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Review

The Association of Homocysteine and Coronary Artery Disease

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Summary: Hyperhomocysteinemia has been associated with increased risk of atherosclerosis and myocardial infarction by a number of prospective case-control studies. A variety of genetic mutations, nutritional deficiencies, disease states, and drugs can elevate homocysteine concentrations. Treatment with folic acid with or without B-complex vitamins effectively lowers homocysteine levels. Whether therapy corresponds with decreased risk of coronary events is unknown, but may be promising. This article reviews the biochemistry of homocysteine metabolism, pathogeneisis, and etiology of hyperhomocysteinemia, along with its association with coronary artery disease, screening, and treatment.

Key words: homocysteine, coronary artery disease

Introduction

In 1969, Dr. Kilmer S. McCully, M.D., examined the relationship of acute vascular thrombotic events by comparing an 8-year-old patient with homocysteinuria who died of a stroke and an infant with an inherited defect in cobalamine metabolism who died of cardiac arrest. After analysis he proposed a novel and controversial theory: elevated homocysteine (Hcy) concentrations result in premature atherosclerosis.[1] The initial reaction to his theory was intense and highly critical.[2] Since the early 1970s, research regarding the association between hyperhomocysteinemia and atherosclerotic vascular disease has grown exponentially. Studies have suggested that elevated Hcy concentrations are associated with an increased rate of stroke, coronary artery disease (CAD), peripheral vascular disease, and deep venous thrombosis.[3–6]

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Biochemistry of Homocysteine

Homocysteine is a sulfur containing nonessential amino acid that is not found in the diet. It exists in a state of flux, constantly interchanging among one of its four forms. Approximately 1% is free, 70–80% is bound to albumin via a disulfide link, and the remaining 20–30% is found either as a Hcy dimer or a cysteine-Hcy-mixed disulfide.[7] The type(s) of species that contributes to the pathologic process is unknown.

Homocysteine metabolism is well defined (Fig. 1). The entry point of the pathway is the transport of dietary methionine derived from protein food sources into the cellular space. Methionine is eventually converted into Hcy, which can enter one of the two major pathways: transsulfuration or remethylation.[8] In the transsulferation pathway, pyridoxine (vitamin B_6) is an essential cofactor, while in the remethylation pathway folate serves as a substrate and cobalamine (vitamin B_{12}) acts as a cofactor (Fig.1).[8]

Etiology of Hyperhomocysteinemia

Disruption in the metabolic pathway causes intracellular accumulation of Hcy that is exported into the plasma before cytotoxic concentrations are reached.[8] Genetic mutations, nutritional deficiencies, disease states, and drugs can alter the metabolic pathway leading to hyperhomocysteinemia. In addition, certain demographic features are associated with elevated Hcy concentrations.[7, 9]

There are four inherited disorders that lead to hyperhomocysteinemia. The most common is the 5-methylenetetrahydrofolate reductase (MTHFR) polymorphism due to a point mutation on chromosome 1.[10, 11] Folate-deficient individuals will develop hyperhomocysteinemia, which may increase the risk for CAD. Cystathionine β-synthase deficiency (homocystinuria), methionine synthase deficiency, and MTHFR enzyme deficiency are rare autosomal recessive disorders that are associated with hyperhomocysteinemia and vascular thrombosis.[8, 10, 12-14]

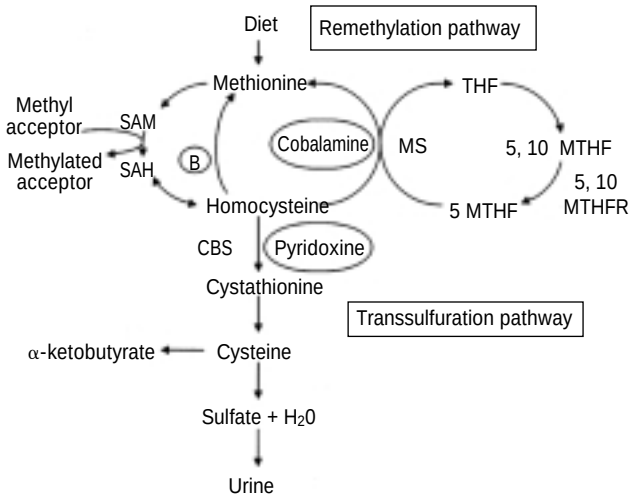

FIG. 1 Metabolism of homocysteine. SAM = S-adenosylmethionine, SAH = S-adenosylhomocysteine, B = betaine, MS = methionine synthase, THF = tetrahydrofolate, MTHF = methyltetrahydrofolate, MTHFR = methylenetetrahydrofolate reductase, CBS = cystathionine β-synthase.

Alteration in folic acid, pyridoxine, and cobalamine concentrations through dietary deficiency or medications can result in hyperhomocysteinemia.[15] Folic acid levels are affected by cholestryamine, which impairs folate absorption, methotrexate, which depletes folate metabolites, and antiepileptics (carbemazepine, phenytoin), which lower folate concentrations.[16–19] Theophylline inhibits pyridoxal kinase, resulting in decreased pyridoxine concentrations.[20] Nitrous oxide alters cobalamine metabolism within 1 h of administration, resulting in increased Hcy concentrations that can remain elevated for longer than 1 week.[21] Fenofibrate, bezafibrate, and colestipol in combination with niacin result in hyperhomocysteinemia by yet to be defined mechanisms.[22, 23] Tobacco and caffeinated coffee are also associated with increased Hcy concentrations.[24, 25]

A number of chronic diseases can produce hyperhomocysteinemia. Chronic renal failure regardless of etiology, duration, or type of dialysis elevates Hcy by an unknown mechanism.[26] Severe psoriasis, possibly through increased cell turnover, results in elevated Hcy despite normal serum folate and cobalamine concentrations.[27] Hypothyroidism, via an unclear mechanism, can raise Hcy by an average of 5.8 umol/l compared with euthyroid controls.[28] In systemic lupus erythematosus, Hcy ≥ 14.1 umol/l is an independent risk factor for arterial thrombosis.[29] Pernicious anemia elevates Hcy by causing cobalamine deficiency.[30]

Both cardiac and renal transplant recipients are at risk for hyperhomocysteinemia. Approximately 54 to 87% of orthotopic heart transplant recipients develop hyperhomocysteinemia, which plateaus at 3 months after transplant.[31, 32] The mechanism has yet to be determined, but may be related to folate deficiency or impairment in renal function.[31, 33] After renal transplantation, as many as 29% of patients will have an increase in Hcy correlating with the degree of renal impairment and folate levels.[34–37] Immunosuppressive medications such as azathioprine, prednisone, and tacrolimas do not appear to affect Hcy in either cardiac or renal transplant patients.[33, 38, 39] Cyclosporin is associated with elevated Hcy in heart transplants, but the data in renal transplants are conflicting.[33–35, 40, 41]

Certain demographic features are associated with elevated Hcy concentrations. For every 20 years of age, Hcy increases on average by 1.3 umol/l.[9] Men average 1 umol/l higher Hcy values than women.[9, 42] Postmenopausal women have higher Hcy values than those who are premenopausal.[42] Approximately 5–7% of the general population and up to 30% of those with CAD are estimated to have hyperhomocysteinemia.[9]

Measurement and Laboratory Evaluation of Hyperhomocysteinemia

There are two major techniques for measuring total homocysteine (tHcy): fasting or methionine loading. Fasting levels are preferred because they are more convenient, less expensive, and because a set of standards exists (Table I).[10] Methionine loading measures the rise in tHcy after the oral administration of methionine after an overnight fast. Any defect in the transulfuration pathway, whether inherited or from pyridoxine deficiency, will result in elevated levels.[7]

Homocysteine values can be falsely elevated with an incomplete fast, improper collection technique, and after a myocardial infarction (MI). The patient must fast for at least 12 h and avoid a large protein meal, since this can cause a 15–20% increase in Hcy.[43] Concentrations will rise by 0.5 umol/l/h at room temperature, so samples should be placed on ice (for a maximum of 2 h) or immediately centrifuged.[7] Three studies have shown that after an MI, tHcy rises by 1.4 to 1.7 umol/l by 6–8 weeks.[44–46] Another study showed a smaller rise from baseline at 28 and 180 days: 0.5 and 0.2 umol/l, respectively.[47] Aspirin, nitroglycerin, beta blockers, and streptokinase do not affect concentrations.[45] Ideally, Hcy should be measured 8–12 weeks after MI.[9]

Pathogenesis

Hyperhomocysteinemia may lead to atherosclerosis by causing endothelial dysfunction, endothelial injury, smooth muscle proliferation, and a decrease in nitrous oxide concentrations.[48–51] In addition, hyperhomocysteinemia creates a pro-

TABLE I Suggested fasting total homocysteine concentrations

Normal	< 10 umol/l
Moderate	10–12 umol/l
Intermediate	12–20 umol/l
Severe	> 20 umol/l

thrombotic environment by altering the coagulation and arachidonic acid pathways. Homocysteine affects the coagulation cascade by increasing factors V and X activity, stimulating factor XII, reducing anti-thrombin III-binding capacity, inactivating protein C and thrombomodulin, and promoting the production of tissue factor from endothelial cells.[52–56] Homocysteine alters arachidonic acid metabolism by stimulating thromboxane A2 production and possibly inhibiting prostacyclin synthesis, which tips the balance toward platelet aggregation.[57, 58]

Association of Hyperhomocysteinemia with Coronary Artery Disease

The first study to support the association between premature CAD and elevated Hcy concentrations was published in 1976.[59] Since then, multiple retrospective and case-control trials were conducted, with the majority supporting the association. In 1992, the first prospective case-control study was published.[4]

Four prospective case-control studies support the association of hyperhomocysteinemia with CAD (Table II).[4, 60–62] All studies compared those with a history of MI (cases) with those without CAD (controls). The mean tHcy between the cases and controls was significant. Multivariate analysis with adjustment for factors such as age, aspirin, tobacco, diabetes, hypertension, cholesterol, angina, and body mass index showed that a statistically significant association existed.[4, 60–62] In the Physicans Health Study, the relative risk (RR) for tHcy in the 95th percentile (tHcy > 15.8 umol/l) was 3.4 (95% confidence interval [CI] 1.3–8.8) compared with the bottom 90%.[4] At 7.5 years of follow-up, the RR for MI decreased to 1.7 (95% CI 0.9–3.3) for unclear reasons.[63] In the Tromso Health Study, the RR for a 4 umol/l increase in tHcy was 1.32 (95% CI 1.05–1.65).[60] In the European Concerted Action Project (ECAP), a fasting tHcy ≥ 12 umol/l was 2.0 (95% CI 1.4–2.8) and a 5 umol/l elevation of tHcy had a relative risk of 1.3 (95% CI 1.1–1.6).[61] In the Mobile Clinic Health Examination Survey (MCHES) in Finland, those with known CAD had a relative risk for future cardiac events of 2.40 (95% CI 1.08–5.35) for tHcy 10.5–12.3 umol/l and 2.23 (95% CI 1.03–4.85) for tHcy ≥ 12.5 umol/l.[62] Comparing the highest and lowest quartile, the RR was 7.11 (95% CI 2.05–24.74).[62]

Four prospective case-control trials have failed to show an association with hyperhomocysteinemia and cardiovascular disease: Finnish, Multiple Risk Factor Intervention Trial (MRFIT), Atherosclerosis Risk In Communities Study (ARIC), and MCHES (Table II).[62, 64–66] In MCHES, the group without baseline coronary disease had no significant association of future cardiac events with hyperhomocysteinemia.[62] In none of the four trials was there a statistically significant difference between case and control tHcy values, suggesting two similar populations. Thus, it is unlikely that there would be a significant difference in outcomes related to tHcy values (Table II). The argument against hyperhomocysteinemia as a risk factor for CAD would be stronger if there were a significant difference in the tHcy concentrations between the cases and controls.

A meta-analysis by Boushey *et al.* examined the relationship between hyperhomocysteinemia and risk of cardiovascular disease.[67] For a 5 umol/l increment increase in tHcy concentration, there was an increased risk for a cardiovascular event. Odds ratios for men and women were 1.6 (95% CI 1.4–1.7) and 1.8 (95% CI 1.3–1.9), respectively. This risk is similar to an increase in total cholesterol of 20 mg/dl.[67]

Support for the Treatment of Hyperhomocysteinemia

Both folic acid and cobalamine can effectively lower homocysteine concentrations as shown by the Homocysteine Lowering Trialists' Collaboration, a meta-analysis of 12 major ran-

TABLE II Prospective case-control homocysteine studies

	Population		tHcy (umol/l)				
Study	Case	Control	Case	Control	p Value	Risk	95% CI
Physicans Health	271	271	11.1	10.1	0.03	RR 3.4	1.3–8.8
Tromso	122	478	12.7	11.3	0.0002	RR 1.32	1.05–1.65
ECAP	750	800	11.3	9.7	< 0.001	RR 1.3	1.1–1.6
Finnish							
Male	134	141	9.99	9.82	> 0.05	OR 1.00	0.95–1.06
Female	131	128	9.58	9.28	> 0.05	OR 1.02	0.95–1.10
ARIC	232	527	8.86	8.53	0.24	RR 1.28	0.5–3.2
MRFIT	240	472	12.7	12.9	> 0.05	OR 0.82	0.55–1.54
MCHES (Hcy in mg/dl)							
No CAD	272	524	0.146	0.152	0.35	RR 0.90	0.51–1.60
CAD	166	311	0.163	0.149	0.03	RR 2.23	1.03–4.85

Abbreviations: ECAP = European Concerted Action Project, ARIC = Atherosclerosis Risk In Community Study, MRFIT = Multiple Risk Factor Intervention Trial, MCHES = Mobile Clinic Health Examination Survery, CAD = coronary artery disease, tHcy = total homocysteine, CI = confidence interval, RR = relative risk, OR = odds ratio.

domized studies.[68] Folic acid 0.5–5 mg/day lowered fasting tHcy by 25% and cobalamine by 0.02–1 mg a day and provided an additional 7% decrease in fasting levels, while pyridoxine had no effect.[68] The addition of other antioxidants such as ascorbic acid, alpha-tocopherol, and beta-carotene does not provide additional benefit.[69] Fortification of food with folic acid has a modest effect, with 449 folic µg folic acid/30 g of cereal and 665 µg folic acid/30 g cereal lowering tHcy by 11 and 14%, respectively.[70]

Current evidence indicates that lowering tHcy concentrations improves clinical outcomes. In a randomized controlled trial, administration of 1 mg folic acid in combination with 400 µg cobalamine and 10 mg pyridoxine for 6 months reduced the Hcy levels, decreased the rate and severity of restenosis after angioplasty, and lowered the need for revascularization.[71] An extension of the study to 1 year showed that these benefits persisted despite discontinuing therapy at 6 months.[72] Neither study showed a significant reduction in rate of nonfatal MI, cardiac death, and overall death.[71, 72]

In those with known CAD, hyperhomocysteinemia portends a worse prognosis with respect to increased risk of fatal MI.[73–75] There appears to be a graded response, with increasing Hcy concentrations correlating with increased risk of fatal MI.[73] In addition, hyperhomocysteinemia at the time of presentation of an acute coronary syndrome may be predictive of future cardiac events.[76, 77] However, a recent open-label study of two years duration calls into question the effectiveness of low-dose folate (0.5 mg) therapy as secondary prevention for those with stable CAD and statin-controlled hyperlipidemia.[78]

Suggestions for Current Homocysteine Screening and Management

Screening for hyperhomocysteinemia should be limited to a select group of patients who are considered at high risk for hyperhomocysteinemia[10] (Table III). The goal is to lower fasting tHcy to < 11 umol/l.[10] A cobalamine level with or without a methylmalonic acid level should be obtained if the Hcy is > 15 umol/l or fails to correct with folate. Hyperhomocysteinemia secondary to cobalamine deficiency cannot be corrected by folic acid alone; rather, it requires the addition of cobalamine for complete correction as well as prevention of neurological sequelae. Once the vitamin deficiency is corrected, a fasting tHcy should be rechecked and, if still elevated, should be treated with a multivitamin (MVI) containing 400 µg folic acid given daily.[10]

If hyperhomocysteinemia is present without cobalamine deficiency, then an MVI with 400 µg of folic acid along with an additional 800 µg of folic acid should be given daily. After 1 to 2 months of therapy, a fasting tHcy level should be drawn, and if the patient is still not yet at goal, the folic acid dosage should be doubled every 8 weeks until a fasting serum tHcy of < 11 umol/l is achieved. The total daily dose of folic acid should be limited to < 10 mg. If after 1 to 2 months the patient has not reached goal, then cobalamine 400 µg and pyridoxine 25–50 mg once a day can be administered. Supplementation with betaine, starting at 3 g twice a day, is experimental and has yielded conflicting results, but can be used in very high-risk patients.[79, 80] Once the patient is within goal range, a fasting tHcy can be repeated on a yearly basis.[9]

TABLE III Recommended screening for hyperhomocysteinemia

Coronary artery disease without traditional risk factors
Premature coronary artery disease
Family history of premature coronary artery disease
Disease states known to elevate tHcy levels
Drugs known to elevate tHcy levels
Part of hypercoagulable work-up for unexplained deep venous thrombosis

Abbreviation: tHcy = total homocysteine.

Conclusion

Hyperhomocysteinemia is an independent risk factor for CAD. In patients known to have cardiovascular disease, higher tHcy levels increase the risk for future events. Selective screening for primary and secondary prevention should be considered for high-risk patients. Homocysteine should be measured 8–12 weeks post MI due to an acute phase reaction. To avoid false elevations, proper specimen handling is important. Checking a cobalamine level before initiating therapy if the tHcy is > 15 umol/l or if the tHcy fails to correct with folic acid supplementation is recommended. Treatment of all patients with hyperhomocysteinemia is recommended, given that the treatment is inexpensive, has minimal to no side effects at doses < 10 mg/day, and can potentially have significant benefits with regard to cardiovascular morbidity and mortality.

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