Medical Science

The International Weekly journal
ISSN 2321 – 7359 EISSN 2321 – 7367

PERSPECTIVE

Coffee intake on homocysteine and CVD: review article

Janaki S

Department of Homescience, Women's Christian College, Chennai – 6, India; Email: janakisk82@yahoo.com

Publication History
Received: 24 December 2014
Accepted: 19 January 2015
Published: 21 January 2015

Citation
Janaki S. Coffee intake on homocysteine and CVD: review article. *Medical Science*, 2015, 16(65), 24-28

Cardiovascular disease (CVD) can roughly be classified into three categories: Coronary heart disease (CHD), Cerebrovascular accidents (CVA) and other vascular diseases. In CHD, the coronary arteries that supply blood to the heart are blocked and in CVA, the arteries that supply blood to the brains are obstructed. The category "Other vascular diseases" comprises occlusions of peripheral arteries or veins and congenital, infectious and rheumatoid heart diseases. Of all vascular diseases, CHD is the most prevalent one (Netherlands Heart Foundation, 2001).A high blood pressure, an unfavorable lipid profile and smoking, explain the majority of all coronary heart disease cases. However, the search for other risk factors remains. One factor that has been associated with coronary heart disease is an elevated plasma homocysteine concentration. A causal role of moderately elevated concentrations of circulating total homocysteine (tHcy) in the pathogenesis of cardiovascular disease was proposed 30yrs ago. Since then, the results of many clinical and epidemiological studies have shown that total homocysteine measured in serum or plasma us a strong predictor of cardiovascular disease risk (Hankey and Eikelboom, 1999).

Homocysteine metabolism

Homocysteine is a sulfur-containing amino acid that is not used for the synthesis of proteins. Foods only contain traces of homocysteine. Homocysteine is formed when cells metabolize the essential amino acid methionine. The intracellular homocysteine concentration is precisely regulated and any excess is transported to plasma. In plasma, approximately 99% is oxidized to disulfides. The vast majority of homocysteine is bound to proteins. Nonprotein bound homocysteine consists of homocysteine (the disulfide of homocysteine) and mixed disulfides of homocysteine with e.g., cysteine. Only about 1% of all homocysteine moieties are reduced "free" homocysteine. The term total plasma homocysteine refers to all these forms of homocysteine in plasma (Mudd et al., 2000). Intracellular homocysteine can be irreversibly degraded to cysteine through the transsulfuration pathway, which is mainly limited to cells of the liver and kidneys. The enzymes in this pathway, cystathionine beta-synthase (CBS) and ♈-cystathionase, are both dependent on pyridoxal-5-phosphate, a biologically active form of vitamin B6, as cofactor.

Homocysteine can also be remethylated to methionine by the enzyme methionine synthase (MS). This enzyme uses methylcobalamin (active form of vitamin B12) as cofactor. The methyl group for the latter reaction is donated by 5-methyltetrahydrofolate (5-methyl-THF). This form of folate is produced by the enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR). This in turn uses flavin adenine dinucleotide (biologically active form of vitamin B2) as cofactor (Guenther et al., 1999). In an alternative remethylation route, which is also mainly restricted to the liver and kidney, betaine is used as the methyl donor by the enzyme betaine-homocysteine methyltransferase (Finkelstein, 1990).

www.discovery.org.in
© 2015 Discovery Publication. All Rights Reserved

Determinants of homocysteine concentration

Age and gender

Increasing age and male gender is associated with a higher total homocysteine concentration (LussierCacan et al., 1996 and De Bree et al., 2001). Giltay et al., (1998) confirmed in a study with transsexual males and females that sex hormones have an influence on plasma homocysteine concentration. Higher plasma homocysteine concentration in post-menopausal women was reported by Wouters et al., (1995) compared with premenopausal women.

Supplemental and dietary B vitamin intake

Several intervention studies have provided evidence for the importance of B vitamins in homocysteine metabolism. Especially supplements with folic acid (synthesis form of folate) and combinations of folic acid, vitamin B2, B6 and B12 effectively reduced the total homocysteine concentration in subjects with normal and elevated baseline levels (Wald et al., 2001). According to Clarke and Armitage (2000) a meta-analyses of 12 randomized trials showed that folic acid supplementation reduced total homocysteine concentrations by 25% with similar effects in a daily dosage of 500 to 5000 µg. Vitamin B12 in an average dose of 500 µg produced an additional reduction in total homocysteine of 7%. Vitamin B6 did not appear to hava a significant effect (Bostom et al., 1995).

Lifestyle factors

1. Coffee

Coffee consumption is positively associated with the total homocysteine concentration in both men and women in most (Nygard et al., 1997 and Koehler et al., 2001), but not all (Rasmussen et al., 2000 and Saw et al., 2001) observational studies. Recent intervention trials shown that this effect of coffee iscausal (Urgert et al., 2000 and Christensen et al., 2001). Caffeine might be the factor that elevates the total homocysteine concentration (Grubben et al.,2000 and Jacques et al., 2001) because it may inhib the conversion of homocysteine to cysteine by acting as a vitamin B6 antagonist (Grubben et al., 2000). Olthof et al., (2001) showed that cholorogenic acid, a polyphenol that is present in coffee in the same amount as caffeine, might also partly be responsible for the increase in the total homocysteine concentration. Regular ingestion of black tea did not alter mean total homocysteine concentrations (Hodgson et al., 2003).

2. Smoking

Smoking is positively associated with the total homocysteine concentration (Giles et al., 1999; Jacques et al., 2001 and Koehler et al., 2001). Smokers generally consume a less healthy diet (Dallongeville et al., 1998). In a study by Saw et al (2001) the effect of smoking disappeared after correction for plasma folate. Cigarette smoke influences the total homocysteine concentration by changing the plasma thiol redox status (Mansoor et al., 1995 and Bergmark et al., 1997) or inhibit enzymes such as methionine synthase (Blom, 1998).

3. Alcohol

Alcohol consumption is probably associated with the total homocysteine concentration in a J-shaped fashion (Halsted, 2001). Alcoholics have elevated total homocysteine concentrations (Cravo et al., 1996). A 3-week randomized crossover trial done by Gaag et al (2000) showed no association with the total homocysteine concentration after intervention with four glasses of beer per day, compared with an elevation of the total homocysteine concentration with four glasses of wine or spirits per day.

4. Physical activity

Physical activity is probably not or weakly inversely associated with the total homocysteine concentration (Gudnason et al., 1998 and Saw et al., 2001).

5. Genetics

The 677C>T polymorphism in the gene that encodes MTHFR (methylene tetrhydrofolate reductase) has been investigated most extensively in relation to its effect on the total homocysteine concentration (Brattstrom et al., 1998). The 677C>T mutation results in a reduced specific MTHFR activity in isolated lymphocytes (Van der Put et al., 1996), which leads to higher total homocysteine concentrations (Frosst et al., 1995).

Drugs

1. Hormones

More recent evidence indicated no difference in the total homocysteine concentration between pill users and non-pill users (Green et al., 1998 and Morris et al., 2000). Postmenopausal hormone replacement therapy with estrogen-like hormones decreases the total homocysteine concentration (Blom, 2001). Tamoxifen, an antiestrogen used to treat women with breast cancer, reduces the total homocysteine concentration (Anker et al., 1995 and Cattaneo et al., 1998).

2. Antiepileptic drugs

Although there are not many human studies on the effects of antileptic drugs on the total homocysteine concentration, drugs like phenobarbital, carbamazepine, primidone and valproate may interfere with the remethylation of homocysteine (Schwaninger et al., 1999).

© 2015 Discovery Publication. All Rights Reserved

3. Methotrexate

Antifolates like methotrexate deplete cells of reduced folates (Refsum and Ueland, 1990). Other antifolates like sulfasalazine, raltritrexed, trimetrexate and trimethoprim will most likely have a similar effect on the total homocysteine concentration (Haagsma et al., 1999).

4. Nitrous oxide

Plasma total homocysteine concentrations increased rapidly in patients given nitrous oxide as an anesthetic (Ermens et al., 1991).

5. Other drugs

Lipid lowering drugs like statins, niacin, cholestyramine and fibrates may besides their effect on blood lipids, have an elevating effect on the total homocysteine concentration (Basu and Mann, 1997). Administration of vitamin B6 antagonist drugs increases total homocysteine concentration. Metformin, a drug used in diabetes and theophylline, used to treat asthmatic patients, are examples of vitamin B6 antagonist (Ubbink et al., 1996). Other drugs that may also act as B6 antagonists are isoniazid, cycloserine, hydralazine, phenelzine and procarbazine (Blom, 2001).

Diseases

1. Kidney dysfunction

The most frequent clinical cause of hyperhomocysteinemia next to nutritional deficiencies in folate and vitamin B12 is renal failure. The kidney may influence or regulate homocysteine metabolism in other tissues and it may convert a major amount of the homocysteine present in blood (Blom, 2001).

2. Proliferating diseases

Disease like cancer and psoriasis are associated with higher total homocysteine concentrations (Refsum and Ueland, 1990).

3. Rheumatoid arthritis

Hyperhomocysteinemia is commonly observed in rheumatoid arthritis and not necessarily dependent on methotrexate use (Schneede et al., 2000).

4. Endocrine disorders

Type 1 diabetes is accompanied by higher total homocysteine concentrations only at advanced stages of the disease (Schneede et al., 2000). Compared with apparently healthy subjects, type 1 and type 2 diabetic subjects had lower total homocysteine concentrations, possible due to hyperfiltration (Wollesen et al., 1999). Concentrations of total homocysteine were higher in hypothyroidism and lower in hyperthyroidism (Nedrebo et al., 1998 and Diekman et al., 2001).

5. Intestinal diseases

Several GI disorders may lead to a deficiency of folate or vitamin B12 or both, which in turn will result in higher total homocysteine concentrations (Schneede et al., 2000).

Role of coffee as beverage

Coffee is an infusion made from the roasted bean of “Coffee Arabica”, “Coffee Robusta” or “CoffeLiberica”. It is taken chiefly for the stimulating effect of its alkaloid, caffeine and also because of its pleasant aromatic flavors which comes from its volatile oil “Caffeol”. The caffeine of coffee is in loose chemical combination with some other substances, probably as caffetinic acid. It has been noted that the stimulation derived from a cup of coffee is slower in reaching its maximum and lasts longert than other caffeine beverages (Mc Lester & Darby, 1950). The manner in which coffee is made determines largely its flavour, strength, whether by boiling, steeping, percolation or filtration. The making of good coffee is an art (Hogan et al., 2002).

Source and amount of caffeine

As a food additive, caffeine is used in various foods for its flavor contribution. The amount of caffeine in food products varies depending on the serving size, type of products and preparation method. The plant variety also affects caffeine content of tea and coffee (Hogan et al., 2002). The caffeine content of a cup of coffee (150ml) is about 100mg (Manay, 2000). Moderate caffeine consumption is generally considered to be about 300mg, which is equivalent to approximately 3cups of coffee (Hogan et al., 2002). Table 2 gives caffeine content of some beverages.

© 2015 Discovery Publication. All Rights Reserved

Table 2
Caffeine content of beverages

Beverages or Confectionery	Caffeine mg
Cocoa 50g	13 +/- 4
Milk chocolate 50g	2 – 30
Dark chocolate 50g	10 – 60
Coffee 150ml	40 – 180
Tea 150ml	20 – 90
Cola 150ml	18

Source: USDA nutrient Database for standard reference (1998)

Physiological effects of caffeine

Caffeine, the most widely ingested methylxanthine, is readily absorbed by the gut and does not accumulate in the body because it is rapidly metabolized by the liver and eliminated. It has an average half-life of approximately four hours, although individual metabolism rates vary between two and ten hours (Gray, 1998). Caffeine raises slightly the blood pressure, slows and strengthens the heart, stimulates renal activity and prevents fatigue and depression. The most noticeable effect of tea and coffee is a mild cerebral stimulation; they clearaway the "cobwebs". It is doubtful; however, if in the long run, the mental labor ultimately accomplished can be increased by coffee or tea (Hogan et al., 2002). The comfort and cheer obtained from a cup of coffee or tea cannot be attributed solely to its caffeine. Coffee contains certain aromatic oils, which are pleasing to the taste and mildly stimulating to the stomach. By retarding slightly, the emptying of the stomach, it also increases the satiety value of the meal. Taken hot these beverages stimulate gastrointestinal motility and when taken cold in hot weather is refreshing (Hogan et al., 2002).

Coffee and heart disease

In studies of the effects of caffeine on the cardiovascular system, no association has been found. Boiled unfiltered coffee has been associated with increased homocysteine concentration and elevated blood cholesterol levels (Grubben et al., 2000). Lewis et al (1993) found no unfavorable effect of caffeine and coffee on serum lipids. In a research conducted by De Roos et al (2001), the coffee diterpenecafestol increases plasma triacylglycerol by increasing the production rate of large VLDL apolipoprotein B in healthy normolipidemic subjects. Rooji (1995) studied the role of diterpenes in the rise of serum cholesterol and alanine aminotransferase after consumption of boiled coffee.Ranhein (1995) concluded that cafestol promotes an enhanced rate of uptake and degradation of LDL. A meta-analysis of randomized clinical trials showed a dose response relation between coffee consumption and both total cholesterol and LDL cholesterol (Ha Jee et al., 2001). Halvorsen et al., (1998) suggested that intake of cafestol may cause increased concentration of plasma cholesterol. According to Rakic et al., (1999) restriction of coffee intake might be beneficial in older hypertensive individuals. Terry et al., (2000) concluded that hypertension risk status should take priority in future research regarding pressor effects of dietary intake of caffeine.

Conclusion

Current epidemiological evidence does not provide strong evidence that elevations in the total homocysteine concentration are harmful in healthy subjects, but lowering total homocysteine concentrations through administration of folic acid and vitamin B6 favorably influenced the progress of atherosclerotic disease in healthy subjects measured with an exercise electrocardiography test. Elevated plasma homocysteine levels are reported to be a positive risk factor in coronary heart disease. Therefore, in nutrition counseling for lifestyle modification and primary prevention in delaying the onset of CHD, the deleterious effect of coffee consumption could be advocated.

REFERENCES

1. Anker G, Lonning PE, Ueland PM, Refsum H and Lien EA. Plasma levels of the atherogenic amino acid homocysteine in post-menopausal women with breast cancer treated with tamoxifen. Int J Cancer, 1995,60: 365-368.
2. Basu TK and Mann S. Vitamin B-6 normalizes the altered sulfur amino acid status of rats fed diets containing pharmacological levels of niacin without reducing niacin's hypolipidemic effects. J Nutr, 1997, 127:117-121.
3. Blom HJ. Diseases and drugs associated with hyperhomocysteinemia, in Homocysteine in Health and Disease (Carmel R and Jacobsen D. W eds) 2001,pp 331- 340, Cambridge University Press, Cambridge, UK.
4. Bostom AG, Jacques PF, Nadeau MR, Williams RR, Ellison RC and Selhub J. Post methionine load hyperhomocysteinemia in persons with normal fasting total plasma homocysteine: initial results from the NHLBI Family Heart Study. Atherosclerosis, 1995, 116: 147-151.
5. BrattstromL, Wilcken DE,Ohrvik J and Brudin L. Common methylenetetrahydrofolate reductase gene mutation leads to hyperhomocysteinemia but not to vascular disease: the result of a metaanalysis. Circulation, 1998, 98: 2520-2526.
6. Cattaneo M, Baglietto L, Zighetti ML, Bettega D, Robertson C, Costa A, Mannucci PM and Decensi A. Tamozifen reduces plasma homocysteine levels in healthy women. Br J Cancer, 1998, 77: 2264-2266.
7. Clarke R and Armitage J.Vitamin supplements and cardiovascular risk: review of the randomized trials of homocysteine-lowering vitamin supplements. SeminThrombHemost, 2000, 26: 341-348.
8. Cravo ML, Gloria LM, Selhub J, Nadeau MR, Camilo ME, Resende MP, Cardoso JN, Leitao CN and Mira FC. Hyperhomocysteinemia in chronic alcoholism: correlation with folate, vitamin B-12 and vitamin B-6 status. Am J Clin Nutr,1996, 63: 220-224.

© 2015 Discovery Publication. All Rights Reserved

9. De Bree A, Verschuren WMM, Blom H, De Graaf-Hess A, Trijbels FJM and Kromhout D. The homocysteine distribution: (mis) judging the burden. J ClinEpidemiol, 2001, 54: 462-469.
10. De Roos, Baukje, Stalenheof, Anton FH, Bedford, Dorothy. The coffee diterpene increases plasma triacylglycerol by increasing the production rate of large VLDL apolipoprotein B in healthy normolipidemic subjects. Am J ClinNutr, 2001, 73: 45-52.
11. Diekman MJ, van der Put NM, Blom HJ, Tijssen JG and Wiersinga WM. Determinants of changes in plasma homocysteine in hyperthyroidism and hypothyroidism. ClinEndocrinol, 2001, 54: 197-204.
12. ErmensAA, Refsum H, Rupreht J, Spijkers LJ, Guttormsen AB, Lindemans J, Ueland PM and Abels J. Monitoring cobalamin inactivation during nitrous oxide anesthesia by determination of homocysteine and folate in plasma and urine. ClinPharmacolTher, 1991, 49: 385-393.
13. Finkelstein JD. Methionine metabolism in mammals. J NutrBiochem, 1990, 1:228-237.
14. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, Den Heijer, M, Kluijtmans LA, Van den Heuvel LP, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet, 1995, 10: 111-113.
15. Gaag MS, Ubbink JB, Sillanaukee P, Nikkari S and Hendriks H. Effects of consumption of red wine, spirits and beer on serum homocysteine. Lancet, 2000, 355: 1522.
16. Giltay EJ, HoogeveenEK, Elbers JM, Gooren LJ, Asscheman H and Stehouwer CD. Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. J ClinEndocrinolMetab, 1998, 83: 550-553.
17. Gray J. Caffeine, coffee and health. Nutrition and Food science, 1998, 6: 314-319.
18. Green TJ, Houghton LA, Donovan U, Gibson RS and Oconnor DL.Oral contraceptives did not affect biochemical folate indexes and homocysteine concentrations in adolescent females. J Am Diet Assoc, 1998, 98: 49-55.
19. Grubben MJ, Boers GH, Blom HJ, Broekhuizen R, de Jong R, van Rijt J, de Ruijter E, Swinkels DW,Nagengast FM and Katan MB. Unfiltered coffee increases plasma homocysteine concentrations in healthy volunteers: a randomized trial. Am J ClinNutr, 2000, 71: 480-484.
20. Gudnason V, Stansbie D, Scott J, Bowron A, Nicaud V and Humphries S. C677T (thermolabile alanine / valine) polymorphism in methylenetetrahydrofolate reductase (MTHFR): its frequency and impact on plasma homocysteine concentration in different European populations. Atherosclerosis, 1998, 136: 347-354.
21. Haagsma CJ, Blom HJ, van Riel PL, vant Hof MA, Giesendorf BA, Openraaij-Emmerzaal, D and van de Putte LB. Influence of sulphasalazine, methotrexate and the combinationof both on plasma homocysteine concentrations in patients with rheumatoid arthritis. Ann Rheum Dis, 1999, 58:79-84.
22. Halsted CH. Lifestyle effects on homocysteine and an alcohol paradox. Am J ClinNutr, 2001, 73: 501-502.
23. Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. Lancet, 1999, 354: 407-13.
24. Hodgson JM, Burke Valerie, Beilin Lawrence J, Croft KD and Puddey IA. Can black tea influence plasma total homocysteine concentrations. Am J ClinNutr, 2003, 77: 907-911.
25. Hogan E, Howard H, Betsy A. Communicating the message: Clarifying controversies about caffeine. Nutrition Today, 2002, 37: 28-35.
26. Koehler KM, Baumgartner RN, Garry PJ, Allen RH, Stabler SP and Rimm EB. Association of folate intake and serum homocysteine in elderly persons according to vitamin supplementation and alcohol use. Am J ClinNutr, 2001, 73: 628-637.
27. Lewis CE,Caan B, Funkhouser E. Inconsistent association of caffeine containing beverages with blood pressure and with lipoproteins, Am J Epidemiol, 1993, 138: 502-507.
28. LussierCacan S, Xhignesse M, Piolot A, Selhub J, Davignon J and Genest J. Plasma total homocysteine in healthy subjects: sex specific relation with biological traits. Am J Clin Nutr, 1996, 64: 587-593.
29. Manay, Shakuntala N, Shadaksharaswamy M. Foods, facts and principles, New age internationals (p) Ltd publications, New Delhi. 2000, Pg. 244-247.
30. McLester and Darby. Nutrition and Diet in Health and Disease, Fifth edition, 1950, pg. 224-225.
31. Morris MS, Jacques PF, Selhub J and Rosenberg IH. Total homocysteine and estrogen status indicators in the Third National Health and Nutrition Examination Survey. Am J Epidemiol, 2000, 152: 140-148.
32. Mudd SH, Finkelstein JD, Refsum H, Ureland PM, Malinow MR, Lentz SR, Jacobsen DW, Brattsrom L,WilckenB, Wilcken DE, et al. Homocysteine and its disulfide derivatives: a suggested consensus terminology. ArteriosclerThrombVascBiol, 2000, 20: 1704-1706.
33. Nedrebo BG, Ericsson UB, Nygard O, Refsum H, Ueland PM, Aakvaag A, Aanderud S and Lien EA. Plasma total homocysteine levels in hyperthyroid and hypothyroid patients. Metabolism, 1998, 47: 89-93.
34. Netherlands Heart Foundation. Cardiovascular diseases in the Netherlands, The Hague, 2001, Netherlands Heart Foundation.
35. Nygard O, Refsum H, Ueland PM, Stensvold I, Nordrehaug JE, Kvale G and Vollset SE. Coffee consumption and plasma total homocysteine: the Hordaland Homocysteine study. Am J ClinNutr, 1997, 65: 136-141.
36. Olthof MR, Hollman PC, Zock PL and Katan MB. Consumption of high doses of chlorogonic acid, present in coffee or of black tea increases plasma total homocysteine concentrations in humans. Am J ClinNutr, 2001, 73:532-538.
37. Rakic Valentina, Burke Valeria, BeilinLawerence J. Effect of coffee on ambulatory blood pressure in older men and women – a randomized controlled trial. Hypertension, 1999, 33: 369-373.
38. Ranheim T, Halvorsen B. Effect of coffee lipid (cafestol) on regulation of lipid metabolism in caco-2 cells. J of Lipid Research, 1995, 36: 2079-2089.
39. Rasmussen LB, Ovesen L, Bulow I, Knudsen N, Laurberg P and Perrild H. Folate intake, lifestyle factors and homocysteine concentrations in younger and older women. Am J ClinNutr, 2000, 72: 1156-1163.
40. Refsum H and Ueland PM. Clinical significance of pharmacological modulation of homocysteine metabolism. Trends Pharmacol Sci, 1990, 11:411-416.
41. Rooij, Van Stegan GH, Cohan AF, Smelt AH. A placebo controlled parallel study of the effect of two types of coffee oil on serum lipids and transaminases: identification of chemical substances involved in the cholesterol raising effect of coffee. Am J ClinNutr, 1995, 61: 1277-1283.
42. Saw SM, Yuan JM, Ong CN, Arakawa K, Lee HP, Coetzee GA and Yu MC. Genetic, dietary and other lifestyle determinants of plasma homocysteine concentrations in middle-aged and older Chinese men and women in Singapore. Am J ClinNutr, 2001, 73: 232-239.
43. Schneede, J., Refsum, H and Ueland, P.M. Biological and environmental determinants of plasma homocysteine. SeminThrombHemost, 2000, 26: 263-279.
44. Schwaninger M, Ringleb P, Winter R, Kohl B, Fiehn W, Rieser PA and Walter-Sack I. Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. Epilepsia, 1999, 40: 345-350.
45. Terry R, Hartley, Whitsett Thomas L, Pincomb Gwendolyn A. Hypertension risk status and effect of caffeine on blood pressure. Hypertension, 2001, 36: 137.
46. Ubbink JB, van der MA, Delport R, Allen RH, Stabler SP, Riezler R and Vermaak WJ. The effect of a subnormal vitamin B-6 status on homocysteine metabolism. J ClinInvestig, 1996, 98: 177-184.
47. Urgert R, van Vliet T, Zock PL and Katan MB. Heavy coffee consumption and plasma homocysteine: a randomized controlled trial in healthy volunteers. Am J ClinNutr, 2000, 72: 1107-1110.
48. Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J and Scott J. Randomized trial of folic acid supplementation and serum homocysteine levels. Arch Intern Med, 2001, 161: 695-700.
49. Wollesen F, Brattsrom L, Refsum H, Ueland PM, Berglund L and Berne C. Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus. Kidney Int, 1999, 55: 1028-1035.
50. Wouters MG, Moorrees MT, van der Mooren MJ, Blom HJ, Boers GH, Schellekens LA, Thomas CM and Eskes TK. Plasma homocysteine and menopausal status. Eur J ClinInvestig, 1995, 25: 801-805.

© 2015 Discovery Publication. All Rights Reserved