Importance of Folic acid in Biological System

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ABTRACT

Folic acid is crucial for proper brain function and plays an important role in mental and emotional health. It aids in the production of DNA and RNA, the body's genetic material, and is especially important when cells and tissues are growing rapidly, such as in infancy, adolescence, and pregnancy. Pregnant women need more folic acid to lower the risk of neural tube birth defects, including cleft palate, spina bifida, and brain damage. There is evidence that getting enough folic acid in your diet can reduce your risk of heart disease as it helps lower homocysteine levels. One study suggests that folic acid supplements help slow the progression of age-related hearing loss in elderly people with high homocysteine levels and low folate in their diet. Some studies show that people with depression have low folate levels in their bodies. Folic acid in the diet seems to protect against the development of some forms of cancer, particularly cancer of the colon, as well as breast, cervical, pancreatic, and stomach. Possible Interactions If currently being treated with various medications should not use folic acid supplements without first talking to your health care provider. These are like Tetracyclines,methotrexate,daraprim etc.Keeping all these things in mind a possible chart was lined.

Key words *: Folate, NTD, homocysteine, myocardial infarction*

Folate is the commonly used group name for folic acid (pteroyl glutamic acid, or PGA) and its derivatives with similar activity. In foods and in the body folates are usually in the reduced form (tetrahydrofolate, or THF) and conjugated with up to seven glutamate residues and one of several types of one-carbon groups. PGA is used in supplements and for food fortification as it is more stable than the other derivatives.

Folate functions as a coenzyme in single-carbon transfers in the metabolism of nucleotides and amino acids. It is essential for the formation of thymidylate (TMP) for DNA synthesis, so that without folate, living cells cannot divide. The need for folate is higher when cell turnover is increased, such as in foetal development. It is also involved in purine synthesis, in the generation of formate and in amino acid interconversions. Homocysteine is methylated by methyl-THF to produce methionine, which is in turn used for the synthesis of S-adenosyl-methionine an important methylating agent in vivo (Wagner 1996).

Food folates are hydrolysed to monoglutamate forms in the gut to allow their absorption across the intestine. The monoglutamates enter the portal circulation and are metabolised to polyglutamate derivatives in the liver. They are either retained, or released to the blood as reconverted monoglutamates or to bile. The liver contains about 50% of the body stores of folate.

Folate is a substrate and vitamin B12 is a coenzyme for the formation of MTHF that depends on the regeneration of THF, the parent compound in the homocysteine-to-methionine conversion. If either folate or vitamin B12 is deficient, megaloblastic changes occur in bone marrow and other replicating cells from lack of 5,10-MTHF for DNA synthesis.

The bulk of excretion products are folate cleavage products. Intact urinary folate accounts for only a small percentage of dietary folate. Biliary excretion of folate can be as high as 100 µg/day (Herbert & Das 1993, Whitehead 1986), however much of this is reabsorbed.

Folate is difficult to measure in foods because it is present in different forms, so food databases can be inaccurate. However, the main sources of folate are cereals, cereal products and dishes based on cereals (about 27%) and vegetables and legumes (about 29%). Fruit provides about 8-10%. Orange juice is contributing a greater amount than in the past due to the recent introduction of fortification with

Also, certain medications may lower levels of folic acid in the body. Folic acid deficiency can cause poor growth, tongue inflammation, gingivitis, and loss of appetite, shortness of breath, diarrhea, irritability, forgetfulness, and mental sluggishness. Pregnant women need more folic acid to lower the risk of neural tube birth defects, including cleft palate, spina bifida, and brain damage. Neural tube defects are birth defects caused by abnormal development of the neural tube; a structure that eventually gives rise to the brain and spinal cord.

Bioavailability Folic acid as a supplement is almost 100% bioavailable on an empty stomach. Picciano et al (2004) have recently demonstrated that the inclusion of cows' milk in the diet enhances the bioavailability of food folate. Some controlled studies to assess requirements have used a defined diet containing food folate and supplemented with folic acid, so the term dietary folate equivalents (DFE) has been used to accommodate the varying bioavailabilities.

1 µg dietary folate equivalent (DFE) = 1 µg food folate = 0.5 µg folic acid on an empty stomach = 0.6 µg folic acid with meals or as fortified foods

Inadequate folate intake leads to decreased serum folate, then decreased erythrocyte folate, a rise in homocysteine and megaloblastic changes in bone marrow and other rapidly dividing tissues (Eichner & Hillman 1971). As depletion progresses, macrocytic cells are produced and macrocytic anaemia develops. Eventually, full-blown anaemia results in weakness, fatigue, irritability and palpitations. Folic acid supplementation in pregnancy can reduce both the occurrence and recurrence of neural tube defects in the newborn (Bower & Stanley 1989, CDC 1992, Czeizel & Dudas 1992, Kirke et al 1993, Laurence et al 1981, Wald et al 1991).

Indicators of folate requirement include erythrocyte, serum or urinary folate, plasma homocysteine and haematological status measures as well as clinical endpoints such as neural tube defects or chronic degenerative disease. Of these, erythrocyte folate is generally regarded as the primary indicator as it reflects tissue folate stores. For some age groups, erythrocyte folate is used in conjunction with plasma homocysteine and plasma or serum folate.

Birth Defects

As mentioned, pregnant women who don’t get enough folic acid are more likely to have children with birth defects. Pregnant women should get 600 mcg of folic acid per day. Women who plan to become pregnant should make sure to get the recommended 400 mcg per day, since many neural tube defects can happen shortly after conception, before a woman even knows she is pregnant. Prenatal vitamins contain the needed amount of folic acid for pregnant women.

Studies show that women who take folic acid supplements before conception and during the first trimester may reduce their risk of having children with neural tube defects by 72 - 100%.

Folic acid may also help prevent miscarriage, although the evidence isn't clear.

Heart Disease

Folate may help protect the heart through several methods.Also, many studies suggest that people with high levels of the amino acid homocysteine are roughly 1.7 times more likely to develop coronary artery disease and 2.5 times

more likely to have a stroke than those with normal levels. B complex vitamins -- especially vitamins B9, B6, and B12 -- help lower homocysteine levels. For most people who are concerned about heart disease, the goal should be getting enough B vitamins from healthy foods

Age-related Hearing Loss
One study suggests that folic acid supplements help slow the progression of age-related hearing loss in elderly people with high homocysteine levels and low folate in their diet.

Age-Related Macular Degeneration
One large study found that women who took 2,500 mcg of folic acid along with 500 mg of vitamin B6 and 1,000 mcg of cyanocobalamin (vitamin B12) daily reduced their risk of developing AMD, an eye disease that can cause loss of vision.

Depression
The evidence about whether folic acid can help relieve depression is mixed. Some studies show that 15 - 38% of people with depression have low folate levels in their bodies, and those with very low levels tend to be the most depressed. And one study found that people who did not get better when taking antidepressants had low levels of folic acid. One double-blind, placebo-controlled study found that taking 500 mcg of folic acid daily helped the antidepressant Prozac work better in women.

Cancer
Folic acid in the diet seems to protect against the development of some forms of cancer, particularly cancer of the colon, as well as breast, cervical, pancreatic, and stomach. However, researchers don't know exactly how folate might help prevent cancer. Some think that folic acid keeps DNA healthy and prevents mutations that can lead to cancer. The best course of action is to make sure a balanced diet with enough folate, which will help protect you against a number of diseases.
Low dietary intake of folate may increase the risk of developing breast cancer, particularly for women who drink alcohol. Regular use of alcohol -- more than 1 ½ to 2 glasses per day -- is associated with higher risk of breast cancer. One large study, involving over 50,000 women who were followed over time, suggests that adequate intake of folate may reduce the risk of breast cancer associated with alcohol.

Dietary Sources
Rich sources of folate include spinach, dark leafy greens, asparagus, turnip, beets, and mustard greens, Brussels sprouts, lima beans, soybeans, beef liver, brewer's yeast, root vegetables, whole grains, wheat germ, bulgur wheat, kidney beans, white beans, lima beans, mung beans, salmon, orange juice, avocado, and milk.

Available Forms
Vitamin B9 is found in multivitamins,. It is a good to take folic acid as part of or along with a multivitamin because other B vitamins are needed for it to work. It is available in a variety of forms.

How to Take It
Most people (except pregnant women) should be able to get enough folic acid from their diet.
Daily recommendations for dietary folic acid are listed below:

Pediatric
- Infants 0 - 6 months: 65 mcg (adequate intake)
- Infants 7 - 12 months: 80 mcg (adequate intake)
- Children 1 - 3 years: 150 mcg (RDA)
- Children 4 - 8 years: 200 mcg (RDA)
- Children 9 - 13 years: 300 mcg (RDA)
- Teens 14 - 18 years: 400 mcg (RDA)

Adult

- 19 years and older: 400 mcg (RDA)
- Pregnant women: 600 mcg (RDA)
- Breastfeeding women: 500 mcg (RDA)

Amounts used in studies for heart disease range from 400 - 1,200 mcg. However, high levels of folate can hide a vitamin B12 deficiency, and should be taken only under a health care provider's supervision..

Precautions

At the recommended daily allowance, side effects from folic acid are rare. Very high doses can cause stomach problems, sleep problems, skin reactions, and seizures.

Folic acid can hide the symptoms of an underlying vitamin B12 deficiency, which can cause permanent damage to the nervous system. Taking any one of the B vitamins for a long period of time can result in an imbalance of other important B vitamins. So it is advised to take a B complex vitamin, which includes all the B vitamins.

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Neural tube defects

It is now agreed that a supplement of 400 µg of folic acid taken near the time of conception will prevent most neural tube defects. The recurrence can be avoided in women with a previous NTD birth by taking folic acid 4.0 mg/day because of the high increase in risk in such cases and because that was the amount used in the most definitive trial.Because of the poorer bio-availability and stability of food folate, a diet based on food folate will not be optimum in prevention. One study determined that risk of NTD is 10-fold higher in people with poor folate status than in those with high normal folate status.A further study suggests that an extra 200 mg/day or possibly 100 µg/day if taken habitually in fortified food would prevent most.. This amount could avoid pernicious anaemia in the elderly.. It is suggested that this amount, although not optimal, will prevent most NTDs.

Cardiovascular disease

Plasma homo-cysteine concentration, if only moderately elevated, is an independent risk factor for cardiovascular disease and stroke . Increased risk was associated with values higher than 11 mmol/l , which is well within what is the normal range (5-15 mmol/l) of plasma homo-cysteine levels.Plasma homo-cysteine could be lowered by an extra 100 or 200 µg/day of folic acid.

Colorectal cancer

Evidence suggests a link between colorectal cancer and dietary folate intake and folate status . One study reported that women who take multivitamin supplements containing folic acid for prolonged periods have a significantly reduced risk of colorectal cancer However, the scientific evidence is not sufficiently clear for recommending increased folate intake in populations at risk for colorectal cancer. The main concern is the masking of the diagnosis of pernicious anaemia, because high levels of folic acid correct the anaemia, Consumption of large amounts of folic acid might also pose other less well-defined risks.Savage and Lindenbaum suggest that even at levels of the RNI there is a decreased opportunity to diagnose pernicious anaemia through its presentation via the anaemia.

Possible Interactions

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Antibiotics, Tetracycline -- Folic acid should not be taken at the same time as the antibiotic tetracycline because it interferes with the absorption and effectiveness of this medication. Folic acid either alone or in combination with other B vitamins should be taken at different times from tetracycline. All vitamin B complex supplements act in this way and should be taken at different times from tetracycline.

Phenytoin (Dilantin) -- Phenytoin, an anti-seizure medication, may lower levels of folate in the body.

Pyrimethamine (Daraprim) -- Folic acid may make pyrimethamine, a drug used to prevent and treat malaria and to treat toxoplasmosis, less effective.

Chemotherapy medications -- Folic acid may raise the amounts of 5-fluorouracil and capecitabine (Xeloda) to dangerous levels in the body.

Drugs That Lower Levels of Folic Acid -- These drugs may interfere with the body's absorption of folate, and may mean you need to take a folic acid supplement. Talk to your doctor first.

- Antacids
- H2 blockers -- used to reduce stomach acid; include cimetidine (Tagamet), famotidine (Pepcid), ranitidine (Zantac)
- Proton pump inhibitors -- used to reduce stomach acid; include someprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), rabeprazole (Aciphex)
- Bile acid sequestrants -- used to lower cholesterol; include colestipol (Colestid), cholestyramine (Questran), and colsevelam (Welchol)
- Anti-seizure medications -- including phenobarbital, primidone (Mysoline), carbamazepine (Tegretol)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) -- include ibuprofen (Advil, Motrin) and naproxed (Aleve)
- Sulfasalazine (Azulfidine) -- used to treat inflammatory bowel disease and rheumatoid arthritis
- Triamterene (Dyrenium) -- a diuretic (water pill)
- Cycloserine -- an antibiotic
- Pyrimethamine (Daraprim) -- used to prevent and treat malaria and to treat toxoplasmosis
- Trimethoprim -- an antibiotic used to treat urinary tract infections

When taken for long periods of time, these medications, as well as other anti-inflammatory medicines, can increase the body's need for folic acid.

Methotrexate -- Methotrexate, a medication used to treat cancer, rheumatoid arthritis (RA), and psoriasis, reduces the amount of folic acid needed in the body. If methotrexate is being taken for RA or psoriasis, higher dose of folic acid is,reduces the side effects of methotrexate. People taking methotrexate for cancer, however, should not take folic acid .This may interfere with methotrexate's effects on cancer.

Diagnosis and Tests

If deficiency is suspected, it is wise to get a blood folate level test as well as a B12 level before treatment with supplements. A red-blood-cell folate level may more accurately reflect body stores of folic acid.

Treatment and Prevention

Folic acid supplements are usually prescribed, and self-care includes avoiding:

Complications

Folic acid-deficiency anemia is not correctable with iron and, as it progresses, it will appear very different from iron-deficiency anemia. The blood will show large, irregular red blood cells, while low iron causes small red blood cells. In pregnancy, this megaloblastic anemia is of great concern. Folic acid deficiency is very common during pregnancy, when the requirements are at least double those for the nonpregnant state. Since folic acid stores in the liver can last several months, deficiency symptoms are more likely in later pregnancy. The fetus can readily draw on the folic acid of the mother, and deficiencies can cause problems in both. The mother's folacin-deficiency mental symptoms of indifference, lack of motivation, withdrawal, or depression may be passed over as hormonal. Serious problems can result from a major deficiency. Toxemia of pregnancy, premature birth, and hemorrhage are all possible in addition to the anemia of the mother. The fetus could develop birth deformities, brain damage, or show poor growth as a child. It is very important to supplement folic acid during pregnancy.

More recently, folid acid deficiency (along with vitamin A deficiency) has been associated withncervical dysplasia and cancer.

Severe deficiencies can result in congestive heart failure.

Role of folate and folic acid in human metabolic processes

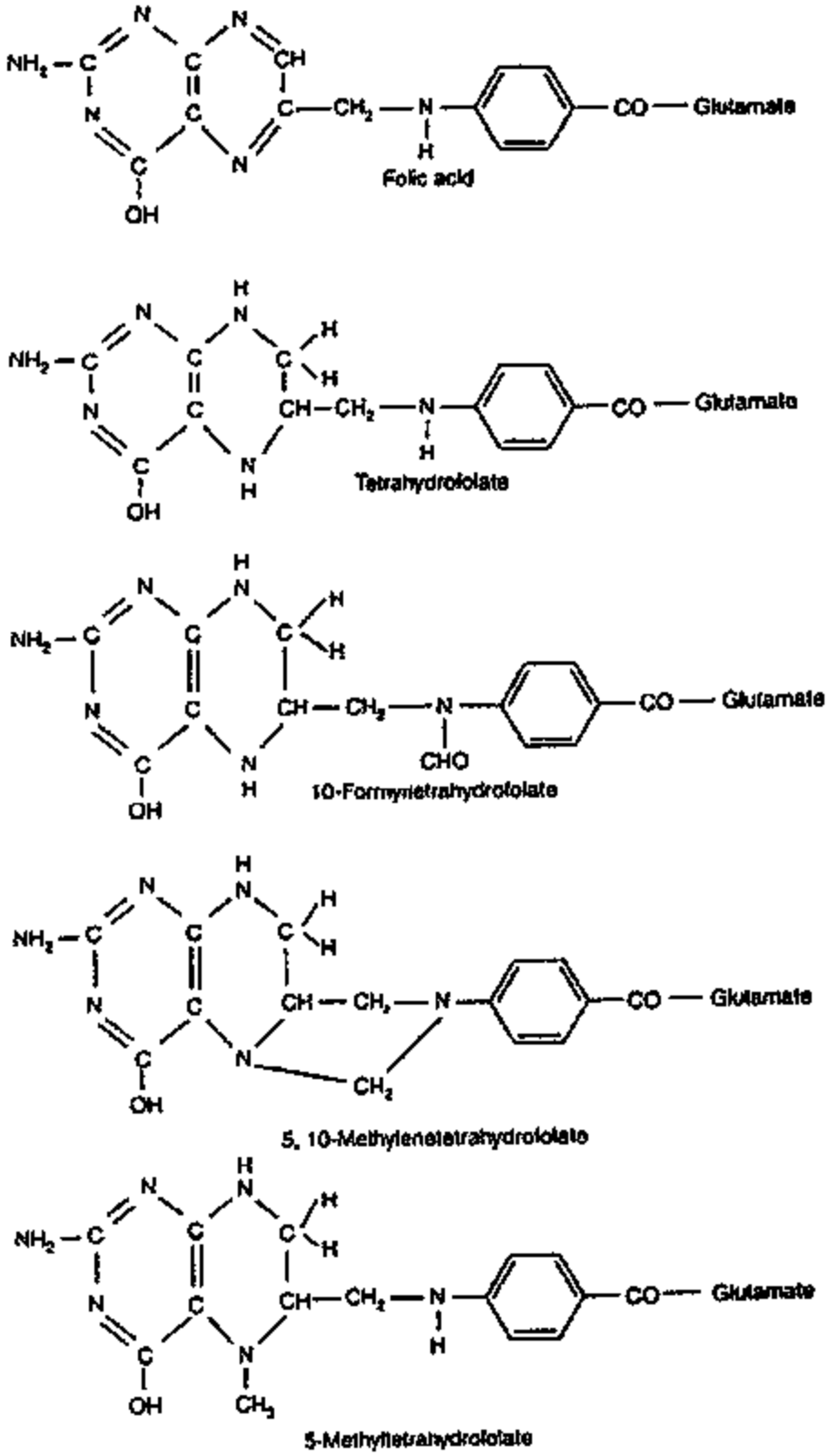
Folates accept one-carbon units from donor molecules and passes them on via various biosynthetic reactions. In their reduced form cellular folates function conjugated to a polyglutamate chain. These folates are a mixture of unsubstituted polyglutamyl tetrahydrofolates and various substituted one-carbon forms of tetrahydrofolate (e.g., 10-formyl, 5,10-methylene, and 5-methyl).The reduced forms of the vitamin, particularly the unsubstituted dihydro and tetrahydro forms, are unstable chemically. They are easily split between the C-9 and N-10 bond to yield a substituted pteridine and *p*-aminobenzoylglutamate, which have no biologic activity . Substituting a carbon group at N-5 or N-10 decreases the tendency of the molecule to split; however, the substituted forms are also susceptible to oxidative chemical rearrangements and, consequently, loss of activity. The folates found in food consist of a mixture of reduced folate polyglutamates.

Although natural folates rapidly lose activity in foods over periods of days or weeks, folic acid (e.g., in fortified foods) is almost completely stable for months or even years. The chemical lability of all naturally occurring folates results in a significant loss of biochemical activity during harvesting, storage, processing, and preparation. Half or even three-quarters of initial folate activity may be lost during these processes. This is in contrast to the stability of the synthetic form of this vitamin, folic acid . In this form the pteridine (2-amino-4-hydroxypteridine) ring is not reduced , rendering it very resistant to chemical oxidation. However, folic acid is reduced in cells by the enzyme dihydrofolate reductase to the di- and tetrahydro forms.This takes place within the intestinal mucosal cells, and 5-methyltetrahydrofolate is released into the plasma.

Natural folates found in foods are all conjugated to a polyglutamyl chain containing different numbers of glutamic acids depending on the type of food. This polyglutamyl chain is removed in the brush border of the mucosal cells by the enzyme folate conjugase, and folate monoglutamate is subsequently absorbed.The primary form of folate entering human circulation from the intestinal cells is 5-methyltetrahydrofolate monoglutamate. This process is, however, limited in capacity. If enough folic acid is given orally, unaltered folic acid appears in the circulation , is taken up by cells, and is reduced by dihydrofolate reductase to tetrahydrofolate

The bio-availability of natural folates is affected by the removal of the polyglutamate chain by the intestinal conjugase. This process reduces the bio-availability of natural folates by as much as 25-50 percent. In contrast, synthetic folic acid appears to have a bio-availability of close to 100 percent . The low bio-availability and - more importantly - the poor chemical stability of the natural folates has a profound influence on the development of nutrient recommendations. This is particularly true if some of the dietary intake is in the synthetic form, folic acid, which is much more stable and bio-available. Food fortification of breakfast cereals, flour, etc. can add significant amounts of folic acid to the diet.

Functional folates have one-carbon groups derived from several metabolic precursors (e.g., serine, *N*-formino-L-glutamate, folate, etc.). With 10-formyltetrahydrofolate the formyl group is incorporated sequentially into C-2 and C-8 of the purine ring during its biosynthesis. Likewise the conversion of deoxyuridylate (a precursor to RNA) into thymidylate (a precursor to DNA) is catalysed by thymidylate synthase, which requires 5,10-methylenetetrahydrofofate.



Alternatively 5,10-methylenetetrahydrofolate can be channelled to the methylation cycle. This cycle has two functions. It ensures that the cell always has an adequate supply of *S*-adenosylmethionine, an activated form of

methionine, which acts as a methyl donor to a wide range of methyltransferases. These enzymes methylate a wide range of substrates including lipids, hormones, DNA, proteins, etc. One such important methylation is that of myelin basic protein, which acts as insulation for nerves cells. When the methylation cycle is interrupted as it is during vitamin B_{12} deficiency, one of the clinical consequences is the demyelination of nerve resulting in a neuropathy which leads to ataxia, paralysis, and, if untreated, ultimately death. Other important methyltransferase enzymes down-regulate DNA and suppress cell division.

In the liver the methylation cycle also serves to degrade methionine. Methionine is an essential amino acid in Humans and is present in the diet of people in developed countries at about 60 percent over that required for protein synthesis and other uses. The excess methionine is degraded via the methylation cycle to homo-cysteine, which can either be catabolised to sulfate and pyruvate (with the latter being used for energy) or remethylated to methionine. The need to maintain intracellular *S*-adenosylmethionine levels is related to the amount of methionine metabolised via homo-cysteine.

The DNA and methylation cycles both regenerate tetrahydrofolate. However, there is a considerable amount of catabolism of folate and a small loss of folate via excretion from the urine, skin, and bile. There is a need to replenish the body's folate content by uptake from the diet. If there is inadequate dietary folate, the activity of both the DNA and the methylation cycles will be reduced. A decrease in the former will reduce DNA biosynthesis and thereby reduce cell division. Although this will be seen in all dividing cells, the deficiency will be most obvious in cells that are rapidly dividing, for example, in a decrease in red cell production, producing anaemia. Other cells derived from bone marrow also decrease, leading to leucopenia and thrombocytopenia. Likewise there is a reduction in cell division in the lining of the gut. Taken together, this reduction in the DNA cycle results in an increased susceptibility to infection, a decrease in blood coagulation, and secondary malabsorption. In folate deficiency, the flux through the methylation cycle is decreased but the DNA cycle may be more sensitive. The most obvious expression of the decrease in the methylation cycle is an elevation in plasma homo-cysteine. This is due to a decreased availability of new methyl groups provided as 5-methyltetrahydrofolate, necessary for the remethylation of plasma homo-cysteine. Previously it was believed that a rise in plasma homo-cysteine was nothing more than a biochemical marker of possible folate deficiency. However, there is increasing evidence that elevations in plasma homo-cysteine are implicated in the aetiology of cardiovascular disease.This moderate elevation of plasma homo-cysteine occurs in subjects with a folate status previously considered adequate..

Interruption of the methylation cycle resulting from impaired folate status or deceased vitamin B_{12} or vitamin B_6 status may have serious long-term risks. Such interruption, as seen in vitamin B_{12} deficiency (e.g., pernicious anaemia), causes a very characteristic demyelination and neuropathy known as subacute combined degeneration of the spinal cord and peripheral nerves. If untreated, this leads to ataxia, paralysis, and ultimately death. Such neuropathy is not usually associated with folate deficiency but is seen if folate deficiency is very severe and prolonged.The explanation may lie in the well-established ability of nerve tissue to concentrate folate to a level of about five times that in the plasma. This may ensure that nerve tissue has an adequate level of folate when folate being provided to the rapidly dividing cells of the marrow has been severely compromised for a prolonged period. The resultant anaemia will thus inevitably present clinically earlier than the neuropathy.

Delineation of dietary sources

Although folate is found in a wide variety of foods, it is present in a relatively low density except in liver. Diets that contain adequate amounts of fresh green vegetables (i.e., in excess of three servings per day) will be good folate sources. Folate losses during harvesting, storage, distribution, and cooking can be considerable. Likewise, folate derived from animal products is subject to loss during cooking. Some staples, such as white rice and unfortified corn, are low in folate. It may be necessary to consider fortification of foods or selected supplementation of women of child-bearing years

In view of the increased requirement for folate during pregnancy and lactation and by select population groups and in view of its low bio-availability,.

Future research

There are many areas for future research:

- Folate status may be related to birth weight. Therefore it is important to study the relationship between folate status and birth weight, especially in populations where low birth weight is prevalent.
- Folate status probably differs widely in different developing countries. Red cell folate levels are an excellent determinant of status. Such estimates in representative populations would determine whether some communities are at risk from poor folate status.
- Some evidence indicates that elevated plasma homo-cysteine is a risk factor for cardiovascular disease and stroke. Elevated plasma homo-cysteine is largely related to poor folate status, with poor vitamin B_6 status, poor vitamin B_{12}status, or both also contributing. There are also genetic differences.The prevalence of elevated plasma homo-cysteine and its relationship to cardiovascular disease should be established in different developing countries.
- More data should be generated on the bio-availability of natural folate from diets consumed in developing countries.
- Because the absorption of folate may be more efficient in humans with folate deficiency, folate absorption in these populations requires additional research.
- The relationship between folate deficiency and the incidence of NTDs in developing countries needs further investigation.
- Quantitation of the folate content of foods typically consumed in developing countries should be established for the different regions of the world.

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