Methionine Restricted Diet; Clinical Application

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To review nutritional therapy of hyperhomocysteinemia observed in Methylenetetrahydrofolate Reductase (MTHFR) gene polymorphisms. The researches and review articles about the subject has been read, investigated, compiled and integrated with our clinical experience. In the therapy of MTHFR gene polymorphisms, nutritional therapy is an integral part of the therapy and methionine restricted diet should be encouraged with vitamin supplementation which have important functions in methionine-homocysteine pathways. Methionine restricted diet may hneave beneficial effects on serum/plasma total homocysteine levels of the patients with MTHFR enzyme polymorphisms.

Key Words: Methionine, Homocysteine, Methylenetetrahydrofolate reductase, Methionine restricted diet.

Homocysteine, Methionine And Metabolism

Homocysteine is a sulfur-containing nonproteinogenic amino acid. It is an intermediate product in the normal metabolism of methionine (Figure 1)[1,2] Apart from its significance as an independent risk factor of additional prognostic value, homocysteine is a sensitive diagnostic indicator of folate, vitamin B12, and vitamin B6 deficiencies. The determination of the plasma homocysteine concentration is also useful for documenting response to vitamin supplementation.[1]

Methionine is an essential sulfur-containing amino acid, mainly ingested in animal-derived foods.[3,4] It is the sole precursor of homocysteine, and dietary protein is the main source of methionine.[5,6] The daily intake of methionine in the general population varies from 1 to 4 g/d. A single oral dose of free methionine increases the plasma concentration of total homocysteine in a dose-dependent manner within hours. Verhoef et al[5] showed that protein-bound methionine (ie, that from a protein-rich meal) increases postprandial plasma concentrations of tHcy but does so more modestly than does the same dose of free methionine. It is a potential mediator of adverse effects of excess animal protein intake, and, at high intake levels, is associated with increased homocysteine levels, Body Mass Index, cardiovascular risk and bad obstetrical history.[3] In humans, elevated plasma homocysteine concentrations are associated with common pregnancy complications and adverse outcomes, including preeclampsia, spontaneous abortion, placental abruption, neural tube defects and recurrent pregnancy loss. Extreme elevation of homocysteine may also be associated with neural tube defects.[7-9] A high plasma concentration of tHcy is also a potential risk factor for cardiovascular disease, Alzheimer disease, dementia in the elderly and inflammatory bowel disease.[9-11]
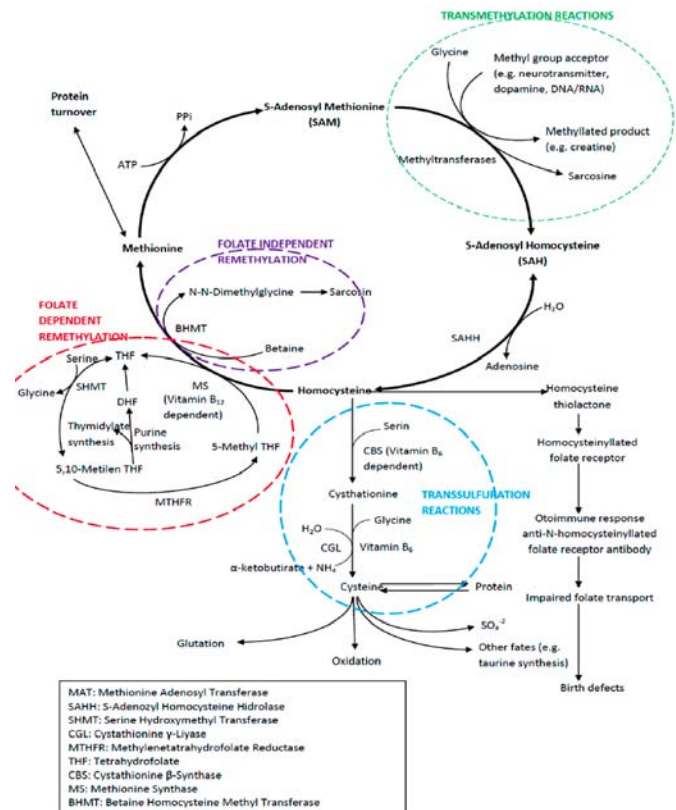

Figure 1: Metabolic pathways of methionine and homocysteine

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There are three pathways in the metabolism of methionine and homocysteine; transmethylation, remethylation and transsulphuration pathways. In transmethylation pathway, which is present in most mammalian tissues, intracellularly, methionine is formed into S-adenosylmethionine ("active methionine") (SAM) by methionine adenosyltransferase (MAT). [12,13] SAM is the most important universal methyl group donor for a variety of methyltransferases, resulting in the methylation of substrates such as nucleic acids, lipids, proteins, neurotransmitters, hormones.[2,3,13] SAM is derived in part from dietary methyl group intake.[12] All SAM-dependent methyltransferase reactions result in the production of S-adenosylhomocysteine (SAH), which can subsequently be converted to homocysteine by SAH hydrolase.[13,14] SAM:SAH ratio determines the methylation capability of particular tissues.[15] Homocysteine, is either remethylated to methionine or broken down to cysteine and sulfate in the transsulfuration pathway. [5,16] Homocysteine may be remethylated back to methionine by either folate-dependent or folate-independent mechanisms.[13] In folate dependent remethylation pathway, methylenetetrahydrofolate reductase (MTHFR) reduces 5,10-methylenetetrahydrofolate (5,10-methylene-THF) to 5-methyltetrahydrofolate (5- methyl-THF).[3,17] This enzyme contains flavine adenine dinucleotide (FAD) as a prosthetic group.[17] By acquiring a methyl group from 5-methyl-THF, homocysteine is remethylated to methionine. This reaction is catalyzed by the enzyme methionine synthase (MS), and vitamin B12 is required as a cofactor.[2,3,13,16] Betaine-homocysteine S-methyltransferase (BHMT) catalyzes the folate-independent remethylation of homocysteine using betaine, a methyl group donor derived from choline oxidation.[13,15] The remethylation pathway is favored during relative methionine deficiency. This recycling and conservation of homocysteine ensures adequate methionine maintanence and is dependent on the availability of choline, betaine, and folic acid in the diet.[7,18] Alternatively, in transsulphuration pathway, homocysteine can, by condensation with serine and via cystathionine by cystathionine b-synthase (CBS), be irreversibly broken down to cysteine and glutathione. The activities of both enzymes involved in this metabolic pathway, i.e., CBS and γ- cystathionase, depend on the cofactor vitamin B6. It can in turn be converted to cysteine via the intermediate, cystathionine.[2,3] Release of homocysteine into the extracellular medium represents another route of homocysteine removal from the cell. Such export is enhanced when production of homocysteine is increased, and reduced when production is inhibited. Thus, the amount of homocysteine in the extracellular media, such as plasma and urine, reflects the balance between intracellular production and utilization.[18,19] Burrin et al[11] stated that the intestine has the enzymatic capacity for transmethylation, remethylation and transsulfuration of methionine, and for conversion of cysteine into glutathione and taurine. Whereas SAM-dependent trans-methylation occurs in nearly all tissues, the transsulfuration pathway and the remethylation of homocysteine by BHMT are tissue specific, existing primarily in the liver, kidney, intestine, and pancreas.[13,16]

Plasma Homocysteine Level

The plasma homocysteine concentration is affected by various factors, such as nutritional, physiological, hormonal, pharmacological, lifestyle, disease and genetic factors. Of these factors genetic and nutritional factors are thought to have a greater influence on plasma homocysteine concentration.[20] The size of the homocysteine pool is determined by the rate of its production, the rate of reconversion to methionine, and also the rate of transsulfuration of homocysteine to produce cysteine and taurine. Changes in plasma homocysteine are believed to reflect the activity of the methionine cycle.[7,15,21] Homocysteine exists in plasma in several forms. In normal subjects, approximately 70-85% of the aminoacid homocysteine is protein bound via disulfide linkages, primarily to albumin. The remaining homocysteine in plasma rapidly oxidizes to the disulfides homocystine (two homocysteine molecules linked together) and cysteine-homocysteine. The amount of total plasma/serum homocysteine is the sum of these three components and is referred to as homocysteine or tHcy.[1,22] Being cytotoxic, homocysteine is increasingly exported from the cell to become detectable in plasma.[2]

Polymorphism in genes involving homocysteine metabolism could affect the plasma levels.[17] Elevated levels of homocysteine can result from several mutations in the MTHFR gene and have been identified as risk factors for thrombosis.[8] Data on the homocysteine levels are contradictory. When folate status is low, the presence of the MTHFR C677T polymorphism (TT genotype) is associated with an increase in homocysteine concentration and DNA hypomethylation.[17] Homozygotes for the TT genotype have higher total homocysteine levels compared with heterozygotes (CT) and normal homozygotes (CC).[22] Individuals homozygous (TT) and heterozygous (CT) for C677T MTHFR polymorphism exhibited mean MTHFR activities of 30% and 65%, respectively, relative to the mean activity of normal homozygotes (CC). The A1298C mutation reduces MTHFR activity, albeit to a lesser extent than C677T, but neither homozygous recessive nor heterozygous individuals have significantly higher plasma homocysteine levels compared to controls. However, individuals who carry C677T and A1298C mutations on different alleles (compound heterozygotes) have slightly elevated plasma homocysteine levels.[23] Koc et al found that TT genotype of MTHFR C677T is an influencing factor on homocysteine levels in Turkish population.[24] However, Yilmaz et al reported that pre-eclamptic patients bearing the non-mutated cytosine-cytosine genotype had significantly higher homocysteine levels than those with an uncomplicated pregnancy (P=0.009).[25]

Deficiencies of vitamin B12 and B6, folic acid, riboflavin, betaine and choline are associated with elevated plasma homocysteine levels.[16,26,27] Plasma homocysteine levels >12 µmol/l and <30 µmol/l are traditionally referred to as "moderate hyperhomocysteinemia" (commonly found in people with vitamin deficiency); the range from 30 to100 µmol/l has been termed "intermediate hyperhomocysteinemia" (often found in individuals with homozygous enzyme defects as well as in patients with chronic kidney disease); and plasma homocysteine concentrations >100 µmol/l are traditionally defined as "severe hyperhomocysteinemia" (typically found in individuals with severe congenital disorders or homocystinuria) (Table 1).[1,2,28, 29]

Prevalance of Hyperhomocysteinemia

The prevalence of hyperhomocysteinemia in the general population is between 5% and 10%, according to a threshold set at the 90th or 95th percentile (about 15 µmol/L). However, rates may be as high as 30%-40% in the elderly population.[29] Sazci et al has determined allelic frequencies of C677T and A1298C polymorphisms of the MTHFR gene around Turkey. The authors reported the frequency in Turkey of the C677T as 42.9%; of C677C, 47.4%; and of T677T, 9.6%. The frequency in Turkey of A1298C was 43.7%; of A1298A, 46.3%; and of C1298C, 10.0%. The allelic frequencies of the Tallele of MTHFR 677 and the C allele of MTHFR 1298 were 33.34 and 33.16%, respectively. The frequency of C677T/A1298C compound heterozygosity is highest in Turkey (21.6%), as compared to Canada (15%), the United States (17%) and The Netherlands (20%).[30]

Causes of Hyperhomocysteinemia

Age and Gender

Plasma homocysteine increases with age, and younger men normally have higher levels than women of the same age. In people around age 40, the gender difference is approximately 2 µmol/l and can be explained by the effect of estrogen in women because this difference disappears rapidly after menopause. The age-related increase in plasma homocysteine can be explained, at least in part, by the physiologic decline in renal function with age. Plasma homocysteine levels show an essentially linear increase up to age 60-65 but a much faster rise thereafter, increasing by approximately 10 percent or 1 µmol/l per decade.[1]

Genetic Factors

The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) irreversibly reduces 5,10 methylene-THF to 5-methyl-THF.[1] MTHFR activity is reduced by approximately 70% in affected individuals. Carriers of the mutation are therefore particularly sensitive to folate deficiency, experiencing an increase in plasma homocysteine by approximately 25% (or about 2.6 µmol/l). Carriers of CBS gene mutation show elevated homocysteine concentrations after oral methionine loading. Other mutations with a possible impact on homocysteine metabolism (MS, methionine synthase reductase (MSR)) are very rare, and their clinical significance is all but unexplored.[1,9]

Vitamin Deficiency

Vitamin deficiency is by far the leading cause of hyperhomocysteinemia, and it may be due to inadequate intake, reduced absorption from the gastrointestinal tract, increased consumption, and (drug) interactions. Individuals who do not eat a balanced diet (e.g., vegetarians, those on low incomes), elderly people, people with increased requirements (e.g. pregnant or breast feding women), patients with renal disease, malabsorption (inflammatory bowel disease) or malignant disease are at risk for clinically significant vitamin deficiency. In addition, alcohol abuse (poor dietary intake, reduced absorption or increased excretion by the kidney) and use of drugs affecting vitamin absorbtion and metabolism may lead to vitamin deficiency.[1,31] Mutations of the genes encoding the enzymes involved in homocysteine metabolism may also result in increased vitamin requirements. The best known example is the MTHFR C677T polymorphism.[2] Deficiencies of vitamin B12 and B6, folic acid, riboflavin are associated with elevated plasma homocysteine levels.[16] The effect of the C677T polymorphism can be reversed by additional folic acid intake.[32] Folate deficiency is the most common vitamin deficiency in Europe, partly because of a lack of fresh fruits and veges.[1]

As vitamin B12 acts as a cofactor for MS and is involved in folate metabolism, vitamin B12 deficiency may, even with adequate folate intake, lead to reduced remethylation as well as to hypomethylation. This results in elevated plasma homocysteine levels and functional folate deficiency, despite (seemingly) adequate plasma folic acid concentrations.[2] Vitamin B12 deficiency in elderly people is frequently due to inade-

Table 1: Classification of plasma homocysteine levels by need to treat[2]

Homocysteine level	Classification	Treatment
>12 to 30 µmol/l	Moderate hyperhomocysteinemia	Intervention required for all (apparently healthy individuals and patients)
10 to 12 µmol/l	Tolerable (in healthy subjects)	Need to treat patients at increased risk
<10 µmol/l	Safe	No need to treat (target level of intervention)

quate absorption resulting from an age related decrease in gastric acid secretion or a slight increase in (gastric) pH, or to intrinsic factor deficiency.[1]

Other causes of changes in plasma homocysteine

Numerous agents, drugs (theophylline, Nitrous Oxide (N2O), lipid lowering drugs, antifolates, postmenopausal hormone replacement therapy, oral contraceptives, antiepileptic drugs, antiestrogens), diseases ((hyper)proliferative conditions, thyroid disorders, renal impairment) and life style factors (smoking, coffee/caffeine; alcohol) have an impact on homocysteine metabolism, especially when acting as direct or indirect antagonists of cofactors and enzyme activities but also as a consequence of disulfide exchange reactions, impairment of absorption, and enzyme induction. Most of the resultant clinically significant changes may therefore be important to interpreting the overall clinical picture. Moreover, plasma homocysteine levels are a useful indicator of the efficiency of treatment.[1]

Treatment

Stanger et al recommend a target plasma homocysteine level of <10 μmol/l for patients with manifest vascular disease and high-risk individuals. Renal impairment and thyroid dysfunction as well as vitamin deficiency should be ruled out as the cause of hyperhomocysteinemia in individuals with plasma homocysteine levels >12 μmol/l.[1] Treatment of hyperhomocysteinemia subsumes methionine restricted diet, vitamin supplementation and medical/pharmacological therapy (low dose acetylsalicylic acid and heparin).

Methionine Restricted Diet

The aminoacids in most aminoacidopathies are essential, that is they can not be synthesized by the body and therefore must be provided in the diet. In some disorders, decreasing the substrate avalaible for the reaction, enhancing enzyme activity by supplying its cofactor supplementing the product to "normal" levels can be helpful and prevent or decrease the deleterious effects of the disorder. The two major principles of treatment are (1) to identify the missing or inactive enzyme, (2) to mitigate the effect of the altered gene by modifying components of diet to adjust the environment at the cellular level, and (3) to provide protein, energy, and nutrients. If sufficient energy is not provided in the diet, the body will use protein as an energy source to meet essential energy needs. When protein is used as an energy source, it is not avalaible for incorporation into protein containing substances such as muscle, enzymes, and hormones. Protein catabolism can have significant metabolic consequences. In homocysteinemia caused by MTHFR enzyme deficiency, methionine restricted diet and vitamin (folic acid, vitamin B2, B6 and B12) supplementation is advisable.[33]

Many epidemiological studies indicate that maternal undernutrition during pregnancy is associated with an increased risk of complex diseases in the offspring's adult life.[15] The process of DNA methylation is dependent on the methyl group donors and cofactors found in ingested food, which are involved in methionine and folate metabolism.[34,35] For humans, the major sources of methyl groups in foods come from methionine (~10 mmol of methyl/d), one-carbon metabolism via methylfolate (~5–10 mmol of methyl/d), and from choline [~30 mmoles methyl/d].[12] Analysis of the DNA from the fetuses of dams fed the methionine-imbalanced low-protein diets shows that in some tissues, particularly the fetal liver, the methylation of DNA increases.[34] Ingestion of large quantities of methionine is known to induce increased concentrations of circulating homocysteine. This is probably due to its production as an intermediate in the conversion of excess methionine to cysteine.[36] In a study, it is found that, in comparison with controls, patients with hyperhomocysteinemia, had higher total DNA hypomethylation and altered allelic expression of the sex-linked and imprinted genes. Nutritional therapy with 15 mg oral methyl-THF a day for 8 weeks reversed this effect.[15] Langley-Evans[37] found that maternal hyperhomocysteinaemia as a potential basis for altered patterns of DNA methylation in rat offspring exposed to a lowprotein diet in utero. It is reported that offspring of maternal low protein fed rat dams exhibit hypertension, disturbed glucose handling, impaired renal development and have a shorter lifespan.[37] Rees et al[34] stated that an excess of methionine or homocysteine is in some ways similar to a dietary folate deficiency. Clinical studies have revealed that folate deficiencies, either diet-induced or arising from polymorphisms in the genes encoding enzymes involved in the folate cycle, are associated with elevated concentrations of homocysteine, glycine, serine and threonine in the maternal plasma, and this is exacerbated by the methionine restricted diets.[21,36]

Intervention studies in humans have tested effects of high protein diets or pure methionine supplements.[10] Verhoef et al [10] showed that a protein-rich meal providing on average 2.4 g methionine produces a 24-h response in circulating tHcy concentration that is only about one-quarter of that produced by a similar amount of free methionine ingested with a low-protein meal. Methionine dosage of dietary intake is 30 mg/kg body weight and the dosage routinely used in methionine-loading tests is 100 mg/kg body weight. -a classical methionine-loading test, which was developed to diagnose subjects with enzymatic defects in the transsulfuration pathway.- A single, high, oral dose of free methionine forms an acute burden to the transsulfuration pathway, and any excess of intracellular homocysteine is exported to the blood, plasma tHcy concentrations increase 3-4 fold after ~6 hours.[10] Verhoef et al[5] reported that a high-protein diet increases tHcy concentrations throughout the day but does not increase fasting tHcy concentrations.

The tHcy response after dietary methionine is smaller and slower than that after a similar amount of free methionine.[10] In young adults ingesting a diet containing 1-1.5 g protein/kg/day, about 43% of the homocysteine pool was remethylated, and 57% was metabolized through the transsulfuration pathway (transmethylation=9.7, transulfuration=5.4, remethylation =4.4 µmol/kg/h).[16] The authors mentioned that, there are several possible explanations for this observation. First, it may be explained by an attenuating effect on the postmethionine tHcy response caused by serine and cystine present in the proteins. Second, the methionine from the protein-rich meal may be absorbed more slowly than free methionine, because time is needed to break down the proteins. Third, in contrast with free methionine, part of the methionine from the high-protein meal may be used for protein synthesis, because other amino acids necessary for protein synthesis were ingested at the same time. This may reduce the amount of methionine that was directed toward demethylation to homocysteine.[10] Despite that, in some of the intervention studies, which have been conducted on genetically healthy individuals, higher dietary protein intakes did not increase plasma concentrations of fasting tHcy.[5] Haulrik et al[6] reported that increasing dietary protein intake from 12% to 22% of total energy, with a corresponding increase in methionine intake, does not increase plasma homocysteine concentrations. These results can be interpreted in several ways. First, like rats, humans may adapt to increased methionine intakes by improved homocysteine catabolism, and hence tHcy is completely removed overnight. Second, a protein composition with a high ratio of serine to methionine or of cysteine to methionine may temper the postprandial tHcy rise and hence leave fasting tHcy unaffected. Third, the extra intake of B vitamins associated with high protein intakes may counterbalance the tHcy-raising effect of methionine.[5]

Deminice et al[38] demonstrated that a low-protein diet (8% protein) reduces plasma levels of Hcy in rats compared to a control diet (20% protein) and plasma Hcy levels are modulated by methionine intake as a reflection of protein intake. In other studies, it is confirmed that protein malnutrition promotes hyperhomocysteinemia in rats. Protein restriction impairs the development of the organism. It was observed that embryos collected from mothers fed a low-protein diet displayed reduced cell numbers within the inner cell mass and trophoectoderm lineages; this was induced by the slower rate of cellular proliferation. The development of particular organs was also abnormal. It was shown that reductions in the weight of the pancreas, spleen, muscle, and liver were greater than reductions in body weight, while the weight of the heart, kidney, and thymus decreased in proportion with body weight. A strong correlation was found between the nephron number and birth weight. A reduction in the nephron number was associated with an elevation in blood pressure and hypertension. Exposure of fetal rats to a low protein diet decreased b-cell

proliferation, islet size, and islet vascularization.[15] It is also reported that exposure to a low protein diet in fetal life modifies feeding behaviour in rats. Low-protein feeding throughout gestation promoted a preference for high-fat foods in the young adult offspring. The magnitude of these effects was found to vary between the sexes, with more pronounced differences in feeding behaviour among females.[39]

It is reported that there is also an increase in tHcy concentrations after consumption of the high-carbohydrate meals. This observation is explained by the low protein content of the high carbohydrate diet. Insulin effects seem less likely because increases in insulin evoked by raised serum glucose reduce expression of cystathionine synthase and hence reduce homocysteine breakdown.[5]

In the view of these researches, in patients with MTHFR gene polymorphism, methionine restricted diet may be helpful for the prophylaxis and treatment of hyperhomocysteinemia (Figure 2).
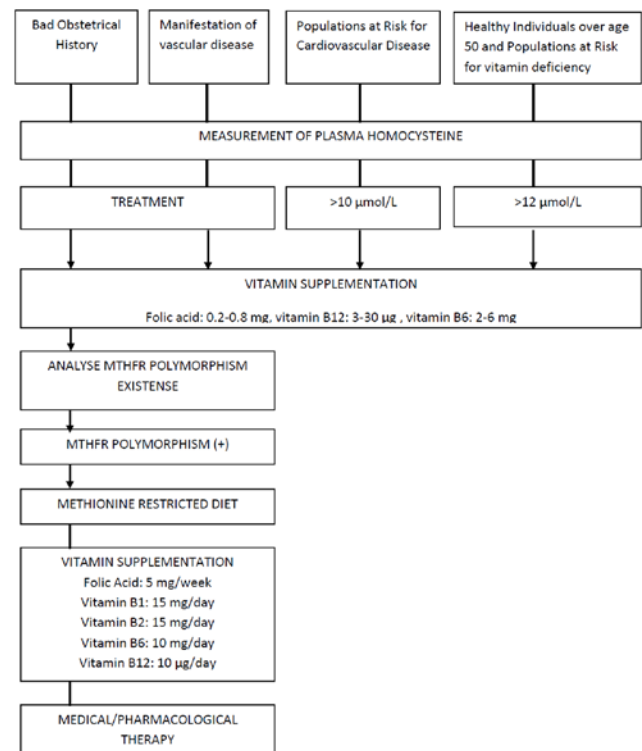

Figure 2: Decision tree for the diagnosis and prophylaxis/treatment of hyperhomocysteinemia (do not apply to patients with renal impairment) (inspired from "reference 2")

Methionine restricted diet should meet the energy and macronutrient requirements of the patients. Diet should be restricted for methionine according to the plasma total homocysteine level of the patient (9-15 mg/kg), but protein content of the diet should not be less than 10-11% of total energy requirement. Because of higher bioavailability of animal products compared with plant based food products, approximately

60% of dietary protein should come from animal derived sources. Methionine content of each food in the diet should be calculated using national nutritional data bases. An exchange list should be prepared for each patient to standardize the serving sizes of each group of foods according to methionine content. Especially, meat and meat products, poultry, seafood and dairy products should be limited. Since fat content of a food is inversely correlated with the methionine content, fatty foods such as full fat dairy products, buttocks of the poultry products, perch and salmon among seafood group, walnut and almond might be recommended. However, other health problems of the patient should also be considered.

Methionine restricted (MR) diet seems to be beneficial for the overall health of an organism. Several studies using rodent models report improved life expectancy by decreasing mitochondrial oxidative stress in addition to inducing.[40]

Vitamin Supplementation

The term "folate" is used as the generic descriptor for all derivatives of pteroic acid that demonstrate vitamin activity in humans. The structure of the parent folate compound, folic acid, comprises a bicyclic pterin moiety joined by a methylene bridge to p-aminobenzoic acid, which in turn is coupled via an α-peptide bond to a single molecule L-glutamic acid. Folic acid is not a common natural physiological form of the vitamin. In most natural foods, the pteridine ring is reduced to give either the 7,8-dihydrofolate (DHF) or 5,6,7,8,-THF. Polyglutamyl folate is an essential biochemical constituent of living cells, and most foods contribute some folateThe folates generally exist in nature bound to proteins and they are also bound to storage polysaccharides (various types of starch and glycogen)in foods.[23] Good dietary sources of folates include dried beans, eggs, green vegetables, orange juice, sweet corn, peas, peanut products, cereals, fruits, yeast, liver (with reservations) and fortified breakfast cereals.[1,23] However, up to 90 percent of folates may be lost during processing of cereals and other foods. Folates are also lost because folic acid is sensitive to heat, storage, and light. As the recommendation to eat a healthy diet has little or limited impact on elevated homocysteine levels, (folate)-fortified foods and/or vitamin supplements are rational and therefore recommended.[1,23] Maintaining a total folate intake of 600 to 650 µg/day, say, by supplementing 400 µg/day, may help lower elevated homocysteine levels; this is usually easy to achieve with fortified foods and/or vitamin supplements. The bioavailability of dietary folates is 55 percent. The extent of absorption of synthetic folic acid added to foods is 90 to 95 percent and that of folic acid in supplement tablets is almost 100 percent.[1] Supplementation with 0.2 to 5 mg of folic acid per day is expected to lower plasma homocysteine by 16 to 39 percent (the average reduction for a standardized baseline concentration of 12 µmol/l is approximately 25%). Body (folate) stores are quite limited. Vitamin supplementation therefore needs to be administered chronically. Once folate (+ vitamin B12+vitamin B6) supplementation is stopped, plasma homocysteine is bound to rise again. The toxicity of folic acid is extremely low even after prolonged use of high doses. Thus, 10 mg/day administered for 5 years has been tolerated without adverse reactions.[1,2]

Naturally occuring vitamin B12 originates solely from synthesis by bacteria and other microorganisms growing in soil or water, in sewage, and in the rumen and intestinal tract of animals.[23] As vitamin B12 can only be synthesized by bacteria, animal foods (fish, meat, eggs, dairy products) are the only good sources of vitamin B12.[1] Unlike folate, vitamin B12 is a relatively stable vitamin and almost all of it is left intact by food processing.[1] Vitamin B12 is non-toxic, even in doses that exceed the minimal daily adult human requirement by 10000 times. Vitamin B12 is not broken down within the body. Ingested amounts that exceed the limited binding capacity in plasma and tissues are excreted unchanged in the urine and faeces.[23]

Meat, dairy products, wholemeal cereals, potatoes, fruits, and vegetables are particularly rich in vitamin B6. Vitamin B6 shows greater stability than folic acid during storage and cooking.[1]

Vitamin supplementation continues to be a recommendable option for prophylaxis. Dosages for low-dose supplementation of folic acid is 0.2 to 0.8 mg/day; for vitamin B12, 3 to 100 µg/day; vitamin B6, 2 to 25 mg/day). Also, everybody is recommended to eat a diet rich in vitamins.[1]

If plasma homocysteine determination suggests moderate hyperhomocysteinemia, a repeat measurement after 4 to 6 weeks may be useful to confirm the diagnosis. Once (moderate) hyperhomocysteinemia is established, vitamin supplementation should be started, supplementing 0.2 to 0.8 mg of folic acid, 3 to 100 µg of vitamin B12 (elderly people should receive at least 100 µg because of malabsorption), and ideally also 2 to 25 mg of vitamin B6. If this supplementation regimen lowers plasma homocysteine to <10 µmol/l within 4 weeks, repeat measurements of plasma homocysteine should be obtained first every 6 months and later on once a year. If response (i.e., plasma homocysteine reduction) is still inadequate, the dosage of folic acid should be increased to, say, 1 to 5 mg of folicacid per day (while supplementation with vitamin B12 and vitamin B6 can be continued unchanged for some time). Repeat determinations of plasma homocysteine should be performed at 4-week intervals.[2]

Conclusion

Methionine, an essential sulfur-containing amino acid and

the sole precursor of homocysteine, a sulfur-containing non-proteinogenic amino acid, is mainly ingested in animal-derived foods. There are three pathways in the metabolism of methionine and homocysteine; transmethylation, remethylation (either folate dependent or independent) and transsulphuration pathways. Vitamin B2, B6, B12 AND folic acid are important micronutrients in these metabolic pathways. Deficiencies of these vitamins are associated with elevated plasma homocysteine levels. Plasma total homocysteine level of >10 µmol/l in pregnant individuals and >12 µmol/l in non-pregnant individuals is considered as elevated plasma homocysteine level. Elevated levels of homocysteine can result from several mutations in the MTHFR gene and have been identified as risk factors for thrombosis. Treatment of hyperhomocysteinemia, observed in MTHFR mutation, subsumes methionine restricted diet, vitamin supplementation (vitamin B1, B2, B6, B12, folic acid) and medical/pharmacological therapy (low dose acetylsalicylic acid and heparin). In patients with a MTHFR polymorphism, methionine content of the diet should be restricted for preventing the patient from hazardous effects of elevated plasma homocysteine level, even in pregnancy.

Metioninden Fakir Diyet: Klinik Uygulama

Metilentetrahidrofolat Redüktaz (MTHFR) gen polimorfizmlerinde gözlenen hiperhomosisteineminin beslenme tedavisini derlemektir.

Konuyla ilgili araştırma ve derleme makaleleri okunmuş, incelenmiş, derlenmiş ve klinik tecrübelerimizle birleştirilmiştir.

Metilentetrahidrofolat Redüktaz gen polimorfizminin tedavisinde beslenme tedavisi tedavinin yapıtaşlarındandır ve metioninden fakir diyet vitamin suplementasyonu ile desteklenmelidir.

Metioninden fakir diyetin, MTHFR gen polimorfizmi olan hastaların serum/plazma total homosistein düzeyleri üzerine olumlu etkisi olabilir.

Anahtar Kelimeler: Metionin, Homosistein, Metilentetrahidrofolat redüktaz, Metioninden fakir diyet

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