



A REVIEW ON IMPACT OF FOOD FOLATE, THEIR BIOLOGICAL ROLES AND DEFICIENCY DISEASES

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Abstract

Folate is the common name for water soluble vitamin B₉, chemically referred to pteroylglutamic acid is heat-sensitive that increases the likelihood of losses that depends further on the type of activity it undergoes along with certain factors that affect it. Folate plays an important biological role by either accepting or contributing one carbon unit to perform essential metabolic functions as a coenzyme and in DNA synthesis. Inadequate intake of folic acid may also cause depression, immune reaction impairment, and nerve damage, DNA replication interference, and thus all division of cells. Hence, it would be the most folate deficiency evident in cells where cell multiplication occurs most, the result is association with major illness as megaloblastic anaemia, incidence of NTDs, certain types of cancer and minor illnesses are Alzheimer's disease, vascular disease. The initial interest in folate has been in the prevention of neural tube defects (NTDs) from occurring. The question of whether the higher concentrations of folate in large sections of the population that occur after fortification can cause harm needs much further research, as does the question of whether the presence of unmetabolized folic acid in the blood will interfere with folate-dependent metabolism. Further investigation is needed to find the connection between the occurrence of NTDs in developing countries and folate deficiency. For the different regions of the world, quantification of food's folate content traditionally eaten or among commonly consumed food should be estimated especially in developing countries where the prevalence of maternal mortality is higher.

Introduction

Folic acid is one of the most nutritionally significant B vitamin with active carbon transfer reactions in many metabolic pathways, such as biosynthesis of purine and pyrimidine and interconversion of amino acids, in particular. Since insufficiency of folate was associated to the occurrence of developing embryo neural tube defects (Daly et al 1995). A low intake of folate was also linked to a variety of health problems including Alzheimer's and heart disease; osteoporosis; increased breast and colorectal cancer risk; impaired cognitive output; hearing loss, etc, were attributed Folate insufficiency (Mason 1995; Morrison et al. 1995; Boushey et al. 1996; Ames 1999). Thus, an exogenous amount of folic acid is needed to avoid nutritional deficiencies, as human mammalian cells are not able to synthesize this essential vitamin (Duttgupta and Sarma 1995).

Reducing risk neural tube abnormalities (birth defects) which is brain and/or spinal cord affecting while pregnant is important, also needed to be normal fetal growth and development (Rahman *et al.*, 2015). Folate is associated with production and maintenance of new cells, and particularly in demand for growth of cells during pregnancy and infancy. Intake of folate is also necessary to prevent cognitive decline in old age, and may increase academic performance among young learners. The main function of folate is to work as a co-enzyme where it either donate or accept 1-carbon unit essential for cellular reactions like; purine and pyrimidine synthesis, basic DNA constituents, de novo methionine biosynthesis and glycine-serine interconversion (Ball, 1998), therefore any deficiency of this vitamin can result in interference. It helps in methionine synthesis; this deficiency leads to a high level of blood homocysteine, which studies have shown to be a cardiovascular disease hazard factor (Raul et al., 2005). Folate is soluble in water, and losses can occur during processing and heating (Dang *et al.*, 2000. Landen and Eittenmiller, 1999). Fe³⁺ along with high levels of dissolved

oxygen and food additives minimize folate stability (Eittenmiller et Landen, 1999). Folate losses also occur during storage and depend on several factors.

Also the possibility of various types of cancer (for example prostate, breast) rises when there is insufficient intake of folic acid (Kim, 1999). Inadequate intake of folic acid may also cause depression, immune reaction impairment, and nerve damage (Rahman et al., 2015). The Folate deficiency therefore is the most apparent in cells where the majorities of the cell's proliferation happens, and hence relate to megaloblastic anaemia as major illness and minor illnesses are Alzheimer's disease, vascular disease (Raul et al., 2005; Ho et al., 2003; Steegers-Theunissen, 1995; Giovannucci et al., 1995). The initial interest in folate has been in the prevention of neural tube defects (NTDs) from occurring (Molloy, 2005). Therefore, everyday folate intake is important.

The Folate discovery

Folate's healing effect was first observed from prepared yeast extract (Ball, 1998) in 1931 a research group headed by Willis extract substances that had similar effects on anaemia were defined as *lactobacillus casei* a growth factor. An investigation conducted by Mitchell in 1941 isolated it from spinach called the folic acid (meaning leaf in the latin word folium). In 1946 a research group headed by Angier finally elucidated the structure of folic acid (Ball, 1998).

Folate structure and chemistry

Folate is the common name for water soluble vitamin B₉. Therefore it is not retained inside the body and must be taken through dietary sources. The parent structure (Fig. 1), also chemically referred to the acid pteroylglutamic, consists a bicyclic pterin, with three parts bound by Bridge of methylene to para-aminobenzoic acid (PABA), connected to a L-glutamic acid molecule (Forssen, 2000). Tetrahydrofolate (H₄

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folate), 5-methyltetrahydrofolate (5-CH₃-H₄ folate), 5-formyltetrahydrofolate (5-CHO-H₄ folate), and 10-formyltetrahydrofolate (10-CHO-H₄ folate) are the most common forms of folate in foods (Koontz et al. 2005). Natural food sources are mainly consisting of 5-methyl THF and most of remainder is 10-formyls (The Vitamins and Minerals Expert Team, 2002). Only monoglutamates are present in the blood as plasma contains enzyme conjugase responsible for hydrolysing the polyglutamates folate to monoglutamates folate (Ball, 1998).

The folate is pale yellow to orange-yellow in color, less stable in acidic solution but more in alkaline. It is nearly water insoluble and also in alcohol, chloroform, acetone and ether but soluble in hydrochloric acid and sulphuric acid (The Vitamins and Minerals Expert Team, 2002). Food items with folate content > 100 µg per serving are considered as rich sources, 50-100 µg folate content as moderate source and 15-50 µg as poor source of folate. The richest sources of folate includes vegetables mainly green leafy vegetables and also cereals & products, liver, wheat germ, beans, yeast, egg yolk, yeast extract, etc (Shrestha and Arcot, 2005; Jagerstad and Witthoft, 2004; The Vitamins and Minerals Expert Team, 2002). According to daily recommended allowances (RDA), 2010 rda of folate for adults is 200 µg, 500 µg for pregnant women and for lactating women is 300 µg respectively (ICMR RDA, 2010).

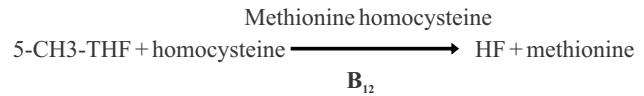
Folate Stability

Folate is heat-sensitive water-soluble vitamin that increases the likelihood of losses that depends further on the type of activity it undergoes along with certain factors that affect it (Fig. 2). First, due to its high liability, folate functions are altered so that the losses are higher during sample preparation, extraction, storage and analysis. Second, heat, oxygen and UV-light induction splits the active folate (Eittenmiller and Landen, 1999) into its two in-active form due to the oxidative cleavage of bond C-9-N-10 (Murphy et al., 1976 and 1978, Scott, 2001; McKillop et al., 2002). Thirdly, the chemical atmosphere (Eittenmiller and Landen, 1999), decreased accessibility of oxygen, and different types of food matrices during food storage and processing often cause folate loss. Fourthly, during canning and cooking, leaching also plays a major role in loss of folate. Fe³⁺, high levels of Oxygen dissolved, and food additives too minimize folate stable conditions (Eittenmiller and Landen, 1999).

Folate: Biological function

Folate plays an important biological role by either accepting or contributing one carbon unit to perform essential metabolic functions as a coenzyme (Bailey and Gregory, 1999). For example, those one carbon atoms formed by the amino acid catabolism Methenyl, formyl -, methyl-, Formino-, methylene- (Jagerstad and Witthoft, 2004). Folate supply carbon atoms used in purine (adenine and guanine) synthesis. The purine synthesis involves seven reactions, of which in six and one reactions two folate coenzymes need to be used. In synthesis of certain Amino acids, folate too plays a major role. It supplies methyl group needed for Methionine synthesis. Methionine is an essential amino acid, because it is not just one for protein overview, but also, it is the forerunner of S-adenosylmethionine that serves as the methyl group source for over 100 enzymatic reactions with crucial metabolism plays (Combs, 1998). The vitamin B₁₂-dependent enzyme methionine synthetase converts 5-methylTHF into THF, unlocking of methyl group into which in addition, homocysteine produces. The consequence is that folate is stored as methyl folate therefore the deficiency of

vitamin B₁₂ and also of folate deficiency leads to increased blood homocysteine levels which causes the cardiovascular risk and identified by many researchers (Raul et al., 2005).



The role of vitamin B₁₂ as demethylated coenzyme of 5-CH₃-THF (Ball, 1998) consequently is of great importance to cell growth, reproduction and servicing (Opladen, 2005).

Folate Absorption, Transport and Excretion

Folate is present in foods in a complex form like other nutrients, and is converted after hydrolysis to a simpler form (Fig. 3). The hydrolysis is based on enzyme and pH. After ingestion food folate goes to the human intestine where, in the presence of enzymes secreted by the microvilli brush border of the intestinal lining, they are converted from complex polyglutamate to simpler monoglutamate and further monoglutamates are absorbed in the jejunum at optimal pH 6.3. Conjugase (glutamylcarboxy peptidase) is the enzyme responsible for that conversion. For storage, monoglutamate converted to 5-methyl tetra hydrofolate (5-MTHF) that is stored in cells and liver where it transferred via venae portae and excreted through bile. In the presence of polyglutamate synthatase enzyme 5-methyl-THF, which is essentially monoglutamate, is metabolized to polyglutamate again. This polyglutamate folate is contained in cells and goes into the bloodstream from where it was transferred to body tissues (The Vitamins and Minerals Expert Team, 2002), and excreted in the urine.

The total daily loss of folate is 5-40 µg through urine (Herbert, 1968). quoted 10 µg / day for a normal person (Basu and Dickerson, 1996; Chanarin 1990; The Vitamins and Minerals Expert Team, 2002) the bioavailability of food folates may be affected by various factors. These include high-fibre, alcohol, food consumption; the involvement feed regulators of conjugase and digestive oxidative cleavage (Eittenmiller and Landen, 1998; Jagerstad and Witthoft, 2004).

Folate deficiency and associated illnesses

Folate plays an important role in DNA synthesis, so deficiency of this vitamin may result in DNA replication interference, and thus all division of cells. Hence, it would be the most folate deficiency evident in cells where cell multiplication occurs most; the result is association with some major illness like Megaloblastic anaemia, incidence of NTDs (Fig. 4), and certain types of cancer.

Major Illnesses: Megaloblastic Anemia: Chief symptom of megaloblastic anemia has a folate deficiency (Raven and Johnson, 1996). Red cells in the blood do not differentiate well, so large, young, fragile red blood cells (RBCs) with just a little life in the blood present. Such red blood cells bear hemoglobin deficiency, thus decreased capacity to carry oxygen, contributing to disease (Lucock, 2000). This type of anaemia may be also caused by vitamin B12 deficiency but this is different megaloblastic anemia with Folate deficiency due to additional nerve damage effects (Sherwood, 2004). All vitamins are involved in the synthesis of DNA and red blood cells (RBC), and therefore the insufficiency contributes to deficient RBCs development (Sherwood, 2004).

Neural tube defect: Lack of folate in pregnant women, shortly before and after pregnancy can lead to neural tube deficiencies (NTDs), which do not close the neural tube after 28 days of pregnancy (Stegers-Theunissen, 1995). It is one

of the main triggers in infants' death that occurs every year in nearly one-quarter million children (Molloy, 2005). Spina bifida, and anencephaly are two most popular. The spinal cord is affected in spina fida (open spine) and occurs in 50 per cent of cases of NTDs. Anencephaly is the more deadly of both, with underdeveloped brain and leads to death before or after childbirth. This does occur in NTDs of 30 per cent (Green, 2002). It's here now agreed the 50-70 per cent of births affected are preventable by ingestion of folic acid by mother in pregnancy on the basis of 20 years of extensive study (Molloy, 2005).

Minor Illnesses: Alzheimer's disease, vascular disease, depression: Folic acid was engaged in homocysteine methionine synthesis (Basu and Dickerson, 1996). Methyltetrahydrofolate is the target of carbon-carrier required to convert homocysteine into methionine for this pathway. There is a reduced methionine and homocysteine synthesis develops in blood when folate is deficient. High blood homocysteine levels have long been observed associated with development of minor illness (Fig. 5) like vascular illnesses, resulting in the clot formation and thickened arterial walls (Raul et al., 2005).

It was also reported, the amino acid responsible as Alzheimer's risk factor is homocysteine (Lao et al., 2004). Ho et al. (2003) research have shown neuronal cultures which deprive folate have undergone neurodegenerative changes indicative of Alzheimer's condition. Sometimes, it was documented that a increased level of homocysteine for eight years could lead to development of Alzheimer's disease. Depression has also related to the high homocysteine content in the blood due to folate deficiency (Bottiglieri, 2005, Reynolds 2002). It proposed that this be done because of the connection between Sadenosylmethionine (Antidepressant also for humans) and 5-HIAA CSF (a serotonin metabolite), used as a serotonin level cerebral predictor (Liu, 1998; Young, 2007). Folate deficiency decreases level of S-adenosylmethionine in the brain causes decreased CSF 5-HIAA levels, suggesting low serotonin (Liu, 1998), and hence depression arising.

Cancer: Folate plays an important role in the replication of DNA and the division of cells as it is involved in purine and thymidylate de novo biosynthesis, the latter being of particular interest here because it is one of the four involved in the synthesis of thymine DNA bases. The presence of low levels of folate in the body result in a high uracil content, leading to uracil being misincorporated into DNA instead of thymine (Rampersaud et al., 2002). To cope with this, cells have a repair mechanism, because uracil is not a common DNA-component. Overloading of this reparation process, however, occurrence of DNA nicks, leading to breakage of the strands, genetic instability and DNA damage (Rampersaud et al., 2002). Recent evidence both epidemiological and clinical suggests could be folate deficiency related to cancer. Disorders in metabolism of folates have been shown to encourage tumor growth. An examination of a western Australian town over a 20 year period has linked folate deficiency with cancer of the breast and of prostate (Rossi et al, 2006). Giovannucci and others (1995) also relate folate deficiency to prostate cancer.

Conclusion

The question of whether the higher concentrations of folate in large sections of the population that occur after fortification can cause harm needs much further research, as does the question of whether the presence of unmetabolized folic acid in the blood will interfere with folate-dependent

metabolism. The studies discussed in this paper shows that there are many essential biological processes in animals are dependent on methylation reactions. These processes may also be influenced by dietary consumption of methyl donors and/or a dietary folate status. Increasing evidence also points to the harmful effect of a folate-vitamin B₁₂ imbalance, which is likely to occur in vegetarians, other ethnic minorities and in the elderly people with malabsorption of vitamin B₁₂. Fortification was originally implemented to avoid NTDs, and it is appreciable that enhanced folate status obtained by increased intakes of folic acid affects biological processes linked to the neural tube. Nonetheless, the question arises that: Which other biological processes are capable of influencing such concentrations of folate, and are the results always beneficial or sometimes harmful? Folate status may have to do with birth weight. Hence, the relation of folate status to birth weight is important to study, particularly in those populations with low birth weight. In different developing countries, folate status is likely to differ widely. Red cell folate concentrations are an excellent status determinant. These assessments will assess whether certain groups are at risk in representative populations with low folate status. There is some evidence that elevated homo-cysteine plasma is both a risk factor for cardiovascular disease and stroke. For the most part, elevated homo-cysteine plasma is associated with poor folate status, poor vitamin B₆ status, poor vitamin B₁₂ status, or both contributing. Genetic disparities exist, too. For different developing countries, the prevalence of increased homocysteine plasma and its relation with cardiovascular disease should be set. Further data on the bio-availability of natural folate, diets consumed in developing countries should be established. Because of folate absorption in humans with folate deficiency may be more efficient; folate absorption in those populations requires further research. Further investigation is needed to find the connection between the occurrence of NTDs in developing countries and folate deficiency. For the different regions of the world, quantification of food's folate content traditionally eaten or among commonly consumed food should be estimated especially in developing countries where the prevalence of maternal mortality is higher.

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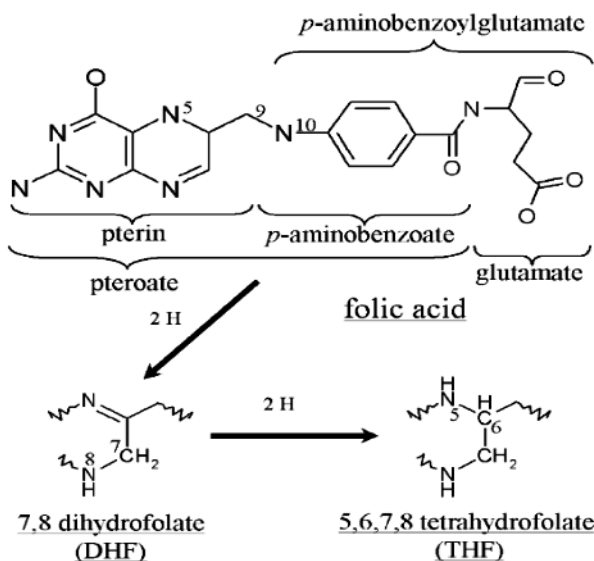


Fig. 1 Chemical Structure of Folate

Folate Losses			
Type	During sample preparation, extraction, storage and analysis	Biological activity is lost by the oxidative cleavage of C-9-N-10 bond	During food processing & storage
Factors	Altered function because of high lability	By induction of UV- light, heat and oxygen which splits in two inactive form of folate	Oxygen availability, differences in food matrices, chemical environment. Occur through leaching

Fig 2. Types and factors affecting folate losses

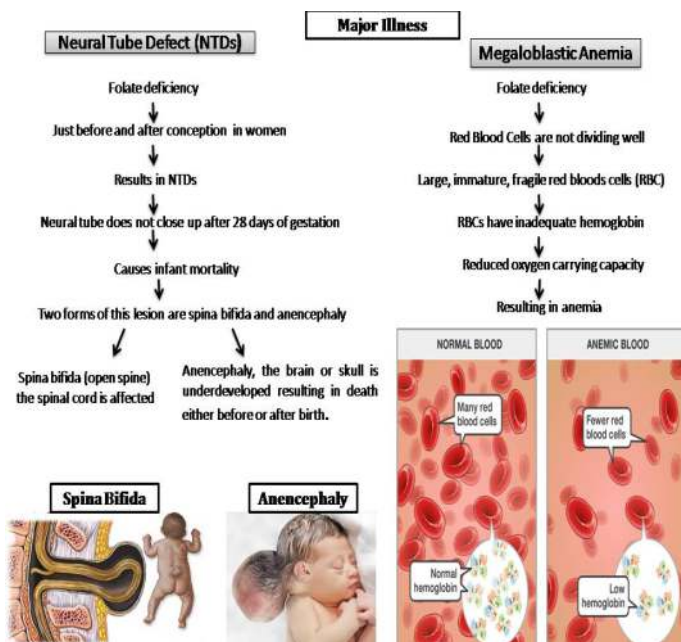


Fig. 4 Major Illnesses associated with folate

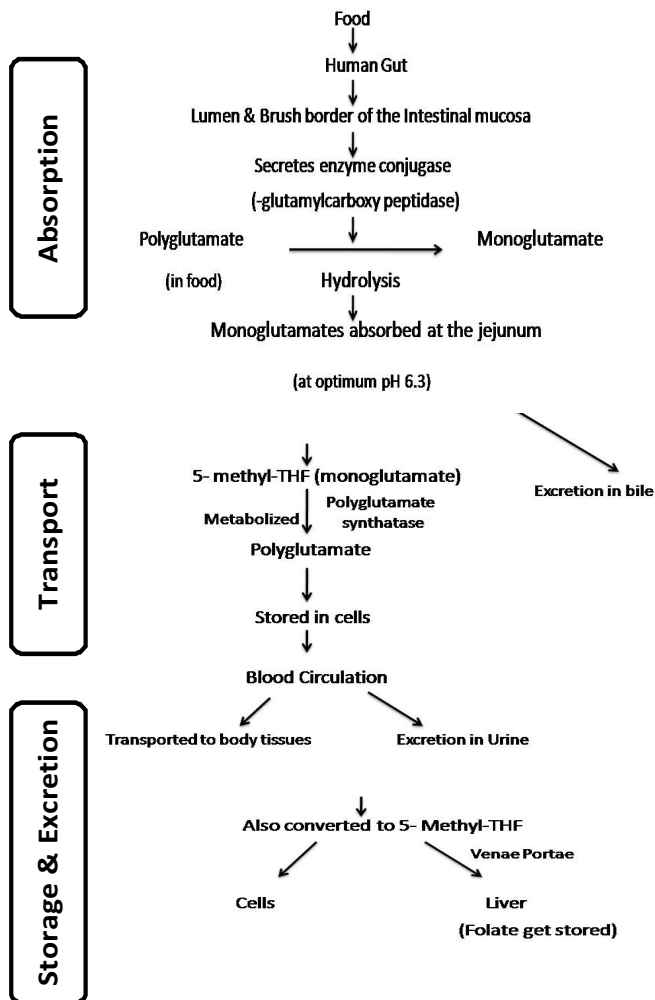


Fig 3. Folate Absorption, Transport and Excretion

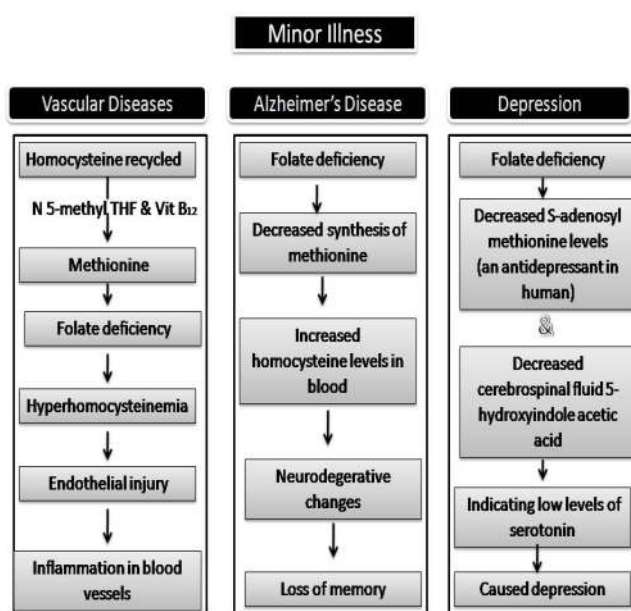


Fig. 5 Minor Illnesses associated with folate