Dietary strategies to treat hyperhomocysteinaemia based on the biochemistry of homocysteine: a review

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Abstract

Hyperhomocysteinaemia is implicated in various diseases, including cardiovascular disease and cancer. Several conditions influence the concentration of homocysteine (Hcy), including demographic, genetic and lifestyle factors. With regard to the latter, dietary components may be manipulated as Hcy can be remethylated to methionine by folate, or metabolised by other one-carbon nutrients, such as betaine and its precursor, choline. This metabolic interplay enables the nutritionist or dietitian to be able to lower Hcy concentrations cost-effectively by tailoring an individual's diet, or by food enrichment and fortification strategies. Evidence supports the safety and benefits of Hcy reduction by simple dietary intervention. B vitamins, and betaine and choline intake lower Hcy, whereas methionine and certain beverages (coffee, tea and alcohol) increase it. Therefore, dietary determinants of Hcy raise the prospect of a simple, inexpensive and safe means of treating and/or preventing diseases contingent on this sulphur-containing protein.

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Introduction

Elevated concentrations of homocysteine (Hcy), the basis of hyperhomocysteinaemia (HHcy), are involved in a myriad of diseases, including cardiovascular disease (CVD),[1,2] and various other conditions, such as impaired bone health,[3] inflammatory bowel disease[4] and cancer.[5] The underlying causes of HHcy arise from the interplay of genetic, biological and environmental factors, which can roughly be divided into two groups: those that are unchangeable, such as genetics, gender and advancing age; and modifiable factors, including smoking, diet and physical activity. In addition, acquired conditions, such as diseases (renal failure, rheumatoid arthritis, malignancies, psoriasis and infection with the human immunodeficiency virus) and certain drugs (methotrexate, nitrous oxide, theophylline and thiazides) can also lead to elevated Hcy concentrations.

Since Hcy can be lowered by diet, the nutritionist and dietitian can play an important role in the prevention and therapeutic treatment of individuals at increased risk of diseases that are contingent on Hcy. The metabolism of Hcy and dietary determinants explored in this review equip these professionals with the knowledge to treat HHcy in ways that are simple, inexpensive and safe.

An overview of the biochemistry and metabolism of homocysteine

Hcy is a sulphur-containing amino acid, i.e. a thiol (–SH), with the chemical formula: $HSCH_2CH_2CH(NH_2)CO_2H$.[6] Hcy is not present in food, but is formed by the body as it metabolises methionine, an essential amino acid.[7]

The structures of methionine and Hcy are identical, except for a conversion that results in removing a one-carbon methyl group ($–CH_3$) from the former.[8] While methionine is chemically stable, the free thiol of Hcy renders it highly reactive in cells and within the circulation.[7] Seventy per cent to eighty per cent of Hcy is bound to the thiol groups of plasma proteins in human plasma.[7] Only 1-4% circulates as free Hcy in its reduced form, whereas the remainder auto-oxidises to form homocystine dimers, or combines with other thiols, such as cysteine (Cys) and glutathione to form mixed disulphides.[6,9] It is not yet clear which complexes are formed by the reduced Hcy molecules within cells, but it seems probable, with the reactivity of the thiol group of Hcy, that similar complexes will form.[7]

The metabolism of B vitamins, methyl groups and Hcy is inextricably linked (Figure 1). The clearance of Hcy from the human circulation depends on folate, vitamin B_2, vitamin B_6 and vitamin B_{12}.

In cells there are approximately 28 enzymes that can be identified as methyltransferases. Methyltransferases are involved in the donation

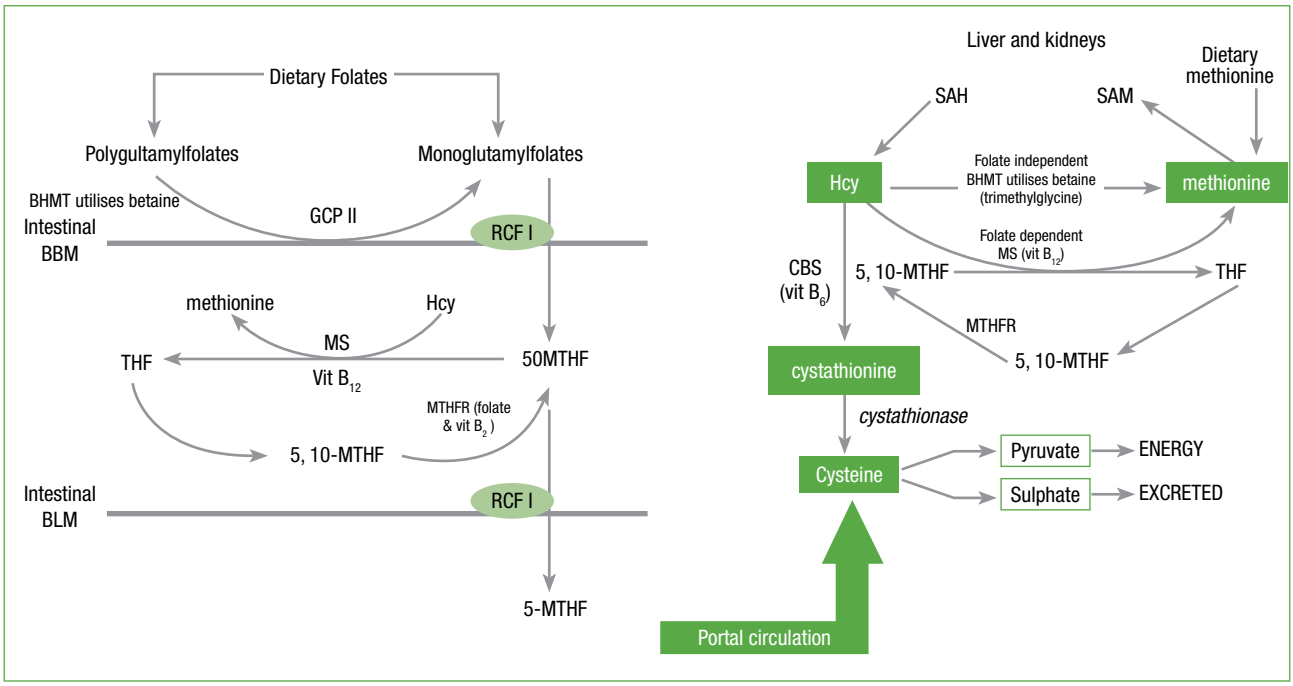

Figure 1: Homocysteine and folate metabolism[10]

5-MTHF: 5-methyltetrahydrofolate, 5,10-MTHF: 5,10-methylenetetrahydrofolate, BBM: brush border membrane, BHMT: betaine-homocysteine methyltransferase, BLM: basolateral membrane, CBS: cystathionine β-synthase, CSE: cystathionine γ-lyase, GCP II: glutamate carboxypeptidase II, Hcy: homocysteine, MS: methionine synthase, MTHFR: methylenetetrahydrofolate reductase, RFC I: reduced folate carrier 1, SAH: S-adenosylhomocysteine, SAM: S-adenosylmethionine, THF: tetrahydrofolate

(or transfer) of a methyl group from the activated form of methionine, namely, S-adenosylmethionine (SAM), to the synthesis of thymine, choline, creatine, epinephrine, the protein 3-methylhistidine or for deoxyribonucleic acid methylation.[7] Methionine adenosyl-transferase converts methionine to SAM by a reaction that includes the addition of a methyl group and the purine base, adenine (from adenosine triphosphate or diphosphate). When SAM donates a methyl group, it is converted to S-adenosylhomocysteine (SAH). All SAM-dependent methyltransferase reactions result in the production of SAH, which can be catabolised immediately in vivo by SAH hydrolase to produce the nucleotide adenosine and Hcy.[7,11] While the accumulation of SAH might in itself impair cellular function by inhibiting methyltransferase enzymes, thereby preventing the repair of aged or damaged cells,[12] Hcy, with its reactive free thiol group, could also be toxic to cells in its own right.[7]

Hcy can follow three possible pathways within cellular metabolism. First, Hcy may be remethylated back to methionine by either folate-dependent or folate-independent mechanisms.[11] During folate-dependent remethylation, methionine synthase (MS) uses a methyl group from 5-methyltetrahydrofolate (5-MTHF), while methylcobalamin (the biologically active form of vitamin B_{12}) acts as the coenzyme. The methyl group for this reaction is produced by the enzyme 5,10-MTHFR. MTHFR, in turn, uses flavin adenine dinucleotide (the biologically active form of vitamin B_2) as a co-factor.[13] In an alternative folate-independent remethylation route, the enzyme betaine-homocysteine methyltransferase (BHMT) catalyses the remethylation of Hcy using betaine (trimethylglycine, which is a generator of methionine and SAM), a methyl group donor derived from choline oxidation, to convert Hcy to methionine and dimethylglycine. BHMT catalyses the synthesis of methionine from betaine and Hcy, using a zinc ion to activate Hcy.[14] Its expression is induced in mice on a methionine-deficient diet.[15] SAM seems to function as a switch between the methionine cycle and the trans-sulphuration pathway. When SAM concentrations become limited, SAH and Hcy concentrations increase, and there is an accompanying reduction in the methylation cycle.[16] High SAM concentrations seem to limit Hcy remethylation by inhibiting MTHF and BHMT. Trans-sulphuration seems to be enhanced by the stimulatory effect of SAM on cystathionine by cystathionine β-synthase (CBS) activity.[16] This interplay is necessary for Hcy homeostasis and to prevent diseases contingent on HHcy.

Second, Hcy can be catabolised further to Cys by trans-sulphuration using pyridoxal 5'-phosphate (PLP) (the biologically active form of vitamin B_6) as a co-factor, beginning with the irreversible conversion to CBS. The enzyme, cystathionine γ-lyase (CSE or cystathionase), then uses CSE to form Cys, which is required for the synthesis of many compounds, including glutathionine, or can be further converted to pyruvate, which can be used for energy and sulphate, which is excreted through the urine.[7] While the trans-sulphuration pathway contributes to the maintenance of normal postprandial Hcy concentrations, the remethylation pathway maintains normal fasting Hcy concentrations.[17]

Third, excess Hcy can be exported from the cell into the circulation, thereby regulating the intracellular Hcy concentrations.[7,16] Earlier studies have indicated that the normal reference range for total plasma Hcy (i.e. the sum of free and protein-bound Hcy, Hcy and Hcy-Cys mixed disulphide) is 5-15 µmol/l (to convert Hcy concentration to µg/ml, multiply by 0.1352), mild to moderate HHcy between 16 µmol/l and 100 µmol/l, and severe HHcy > 100 µmol/l.[18,19] In

2007, Castañon, Lauricella, Kordich and Quintana[1] calculated that Hcy concentrations of > 12 µmol/l significantly increased the risk of developing venous thrombosis. Since the definition of elevated circulating Hcy concentrations should ideally be based on a health outcome, they proposed the use of 12 µmol/l as a cut-off value for HHcy, with clinical significance relating to CVD. The American Heart Association Nutrition Committee has recommended that basal Hcy should be 10 µmol/l as a therapeutic goal for subjects at increased risk of CVD.[19] Cut-off values for diseases associated with Hcy other than CVD should be established in future studies.

It is important to note that standardisation of the methods (chromatography, capillary electrophoresis and immunoassays) used to quantify Hcy is still needed, since between-method and inter-laboratory variations in total Hcy quantification are not yet satisfactory.[20-22] According to Ubbink,[22] fluorescence polarisation immunoassay may become the choice method for routine diagnostic laboratories.

Dietary determinants of homocysteine concentrations

The previously referred to description of the metabolism of Hcy shows that nutrition plays a major role in Hcy concentrations.

B vitamin intake

Insufficient B vitamin intake increases Hcy concentrations, and induces an imbalance of SAM and SAH,[23] whereas supplementation with B vitamins and their synthetic counterparts seems to reduce Hcy concentrations.[24] Hcy has been proposed to be a highly sensitive indicator of folate and vitamin B_{12} status.[25]

Folate status

Folate is a micronutrient found in green leafy vegetables and in some animal products, such as egg yolk. It is an important co-factor and methyl donor in converting Hcy to methionine. Reduced folate status inhibits the methylation cycle by failing to keep it supplied with methyl groups, resulting in reduced Hcy remethylation.[26] Folate deficiency, due to problems of malabsorption or inadequate dietary intake (malnutrition or alcoholism), is considered to be the most important nutritional cause of elevated Hcy.[27]

Although everyone should consume sufficient folate, research highlights the necessity of adequate folate intake in drinkers of alcohol, as well as individuals who harbour the cytosine to thymine substitution at nucleotide position 677 (C677T) in the MTHFR gene, i.e. 677 TT genotype.[28-30] Chiuve et al[28] reported that the adverse effects of moderate, but not excessive, alcohol use on Hcy concentrations may be overcome through adequate folate intake. MTHFR 677 TT homozygous individuals may require more folate for thermolabile MTHFR to function adequately and to ensure normal Hcy concentrations, than individuals who harbour the wild type alleles.[29] The adverse effects of a low intake of the methyl-related nutrients, including folate, with a high intake of alcohol, are additive in relation to cancer risk.[30]

A high intake of natural folate from food reduces plasma Hcy concentrations,[31] but folic acid (a synthetic chemically stable form of folate used in supplements and fortified foods) has been reported to be more effective than dietary folate in this regard, probably owing to its high bioavailability.[32] Fasting Hcy concentrations decreased modestly after mandatory folic acid fortification in America in 1998.[33] Supplementation with folic acid alone, and in combination with other B vitamins, diminishes Hcy concentration.[34] It was concluded in a meta-analysis of 25 randomised controlled trials[34] that ≥ 0.8 mg folic acid per day is required to achieve the maximal reduction in Hcy concentration, and that 0.2 mg and 0.4 mg were associated with a 60% and 90%, reduction of the maximal effect, respectively. Vitamin B_{12} (0.4 mg/day) produced a further reduction of 7% [95% confidence interval (CI): 4-9%] in Hcy concentrations, but vitamin B_6 had no significant effect.

Evidence suggests that folic acid supplementation has a beneficial effect on the vascular endothelium by reducing Hcy, and through other mechanisms, for instance, by reducing oxidative stress.[35] In addition, acute administration of folic acid can restore impaired endothelial function induced by acute HHcy.[36] Folic acid was reported to have antioxidant properties and direct scavenging effects in vitro,[37] and may directly improve nitric oxide production by enhancing the enzymatic activity of nitric oxide synthase.[38] Hcy leads to increased cell proliferation and cell death through apoptosis and necrosis in vitro in smooth muscle cells,[39] but adding folic acid to the culture medium leads to a significant reduction of Hcy concentrations in media. This is probably because of the increased remethylation of Hcy to methionine, and the reduced effects of Hcy on proliferation, apoptosis and necrosis.[39]

Mager et al[40] reported that long-term folate-based vitamin therapy was independently associated with lower all-cause mortality in HHcy patients with CVD, and with reduced Hcy concentrations. By contrast, Albert et al[41] reported that long-term supplementation with folic acid, and vitamins B_6 and B_{12}, did not reduce total CVD events in high-risk women, despite lowering Hcy significantly.

Riboflavin status

Riboflavin, or 7,8-dimethyl-10-ribityl-isoalloxazine (vitamin B_2), is present in a wide variety of foods. It is an essential precursor for the biosynthesis of the biologically active flavin adenine mononucleotide (FMN) and flavin adenine dinucleotide (FAD). FMN and FAD participate in a range of redoxication reactions, some of which are key to the function of aerobic cells.[42] FAD is an essential co-factor for the folate-dependent enzyme, MTHFR, which metabolises folate to the form used in Hcy methylation, and for an enzyme that activates the vitamin B_6 precursor, pyridoxal, to the biologically active form, PLP.[7] Thus, in theory, inadequate intake of riboflavin might give rise to increased plasma Hcy.[7] In addition, riboflavin deficiency may exert some of its effects on Hcy by reducing the metabolism of other B vitamins, notably those of folate and vitamin B_6.[42]

Riboflavin intake emerged as a factor that influences Hcy in the Framingham Offspring cohort.[43] By contrast, Verhoef and

De Groot[27] reported that riboflavin has little influence on fasting Hcy concentrations. It may be relevant in individuals with the MTHFR 677 TT genotype, as riboflavin status was reported to be a modulator of Hcy in healthy adults, especially in those homozygous for the MTHFR C677T mutation.[44] Moat et al[45] confirmed a folate-riboflavin interaction in determining Hcy unrelated to the MTHFR genotype.

Vitamin B_6 status

Reduced vitamin B_6 causes an accumulation of Hcy because CBS and CSE, which catalyse the trans-sulphuration of Hcy, are vitamin B_6 dependent.[46] The metabolism of vitamin B_6 is flavin dependent and impaired synthesis of PLP in the presence of a riboflavin deficiency has been demonstrated in studies on humans and animals.[47] McKinley et al[48] reported that low-dose vitamin B_6 supplementation effectively lowers Hcy in healthy elderly persons who are both folate and riboflavin replete.

Vitamin B_6 supplementation has little influence on fasting Hcy concentrations, although it may improve Hcy catabolism in elderly individuals.[27] It significantly reduces the post-methionine load increase in Hcy, and also reduces cystathionine concentrations, probably owing to enhanced CSE activity.[49]

Vitamin B_{12} status

Folate and cobalamin (as methylcobalamin) are involved as substrate and coenzyme, respectively, in the remethylation pathway of Hcy to methionine. Plasma Hcy increases considerably when there is an intracellular deficiency of folate or cobalamin, and is regarded as a sensitive marker of suboptimal vitamin concentrations.[25]

Vitamin B_{12} deficiencies are most commonly because of problems of malabsorption, e.g. alcoholism[47] or inadequate dietary intake, especially in individuals who follow a strict vegetarian diet since vitamin B_{12} is found only in animal-source foods.[50] A reduced vitamin B_{12} status prevents the proper functioning of the methylation cycle by directly reducing the activity of MS, one of the enzymes needed for the methylation cycle to turn.[7] The enzyme, MS, is dependent on 5-MTHF as a methyl donor, but also on vitamin B_{12} as methylcobalamin.[7] A low vitamin B_{12} status may alter Hcy by reducing its remethylation cycle towards methionine resynthesis in the same manner that low folate status alters Hcy metabolism.[26]

Certain rare and drastic genetic mutations, such as the one described by Mudd et al in 1969,[51] can lead to impaired vitamin B_{12} activation. This results in reduced MS activity, with a rise in urinary and plasma Hcy, as well as a reduction in the activity of methylmalonyl-CoA mutase (the other vitamin B_{12}-dependent enzyme), causing an accumulation of methylmalonic acid.[51]

Dietary lipotropics

Methionine, betaine and choline belong to a group of compounds called lipotropics.[52] Lipotropics are compounds that have an affinity for lipids, and thus prevent or correct the excess accumulation of fat in the liver by promoting the transport of fatty acids from the liver to the tissues, or by accelerating the utilisation of fat in the liver itself.

Methionine

Methionine is an essential amino acid that is naturally found in dietary proteins. A typical Western diet contains 1.6-2.8 g of methionine per day,[53] which is more than that required for protein biosynthesis. Thus, the excess must be catabolised.[7] The transamination of methionine only occurs at non-physiologically high concentrations, and instead, methionine catabolism takes place mainly in the liver, through its sequential conversion to SAM and SAH, and then to Hcy, followed by the trans-sulphuration pathway.[7]

For this reason, methionine loading tests (MLT) are often used to induce "stress" on Hcy metabolism, and could reveal any defect in Hcy metabolism (methionine intolerance) and cause a transient acute increase in Hcy concentrations. MLT permit the screening of 40-55% of persons[54] who may have clinically relevant HHcy which fasting Hcy determination alone may fail to identify. Ubbink et al[55] reported that the rise in Hcy after methionine loading is lower in black Africans than in Caucasians, which points towards a more effective Hcy metabolism. This seems to correlate with the lower prevalence of CVD seen in these subjects. Caucasians with an elevated risk of CVD showed higher Hcy concentrations after oral MLT.[56] It has been suggested that methionine handling capacity is more dependent on (genetically determined) enzyme activities, but fasting (basal) Hcy concentrations are more strongly influenced by environmental factors.[57]

Oral MLT is associated with a small, but significant, enhancement of thrombin generation,[58] and is associated with impaired flow-mediated, endothelium-dependent vasodilatation.[59] Even low-dose methionine and animal protein intake was reported to increase Hcy and lead to the rapid onset of endothelial dysfunction,[60] suggesting that even diet-related increments in Hcy may contribute to the development and progression of atherosclerosis. It is unknown whether or not a diet that is rich in animal protein containing large amounts of methionine might activate platelets, increase thrombin production or induce endothelial dysfunction.

Betaine and choline intake

Betaine or trimethylglycine, and its precursor, choline, are major sources of methyl groups (one-carbon nutrients) in the diet,[61] and thus can act as methyl donors in Hcy remethylation. Betaine generates methionine and SAM, then converts Hcy to methionine, using the enzyme, BHMT, independent of folate or vitamin B_{12}.[7] Betaine can be found in food and it is estimated that a normal diet contains 0.5-2 g/day or can be synthesised endogenously from choline, also found in food.[62] Choline is derived from the diet, as well as from *de novo* synthesis.[63]

The consumption of betaine and choline can lower fasting Hcy concentrations to the same extent as folic acid, particularly in the setting of a high intake of methionine.[27] High doses of betaine (6 g/day and higher) can be used as Hcy-lowering therapy in individuals with HHcy because of inborn errors in their Hcy metabolism. Betaine has been reported to lower plasma Hcy in vitamin B_6-resistant patients.[62] In addition, betaine supplementation seems to lower fasting Hcy dose

dependently, up to 20% for a dose of 6 g/day, in healthy volunteers with normal Hcy concentrations. Betaine also reduces the increase in Hcy after MLT by up to 50%, whereas folic acid has no effect.[62] Betaine could also lower Hcy independent of folate remethylation in the presence of ethanol.[64] In this regard, Chiuve et al[65] reported that total choline and betaine intake was inversely associated with Hcy in women, and that the strongest dose response was observed in women with a low methyl diet (high alcohol and inadequate folate intake). Therefore, Chuive et al[65] concluded that the remethylation of Hcy may be more dependent on the betaine pathway when methyl sources in the diet are low. Betaine and choline depletion in animals plays a role in the pathogenesis of homocystinuria owing to deficiencies of the MTHFR enzyme.[66]

Thus, betaine and choline can be important food components that attenuate Hcy rises after meals. If Hcy plays a causal role in the development of CVD, a diet that is rich in betaine or choline might benefit cardiovascular health through its Hcy-lowering effects. However, betaine and choline may adversely affect serum lipid concentrations, which can increase the risk of CVD. It remains to be established whether or not the potential beneficial health effects of betaine and choline outweigh the possible adverse effects on serum lipids.

Coffee and tea consumption

The consumption of tea and coffee increases Hcy concentrations by up to 20%.[27] Habitual coffee drinking is positively associated with Hcy concentration in most,[43,67-70] but not all,[71-73] observational studies. Intervention trials indicated that the increasing effect of coffee consumption on Hcy concentrations may be causal.[74-76] The vitamin B_6 concentration was markedly lower in a randomised crossover trial in the period when coffee was consumed, rather than when no coffee was drunk, but since vitamin B_6 does not seem to influence fasting Hcy concentrations greatly, the significance of this finding is uncertain.[75] The constituent caffeine, which is a methyl xanthine, might be the culprit,[43,75] because methyl xanthines are known to act as vitamin B_6 antagonists that may inhibit the conversion of Hcy to Cys.[75] The polyphenol, chlorogenic acid, which is present in coffee in the same amount as caffeine, may partly contribute to the increase in Hcy concentration. When polyphenols are metabolised, methyl groups from methionine are necessary, which results in a higher production of Hcy.[77] Both caffeine and chlorogenic acid are also present in tea, although in smaller doses, which explains the absence of a clear association between Hcy and tea consumption.[77] The consumption of one litre of strong coffee daily may affect diet composition and other lifestyle factors. Therefore, it could influence Hcy concentrations indirectly,[78] but this has not yet been explored. It is also possible that the Hcy response to coffee may be modulated by the genetic factors mentioned earlier.[78] Since the habit of coffee drinking is widespread, consequences at population level may not be negligible. However, the effect of coffee consumption on Hcy concentration is modest and much less than the changes associated with a variation in B vitamin status.

Alcohol consumption

Light to moderate alcohol consumption is associated with reduced mortality from CVD (the French paradox).[79] However, intermittent bouts of excessive consumption (binge drinking) and chronic high levels of alcohol consumption result in a sequelae of health problems, such as increased CVD (for example, cardiomyopathy and arrhythmia) morbidity, neurological disorders, certain cancers, chronic pancreatitis and liver cirrhosis.[80] Lifelong abstainers appear to be at a slightly higher risk than light or moderate consumers who are able to control their drinking.[81] Therefore, total abstinence is unnecessary when the consumer can enjoy alcohol sensibly, but abstainers are not advised to start drinking in order to gain any claimed health benefits.[82]

In a meta-analysis, Bagnardi et al[83] reported that regular heavy drinkers and heavy irregular binge drinkers showed significantly different pooled relative risks of 0.75 (95% CI: 0.64-0.89) and 1.10 (95% CI: 1.03-1.17), respectively, as opposed to abstainers, for developing CVD. Therefore, the pattern of drinking, as well as the amount consumed, plays a pivotal role in CVD development.

An elevated Hcy concentration is one of the myriad negative consequences of chronic alcoholism.[84] The Hcy concentration seems to be twice as high, and plasma B vitamins lower, in chronic alcoholics, than in healthy controls. This is probably because of a combination of malnourishment, the direct effects of heavy alcohol intake on folate status and vitamin B_6 (acetaldehyde dislodges vitamin B_6 from its protective binding protein so that it is destroyed, and alcohol interferes with thiamine, folate and vitamin B_{12} absorption), the decreased hepatic uptake and retention, and the increased urinary excretion of folate.[85] A major difficulty in drawing conclusions about the effect of alcohol consumption on Hcy lies in distinguishing between the direct effects of alcohol and alcohol-induced malnutrition. An association between alcohol and Hcy has not been detected in some studies,[86,87] but it has been demonstrated in several that moderate consumption inversely relates to Hcy concentration, compared with abstaining.[88,89] However, moderate alcohol consumption in social drinkers is associated with increased Hcy,[90] and wine consumption, in particular, relates to Hcy in a J-shaped manner, i.e. Hcy is higher when alcohol consumption is high, lower when alcohol consumption is low or moderate, and tends to be slightly increased in individuals who do not consume any alcohol.[68] Thus, the literature on the cardioprotective effects of moderate alcohol consumption, compared with non-drinking, in relation to Hcy, remains contentious.

It may be important to distinguish between the effects that can be attributed directly to alcohol, and those that may result from other constituents of alcoholic drinks. Different types of alcoholic beverages seem to influence Hcy in different ways. The results from studies to determine the effects of different alcoholic beverages are inconsistent.[90,91] Beer consumption might be responsible for the inverse or absence of an association with alcohol consumption and Hcy concentration,[43,68,88,91] but some studies report that it is positively associated with Hcy.[90] Researchers have ascribed the beneficial

Table I: Summary of the effects of dietary determinants on homocysteine concentrations, as a guide for dietitians

B vitamins	Intervention effect on homocysteine	Advice to patient
Riboflavin	↓	Meet DRI through the diet or supplementation
Vitamin B_6	↓	
Vitamin B_{12}	↓	
Folate or folic acid	↓	
Dietary lipotropics		
Methionine	↑	Do not exceed the DRI
Betaine and choline	↓	Meet the DRI through the diet, while monitoring the lipid profile
Beverages		
Coffee and tea	↑	Avoid drinking unfiltered coffee, and do not consume coffee and tea excessively*
Alcohol intake	↑	Use alcohol sensibly, if at all

DRI: dietary reference intakes, ↓: , ↑:
*: Limited data are available. Research is needed to make quantitative recommendations with regard to intake

effect of beer drinking on Hcy to its folate, riboflavin and vitamin B_6 content, all of which are important for enzymatic Hcy conversion. Wine consumption seems to elevate Hcy concentrations.[90,91] It was revealed that Hcy in women showed a U-shaped curve with a minimum of 8.49 mmol/l at 10-20 g alcohol/day, whereas an inverse association was observed in men by Burger et al[92] in a large cross-sectional study. Spirits, on the other hand, seem to elevate Hcy concentrations.[90,91] In Africa, indigenous people brew traditional alcoholic beverages, such as sorghum, millet beers and *Mbamba*, the last of which is a concoction of water, bread, oats, pineapple juice, sugar and yeast. Sorghum beer has been reported to make positive contributions to dietary intake, particularly when the beer is brewed with a sorghum adjunct. Hence, the results for different types of alcoholic beverages are not clear.

The relationship between alcohol consumption and Hcy concentration is complex. Alcohol (ethanol) interferes with both the transmethylation and trans-sulphuration pathways of Hcy metabolism, either directly,[93] or through its metabolite, acetaldehyde,[94,95] or through the indirect effects mediated by interactions with vitamin metabolism. Alcohol studies that have been conducted on humans are scarce, and when using chronic alcoholics, the results are often complicated by liver disease and/or dietary insufficiencies associated with alcohol consumption.

Acetaldehyde inhibits MS activity,[96] which could lead to HHcy, independent of vitamin status. It has been indicated in animal studies that alcohol consumption causes a compensatory increase in betaine, a Hcy methyltransferase that generates methionine from Hcy.[84] Although methionine levels seem to vary, methionine adenosyltransferase activity decreases in most, but not in all studies.[84,97] The SAM to SAH ratio, an important determinant of methylation activity, has been reduced in most animal studies.[98] The alcohol intermediate, acetaldehyde, accelerates the intracellular degradation of PLP, reducing the PLP content of hepatic cells, despite an adequate dietary intake of vitamin B_6.[99] This inhibits the PLP-dependent enzymes, CBS and CSE, compromising Hcy trans-sulphuration. Nitric oxide production, secondary to augmented Hcy, inhibits MS activity, possibly by inactivating cobalamin,[100] which further disrupts MS activity, despite cobalamin supplementation, as well as directly inhibiting MS, owing to acetaldehyde.[96] It was reported in studies conducted on ethanol-fed rats that MS inhibition raises the "trapping" of folate as 5-MTHF.[93,93]

Folate intake, as discussed previously, seems to be inversely associated with Hcy concentration, but this relation seems to be modified by the MTHFR C677T genotype and alcohol intake. Women with the thermolabile variant of MTHFR 677 or moderate alcohol intake demonstrated a significantly higher Hcy concentration at a low intake of folate, but adequate folate intake minimised these differences.[28] In addition, the elevation of Hcy in women who consumed low folate and drank moderate amounts of alcohol was greater in the presence of the variant, MTHFR 677 T allele.[28]

Summary and conclusion

Since numerous clinical conditions are known to be associated with a high Hcy count, a reduction in Hcy concentration may be clinically relevant to prevent disease. However, it remains to be determined whether or not lowering Hcy would prevent clinical disease outcomes, such as stroke events. Randomised controlled trials that incorporate the dietary strategies reviewed here should clarify whether or not the nature of the observed association between Hcy and these diseases is indeed causal. Settling this dispute of causality is necessary since various modifiable factors have been identified that could be manipulated as a strategy to prevent and treat diseases contingent on Hcy if they were found to be causative. As summarised in Table I, Hcy can be lowered by the adequate intake of folate, and vitamins B_2, B_6 and B_{12} (either through a diet containing lots of fruit, vegetables and some animal-derived foods, or the fortification of food with B vitamins), as well as betaine and choline, and the proscription of heavy irregular (binge) alcohol drinking. Dietary changes can modify Hcy concentrations in ways that are relevant to public health. Therefore, dietitians are able to manipulate Hcy, thereby raising the prospect of disease prevention.

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