisable for individuals with athero-thrombotic disease that is out of proportion to their traditional risk factors or who have a family history of premature atherosclerotic disease. Homocysteine-lowering therapy may prove to have a modest clinical benefit. Treating with either folic acid 0.4–5.0 mg/day or vitamin B12 0.5–1.0 mg/day or both is safe and cost effective for preventing cardiovascular events in high risk patients.

REFERENCES

1. Kaul S, Zadeh AA, Shah PK. JACC 2006;48:914-23.
2. Lee M, Hong KS, Chang SC, Saver JL. Stroke. 2010 Jun;41(6):1205-12.
3. Smith AD, Smith SM, de Jager CA et al. PLoS One. 2010 Sep 08;5(9):e12244.
4. Park WC, Chang JH. Vasc Specialist Int. 2014 Dec;30(4):113-9.
5. Faeh D, Chiolero A, Pascaud F. Swiss Med Wkly. 2006;136:745–756.
6. Vereenna V, Zalawadiya SK, Niraj A, et al. J Am Coll Cardiol. 2011;58:1025–1033.
7. den Heijer M, Keijzer MB. Clin Chem Lab Med 2001; 39:710–713.
8. Wald DS, Law M, Morris JK. BMJ 2002; 325:1202.
9. Homocysteine Studies Collaboration. JAMA 2002;288:2015–2022.
10. Yap S, Boers GH, Wilcken B, et al. Arterioscler Thromb Vasc Biol 2001; 21:2080–2085.
11. Homocysteine Lowering Trialists' Collaboration. BMJ 1998; 316:894–898.
12. Huang T, Chen Y, Yang B, et al.. Clin Nutr. 2012;31:448–454.
13. Park JH, Saposnik G, Ovbiagele B, et al.. Int J Stroke. 2016; 11: 206–211.
14. Tan T, Yang KQ, Cui JG, et al. Am J Med Sci.2017;354:379–387.
15. Armitage JM, Bowman L, Clarke RJ, et al. JAMA. 2010;303:2486–2494.
16. Zhang C, Wang ZY, Qin YY, et al.. PLos-One. 2014;9:e107060.
17. Christen WG, Ajani UA, Glynn RJ, et al.. Arch Intern Med. 2000;160:422–434.
18. Malinow MR, Bostom AG, Krauss RM., American Heart Association. Circulation 1999;99:178–182.
19. Refsum H, Smith AD, Ueland PM, et al.. Clin Chem 2004; 50:3–32.
20. Morris CD, Carson S. Ann Intern Med 2003; 139:56–70.

Blue zone diet :

Blue zones are locations with the highest number of centenarians – Lome Linda, California, Nicoya peninsula, Costa Rica, Sardinia, Italy, Ikaria, Greece and Okinawa, Japan. The diet pattern of these people is known as the Blue Zone diet. It comprises locally produced vegetables, legumes, handful of nuts and home cooked fresh food. The diet avoids artificial sweeteners, preservatives. It is low in meet, sugar and dairy products. It advocates avoidance of processed foods and low alcohol.

The body is a cell state in which every cell is a citizen. Disease is merely the conflict of the citizens of the state brought about by action of external forces.

--------**Rudolf Virchow**