Folic acid and diseases – supplement it or not?

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Article received: 1/21/2015
Accepted for publication: 5/31/2015

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http://dx.doi.org/10.1590/1806-9282.62.01.90

Conflict of interest: the author has no relevant interest to declare.

Summary

Introduction: folic acid is a water soluble vitamin, which is synthetically-produced and found in fortified foods and supplements. Folate is found naturally in plants, such as the dark green leafy vegetables. Folate is not synthesized *de novo* by humans, therefore the daily requirements are met from the dietary intake of folic acid supplements or food rich in this vitamin. Folate deficiency could lead to numerous common health problems. Hyperhomocysteinemia and the possibility of malignancy developments are the long term consequences of this deficit albeit contradictory findings on these claims.
Methods: the articles included in this review focused on recent updated evidence-based reports and meta-analyses on the associations of the serum folate/folic acid and the various diseases found globally.
Results: the benefit of folic acid supplementation in the pre-conception period for the prevention of neural tube defects (NTDs) was well established and it was suggested that counseling sessions should be given to women with previous pregnancies affected by NTDs. However, supplementation of folic acid and its medicinal effects in the treatment of other diseases were contradictory and unclear.
Conclusion: more detailed investigations into the health benefits of folic acid are needed before it could be recommended for supplementation, treatment or prevention of some of the diseases discussed in this review.

Keywords: folic acid, homocysteine, diseases classification, dietary supplements.

Introduction

The origin of folate is the Latin word *folium* which means leaf. Folic acid, also known as vitamin B9, is a form of synthetically-produced water soluble vitamin found in fortified food and supplements. Folate is naturally derived from food, particularly from dark green leafy vegetables.[1] Humans are not able to synthesize folate *de novo* and, therefore, the daily requirements of folate are met with consumption of food rich in this vitamin.[2] Folate and the biologically active folic acid, which is converted to dihydrofolic acid in the liver, are essential in meeting the requirements of the function of the human body. Folate is used to synthesize, repair and methylate Deoxyribonucleic acid (DNA);[2] therefore it is especially important in pregnancy and childhood for continuous cell division and growth.[1] Folate deficiency can cause many unwanted health problems, although severe deficiency is only seen months after the depletion of the dietary intake when the folate storage is exhausted. Common unwanted health problems due to folate deficiency is macrocytic anemia, weakness and confusion, memory deficits, shortness of breath, peripheral neuropathy, pregnancy complications and depression.[2,3] Hyperhomocysteinemia and cancer development due to impaired DNA synthesis and repair could be the long-term complications of folate deficiencies. Contradictory findings were found regarding the supplementation of folic acid and its medicinal effects for the treatment of many diseases globally. The rapid expansion on the research pertaining to the benefits of folic acid, which yielded contradictory findings, leads to a need of frequent updates on this topic. The most updated information on the associations of the serum folic acid status and some of the common diseases found globally are discussed in this review.

Methods

Most articles included in this review were published between 2000 and 2014, and focused on recent, updated evidence-based reports and meta-analyses on the associations of the serum folate/folic acid and the various diseases found globally.

Folic acid

Background

Folic acid is also known as folate, folacin, vitamin B9, Vitamin M, Folvite, Acifolic, Folcidin, and scientifically as pteroylglutamic acid.[4] It was first found by Lucy Wills, a consultant pathologist at the Royal Free Hospital in London through her work, which resulted in correcting macrocytic anemia of pregnancy in female textile workers in Bombay.[5,6] In 1941, folic acid was first isolated from spinach hence its name folium (leaf),[7] being subsequently synthesized in pure crystalline form in 1943 by Stokstad and in 1945 by Angier.[8] Synthesized folic acid, therefore, differs structurally from folate as it possesses additional glutamate residues (polyglutamates), reduction to the di- or tetra-hydroforms and the addition of a carbon unit, i.e. the methyl (-CH3), formyl-CHO, methylene=CH2, methenyl=CH4, which are attached to either the N5 or N10 nitrogen atoms.[5] Since its synthesis, folic acid has been used for the treatment of megaloblastic anemia.[9,10]

Sources

Although the terms folic acid and folate are used interchangeably, the metabolic effects can be slightly different. Folic acid which is found in supplements and fortified food is the synthetic form of folate. Folate is found naturally, mainly in plants.[1] Folate is found in plants and vegetables such as dark leafy greens, broccoli, asparagus, citrus fruits (oranges, grapefruits, strawberries), beans, avocado, peas and lentils, okra, Brussels sprouts, nuts and seeds, cauliflowers, beets, corn, celery, carrots and squash.[11] Folate can also be found in meat product including chicken, turkey, lamb, beef and pork liver. Folic acid, on the other hand, can be found in fortified foods, such as cereal, pasta, flour, grains and bread. Folic acid supplements are sold over the counter in tablet or powder forms.[11] The daily recommended allowance (RDA) of folic acid in the United States is 400 mcg/day for teenagers and adults, 500 mcg/day for breast-feeding women and 600 mcg/day in pregnancy.[1]

Chemical structure and properties of folic acid

Folic acid or folate has a molecular formula of C19H--19N7O6 and a molecular weight of 441.39746 g/mol.[4] Folic acid is a yellow or yellowish-orange crystalline powder, a B vitamin which contains pteridine linked to para-aminobenzoic acid by a methylene bridge and is linked to glutamic acid by a peptide linkage. It is very slightly soluble in water and in alkaline hydroxides and carbonates but insoluble in alcohol.[4]

Metabolism of folic acid and folate

The estimated body content of folate is about 10 mg to 30 mg. The normal serum level of total folate is about 5 to 15 ng/mL, while 16 to 21 ng/mL is the normal cerebrospinal fluid level. The normal levels of folate in erythrocytes range from 175 to 316 ng/mL. A higher percentage of folate is stored in the liver, some in the blood and tissues. Levels below 5 ng/mL of serum folate indicate folate deficiency and megaloblastic anemia was seen at a level below 2 ng/mL.[4,12] Food folate in the intestines after consumption are primarily hydrolyzed to monoglutamate form and absorbed via active transport across the small intestinal mucosa. Folic acid when consumed as a supplement is absorbed rapidly, primarily in the proximal portion of the small intestine via passive diffusion.[13] Monoglutamate is then reduced to tetrahydrofolate (THF) in the liver and converted to either the methyl or the formyl forms before entering the bloodstream. Folate is commonly found in the bloodstream as 5-methyl-tetrahydrofolate.[14,15] Erythrocyte folate concentration is sometimes used to measure the long term intake of folate especially in those with variable folate intake and in those who are ill, where a value above 140 ng/mL is considered adequate.[15] Hyperhomocysteinemia or high plasma homocysteine is defined as a level higher than 16 micromoles/L although lower values of 12 to 14 micromoles/L have also been used 13 and is an indicator for the poor conversion of homocysteine to methionine due to a defect in 5-methyl-tetrahydrofolate.[16] The metabolic products of folic acid normally appear in the urine 6 hours after ingestion and complete excretion is generally within 24 hours with a smaller residue found in the feces. Folic acid is also excreted in breast milk.[4] The folic acid metabolism is shown in Figure 1.

The function of folic acid metabolism

DNA synthesis and repair

Folic acid metabolism, which generates nucleic acid building blocks, is important in the synthesis and repair of DNA. Deoxyuridine monophosphate (dUMP) through addition of a methyl group by the enzyme thymidylate synthase results in the *de novo* synthesis of deoxythymidine monophosphate (dTMP) with subsequent phosphorylation to deoxynucleotide triphosphate (dNTP) and thymidine triphosphate (dTTP). Thymidine triphosphate (dTTP) is one of the four deoxyribonucleic acids essential for DNA synthesis and repair. Folate deficiency will block the conversion of dUMP to dTMP leading to the excess of deoxyuridine triphosphate (dUTP). As DNA

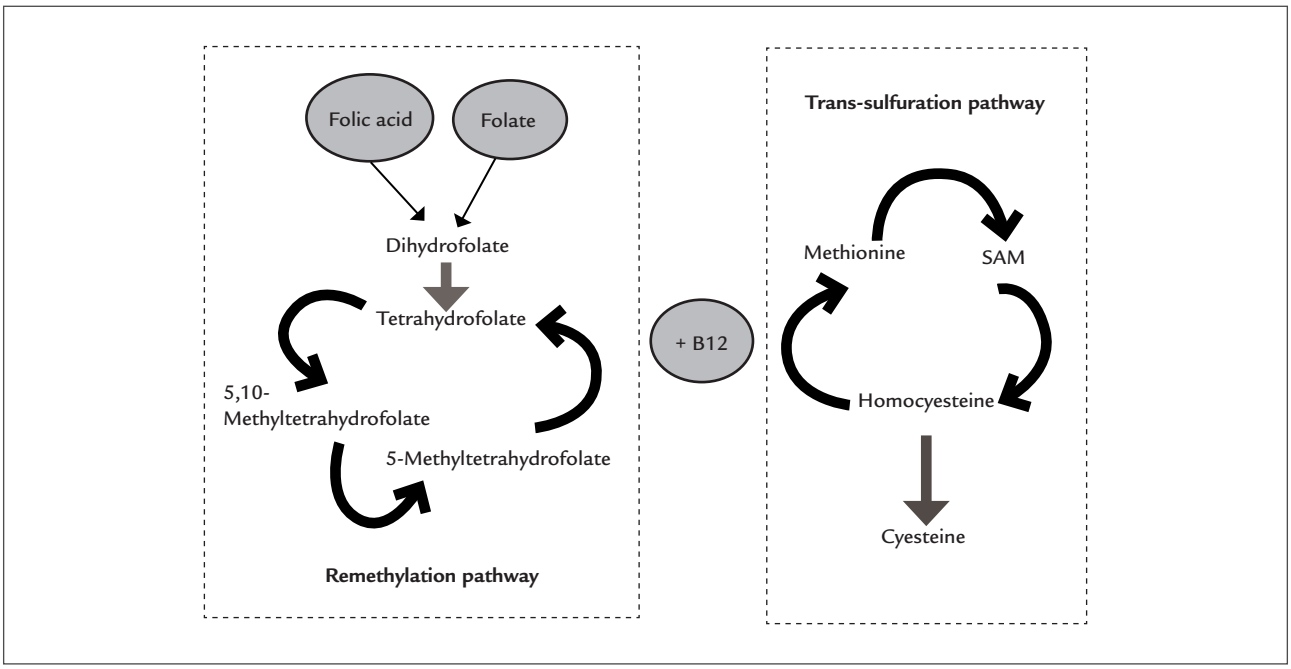

FIGURE 1 The folic acid metabolism.

polymerases are unable to distinguish between dUTP and DTTP, there is a chance of the mis-incorporation of the uracil into the DNA in place of thymidine. With increasing depletion of thymidine due to folate deficiency, the continual mis-incorporation of uracil into DNA will eventually lead to 'futile' or 'catastrophic' DNA repair. DNA destabilization may lead to chromosome aberrations and potentially malignant transformation.[17-21]

Conversion of homocysteine to methionine

A second important folate metabolic reaction is the conversion of homocysteine to methionine by the action of 5-methyltetrahydrofolate (5-methyl-THF). Some of this regenerated methionine is subsequently converted to the enzyme methionine adenosyl transferase to produce its active form, S-adenosylmethionine (SAM). S-adenosylmethionine (SAM) participates in numerous types of methylation reactions of molecules such as lipids and peptides. SAM is the major methyl contributor in the methylation of cytosine to DNA. In folate deficiency, the reduction of methylation of cytosine in DNA might result in pro-oncogene expression and potential malignancy transformation.[20-22]

Cell replication and survival

Folate depletion and subsequent reduction of DNA synthesis and DNA methylation are toxic to both normal and malignant cells because folate metabolism is fundamental to both cancerous and normal cells. Folate deficiency due to insufficient thymidine can result in DNA damage and can also result in hypomethylation of DNA due to reduced levels of S-adenosylmethionine. Ironically, due to the importance of folate metabolism for cell replication and survival, the inhibition of folic acid metabolism has been shown as a successful mechanism for the elimination of malignant cells and has therefore been trialed as antitumor therapeutics. Aminopterin, is a folic acid analog (4-aminofolic acid) that inhibits dihydrofolate reductase, thus, preventing the reduction of folic acid and dihydrofolic acid to tetrahydrofolate (THF). Methotrexate (MTX) is another analog of folic acid that is used to directly inhibit dihydrofolate reductase and to inhibit thymidylate synthase. Other folate structural analogs used in cancer chemotherapy include trimetrexate, permetrexed, and raltitrexed.[23,24]

Folic acid and diseases

There were many studies looking at the effects of folic acid and diseases, therefore yielding an exhaustive list of publications in this area. However, the studies on the association of the folic acid and diseases have resulted in many contradictory findings. The diseases discussed in this review were mainly based on the reported studies and the meta-analyses. Table 1 summarizes the reported studies and meta-analyses on the association of folic acid and diseases discussed in this article.

TABLE 1 Folic acid and diseases.

Diseases research reports
Hyperhomocysteinaemia: Stanger et al., 2004; Welsch et al., 1997; Homocysteine Lowering Trialists' Collaboration, 2005; Homocysteine Lowering Trialists' Collaboratio, 1998.
Coronary artery disease: Qin et al., 2012; Wang et al., 2012; de Bree et al, 2007; Miller et al., 2010; Zhou et al., 2011; Bazzano et al., 2006.
Hypertension: McRae, 2009; Cagnacci et al., 2014; Béchir et al., 2005; Forman et al., 2005.
Stroke: Yang et al., 2012; Wang et al., 2007; Huo et al., 2012; Lee et al., 2010.
Diabetes: Sudchada et al., 2012; Title et al., 2006; Xu et al., 2012; Schneider et al., 2014; Fotiou et al., 2014; Yilmaz et al., 2013; Negrão et al., 2014; Parker et al., 2013.
Pregnancy: Imdad et al., 2011; Grosse and Collins ,2007; Peake et al., 2013; Charles et al., 2005; Lassi et al., 2013; Fekete et al., 2012; De-Regil et al., 2010; Jian et al., 2009.
Cancers:
Prostate: Wien et al., 2012; Collin, 2013; Rycyna, 2013; Jeffrey et al., 2014; Tio et al., 2014.
Colorectal: Paspatis et al., 1995; Paspatis et al., 1994; Carroll et al., 2010; Figueiredo et al., 2011; Castillo-Lancellotti et al., 2012; Keum and Giovannucci, 2014; Kennedy et al., 2011; Ryan et al., 2001; Giovannucci et al., 1995; Takata et al., 2014.
Pancreatic: Bao et al., 2011; Oaks et al., 2011; Skinner et al., 2004; Lin et al., 2013; Keszei et al., 2009; Stolzenberg-Solomon et al., 2001; Larsson et al., 2006.
Breast: Larsson et al., 2007; Stolzenberg-Solomon et al., 2006; Chen e tal., 2014; Zhang et al., 2014; Deghan Manshadi et al., 2014.
Leukaemia: Ajrouche et al., 2014; Lupo et al., 2014; Jain et al., 2014.
Lung: Dai et al., 2013; Shen et al., 2003; Bandera et al., 1997; Slatore et al., 2008; Marchand et al., 2002; Neuhouser et al., 2003; Yang et al., 2013.
Kidney diseases: Qin et al., 2011; Jardine et al., 2012.
Neurology: Schneider et al., 2006; Castillo Lancellotti et al., 2012.
Childhood asthma: Zetstra-van der Woude et al., 2014; Crider et al., 2013.

Hyperhomocysteinemia

Methylenetetrahydrofolate reductase (MTHFR) plays an important role as an enzyme in folate metabolism. The mutation of the *MTHFR* gene at position 677 CT, which converts alanine to valine, results in decreased enzyme activity. A significant reduction of 65% enzymatic activity in the homozygous MTHFR TT genotypes and 30% reduction in the heterozygous CT genotypes has been associated with elevated homocysteine levels, DNA hypomethylation and genomic instability.[25,26] Hyperhomocysteinemia or high plasma homocysteine level has been reported as a risk factor for atherosclerosis and coronary artery diseases.[27] When compared to healthy individuals, forty percent of patients with coronary artery disease, cerebral or peripheral artery disease were found to have high plasma homocysteine level.[28] Homocysteine was postulated to cause atherogenesis and thrombogenesis leading to substantial fibrosis and muscle cell hyperplasia although the exact mechanism is still unknown.[28] Observational studies also suggested that hyperhomocysteinemia is an independent risk factor for cardiovascular related diseases. A maximal reduction in plasma homocysteine concentrations could be achieved with a minimal dose of 0.8 mg/day of folic acid.[29] A reduction of a quarter to a third in blood homocysteine concentrations in Western populations was seen with the supplementations of both 0.5-5 mg/day of folic acid and about 0.5 mg/day of vitamin B12. However, it was suggested that more evidence of its effect in the reduction of the risk factor of vascular disease due to the lowering of blood homocysteine concentrations could be determined with larger-scaled randomized trials of such regimens in high risked population.[30]

Coronary artery disease

A meta-analysis by Qin et al. indicated the effectiveness of folic acid supplementation in the reduction on cardiovascular disease (CVD) risk measured by the progression of carotid *intima*-media thickness (CIMT).[31] A meta-analysis by Wang et al. suggested that coronary heart disease risk was inversely related to dietary folate supplementation and blood folate level.[32] Similarly, a meta-analysis by de Bree et al. suggested that the risk of cardiovascular disease was reduced with high folic acid supplementation due to the improvement on endothelial function.[33] However, Miller et al. commented that although folic acid was suggested from previous studies to have homocysteine-lowering effect and might be beneficial in the prevention of CVD, folic acid on the contrary might also promote progression of atherosclerosis because it also stimulates cell proliferation. Subsequently, a meta-analysis by Miller et al. reported that folic acid supplementation did not have any effect on CVD or stroke.[34] Likewise, Zhou et al. reported in their meta-analysis that folic acid supplementation had no effect on major cardiovascular events, stroke, myocardial infarction, acute coronary syndrome and vascular death compared to placebo.[35] Similarly, Bazzano et al. also reported no reduction in the risk of cardiovascular diseases or mortality rate in those with history of vascular disease with folic acid supplementation. Therefore, it was recommended that trials with large sample sizes

will be needed in the future, in order to answer this important clinical and public health question.[36]

Hypertension

McRae, based on a meta-analysis, reported that in order to lower systolic blood pressure attained through improved endothelial function, folic acid supplementation of 5 mg/day for a minimum of 6 weeks is be required.[37] A double blinded, placebo-controlled study on postmenopausal women who received 5-MTHF (folate/prefolic) yielded a positive correlation between the administration of folate and the reduction of blood pressure in this group of patients.[38] Folic acid (5 mg) has been found to improve cardiac and vascular sympathetic baroreceptor sensitivity in twenty-one hypertensive male patients in a study with matching placebo. The results also suggested improved vagal control and enhanced baroreceptor modulation of sympathetic vasomotor tone; therefore, folic acid may be used as a novel treatment for prevention of orthostatic deregulation and/or arrhythmic complications resulting from baroreceptor dysfunction.[39] A report from a large study that included 7,373 young women and 12,347 older women suggested that a higher total amount (1000 mcg/day) of dietary folate intake and folic acid supplementation in younger women compared with consumption of less than 200 mcg/day was associated with a reduced risk of hypertension.[40]

Stroke

Yang et al. suggested that there might be a potential benefit of stroke prevention with folic acid supplementation.[41] Wang et al. in a meta-analyses concluded that there was a significant reduction in the risk of stroke by 18% with folic acid supplementation and it was more beneficial in those i) with more than 36 months of treatment, ii) with a 20% or more reduction of homocysteine level, iii) with minimal or no fortification of grain in their diet, iv) with no history of stroke. Wang et al. therefore indicated in their findings that the risk of stroke was reduced with folic acid supplementation.[42] Similarly, Huo et al. indicated that in an effort to prevent stroke, folic acid supplementation was effective in statins consumption free populations and in those with partial or without folic acid fortification.[43] Lee at al. suggested that the combination of folate and B vitamins in male patients has a potential benefit in the primary prevention of stroke.[44]

Diabetes

Folic acid supplementation in patient with type 2 *diabetes mellitus* was seen to cause reduction in homocysteine levels and, therefore, contributed to better glycemic control.[45] Diabetes is associated with endothelial dysfunction due to the uncoupling of endothelial nitric oxide (NO) synthase enzyme. Title et al. reported in a study on type 2 *diabetes mellitus* patients who were treated with folic acid (10mg/day for 2 weeks) *versus* placebo that folic acid supplementation improved endothelial dysfunction and was found to significantly improve fasting endothelium-dependent flow-mediated dilatation (FMD). However, no effects were seen on lipid profiles, endothelium-independent nitroglycerin-mediated dilatation (NMD) or inflammatory markers.[46] Xu et al. reported that supplementation with folic acid and vitamin B12 had the effect of protecting the capillaries of the kidney from damage, and the mechanism may have something to do with the effect of anti-oxygenation.[47] On the contrary, Schneider et al. conducted a randomized trial and reported that high-dose folic acid treatment did not improve renal endothelial function and failed to reduce albuminuria in human subjects with diabetic nephropathy.[48] Raised serum homocysteine concentration levels due to reduction of folic acid and vitamin B12 levels increased the risk of diabetic retinopathy.[49] Likewise, folic acid was shown to protect diabetic rats against diabetic peripheral neuropathy and the reason may be related to the improvement of the expression of nerve growth factor levels.[50] The combination of uridine monophosphate, folic acid and vitamin B12 was also shown to improve neuropathic pain in diabetic neuropathy.[51] There was a reported finding that suggested a greater risk of spina bifida in babies of pregnant mothers who were diabetic and had lower folic acid intake.[52]

Pregnancy

During the pre-conception period, risks of stillbirths secondary to neural tube defects (NTDs) were reduced with folic acid supplementation by approximately 41%.[53] It was suggested therefore, for public benefit and significant reduction of the risk of recurrent NTDs, that targeted folic acid counseling should be given to women with a previous pregnancy affected by NTDs.[54] Likewise, it was suggested for folic acid-preventable NTDs that the implementation of targeted, innovative, education campaigns and fortification of ethnic minority foods, especially in non-Caucasian communities that consumed less folic acid during the pre-conception period compared to Caucasians in the United Kingdom, will be required.[55] There were many controversies on the continuous supplementation of folic acid during the second and third trimesters of pregnancy in the prevention of NTDs, un-

like the well-recognized beneficial effects of its supplementation before and shortly after conception. Charles et al. found folic acid supplementation when given from time of initial antenatal appointment onwards to be of no benefit and no difference in birth and placental weight or gestational age of the pregnancy was observed, contrary to the Cochrane review, which reported that high doses of folic acid supplementation could reduce the risk of low birth weight.[56] Similarly, Fekete et al. reported no beneficial effect of folic acid supplementation on either the weight of the placenta or on gestational length. However, when doubling folate intake, there was an observed 2% increase in birth weight. Therefore it was suggested that more research studying the effect of folate supplementation in pregnancy would be necessary and useful in order to develop further guidelines and recommendations for pregnant women.[57,58] Wien et al. reported no statistically significant evidence of any beneficial effects of folic acid supplementations on other birth defects other than NTDs.[59,60] Although Lassi et al. reported a significant reduction in the incidence of megaloblastic anemia in those with folic acid supplementation, the review did not find folic acid to have any impact on the improvement of other hematological indices, such as antenatal anemia, mean pre-delivery hemoglobin level, mean pre-delivery serum folate levels and mean pre-delivery red cell folate levels.[57]

Cancer

Volsett et al. reported that folic acid supplementations did not alter the incidences of cancer in any other specific site nor did it in the first 5 years of cancer treatment reduce the chances of relapse of cancer.[61] Likewise, Qin et al. concluded that besides melanoma, cancer incidences of colorectal carcinoma, prostate, lung, breast or hematological malignancies were not reduced by folic acid supplementation.[62] Baggott et al. in their analysis suggested that cancer incidences were higher in those with folic acid consumption than in those without folic acid consumption. It was therefore suggested that due to contradictory findings on this issue, prior to the commencement of folic acid supplementation studies and trials, evidences of side effects of cancer recurrence with this supplementation should first be made known.[63]

Prostate cancer

Wien et al. explored the risk of prostate cancer and oral supplementation of folic acid in the supplemented groups compared to controls. The incidence of prostate cancer was found to have increased but there were no reported increases in cancer mortality. It was suggested that future studies, especially prospective studies, should investigate whether food fortification similar to folic acid supplementation increases the risk of prostate cancer.[64] However, the association of prostate cancer risk and the supplementation of folate and vitamin B12 on the genetic polymorphism associated with folate-pathway yielded many contradictory findings. Collin et al. reported in a meta-analysis that increased risk of prostate cancer was associated with a high concentration of vitamin B12 and folate. However the reversed was seen with high homocysteine levels. Regarding folate-pathway polymorphisms, only the MTR 2756A > G and SHMT1 1420C > T polymorphisms were positively associated with prostate cancer risk. The high prevalence of prostate cancer in the population and increasing concerns over folic acid fortification presenting probable potential harms warrants investigations, as it has a significant public health outcome.[65] A review reported that there were many evidences that higher circulating folate levels can contribute to prostate cancer progression.[66] However, a more recent report showed that no association was found between the progression of prostate cancer risk and continued consumption of folic acid post treatment.[67] Interestingly, a meta-analysis reported that dietary and total folate intake did not contribute significantly to the risk of prostate cancer but consistently high blood folate levels were associated with an increased risk of prostate cancer.[68]

Colorectal cancer

There have been many contradictory reports on the association between folic acid and colorectal carcinoma. Earlier reports in the 1990s showed that low folate levels predisposed to the development of adenomas but folate supplementation did not reduce the relapse rate at 2 years.[69,70] Folic acid has been identified as a foreseeable mean of chemoprevention of colorectal cancer, but Carroll et al. reported in a systematic review on various populations that folic acid has not been shown to be effective in the chemoprevention of colorectal adenomas or cancer.[71] Figueiredo et al. suggested that the risk of colorectal cancer is increased with lower folate level, therefore folate could be chemoprotective. However, no history of increased or decreased adenoma occurrence after up to 3.5 years of folic acid were observed.[72] Similarly, Castillo-Lancellotti et al. reported that folic acid supplementation was not beneficial in relapses of colorectal adenomas. The risk of cancer have been observed in some studies to differ with the levels of supplementation of folate; therefore, in populations with higher risks, the criteria for supple-

mentations might need to be reviewed and revised.[73] Interestingly, Keum and Giovannucci reported that the increase in colorectal cancer incidence rates in the United States in the later 1990s were unlikely due to folic acid fortification and folate appears to be one of the most promising factors that could explain the downward trend of current colorectal incidence rates.[74] These data helped to reassure women planning a pregnancy to start folic acid intake sufficient to prevent neural tube defects prior to conception.[75] Heavy alcohol consumption was postulated to increase the risk for colorectal cancer due to the increased catabolism of methionine, as well as the depletion of mucosal folate due to alcohol metabolism to acetaldehyde from the colonic *flora*.[76,77] Plasma folate concentration was also reported to be positively associated with colorectal cancer risk among men who may have had pre-neoplastic lesions.[78]

Pancreatic cancer

Inconsistent results have been reported on the association between the risk of pancreatic cancer and folate intake as these studies were mostly small in sample sizes and reported on variable ranges of folate intake. Bao et al. concluded from a large pooled analysis that there was no increased risk of pancreatic cancer with folate supplementation.[79] Similarly, Oaks et al. also reported that folic acid supplementation was not associated with pancreatic cancer. Pancreatic cancer risk was reduced in women with better food folate consumption compared to men.[80] The same was observed by Skinner et al. in two large prospective cohort studies.[81] Dietary folate was also reported to be protective against pancreatic cancer.[82] However, Keszei et al. reported from findings of the Netherlands Cohort Study that the risk of pancreatic cancer was only weakly associated with folate intake[83] and was inversely correlated with dietary folate intake.[84,85]

Breast cancer

Inconclusive findings were also reported on the relationship between breast cancer risk and folate supplementation or serum folate levels. However, it was reported that moderate or high alcohol consumption may increase the risk of breast cancer which may be reduced with adequate folate supplementation.[86-88] Zhang et al. revealed that a daily folate intake of 200–320 µg appeared to be associated with a lower risk of breast cancer, and increased breast cancer risk was associated with a daily folate intake >400 µg/day.[89] However, the latest data by Deghan et al. on a study conducted on female Sprague-Dawley rats suggested that folic acid supplementation in doses of 2.5 to five times of the daily requirement may promote the progression of existing pre-cancerous or cancerous cells in the mammary glands.[90]

Childhood leukemia

The supplementation of folic acid prior to conception may reduce the risk of childhood leukemia.[91] Lupo et al. reported that folic acid supplementation did not have any association with the risk of Acute Lymphoblastic Leukemia (ALL) in children.[92] There was no significant difference in level of folate reported in the survivors of childhood acute lymphoblastic leukemia with or without neuropathy.[93]

Lung cancer

Lung cancer risk could be reduced with a higher folate intake.[94] Shen et al. suggested that there was a possible protective role of dietary folate in lung cancer.[95] The inverse relationship between the risk of lung cancer and folate supplementation was also reported in an earlier research.[96] Long term use of folic acid was also not reported to be beneficial to prevent lung cancer.[97] The study in the South Pacific, amongst the New Caledonian men suggested that the risk of lung cancer may be reduced with a high consumption of dark green leafy vegetables.[98] Likewise, Neuhouser et al. similarly reported that plant food may be preventative for lung cancer in a population at higher risk but both these studies were not folate-specific.[99] As for lung cancer treatment, Pemetrexed (MTA) is a multi-targeted anti-folate drug approved for lung cancer therapy and it was reported that the supplementation of folic acid resulted in better survival in MTA-treated patients.[100]

Kidney diseases

Folic acid supplementation may be effective for the prevention of cardiovascular disease (CVD) in patients with kidney disease without previous consumption of grain fortification with folic acid, diabetics and in those with end stage renal disease (ESRD).[101] Qin et al. also reported the benefit of folic acid supplementation on the reduction of CVD risk in patients with ESRD by 15%. In those with partial or no folic acid fortification and in those with a decrease in Hcy level > 20%, the beneficial effect was seen to be greater.[102] On the contrary, Jardine et al. reported that in those on folic acid-based homocysteine lowering regime with kidney disease, no reduction in the cardiovascular events was seen.[103]

Neurology

The use of folic acid supplementation for the prevention of Alzheimer's disease and cognitive decline had been dis-

cussed and debated in recent years. Schneider et al. reported contradictory results on the use of folic acid supplements in the effort to prevent cognitive decline. A few studies suggested that folic acid supplementation in those with folate deficiencies may provide neuroprotection, however, risk to neurological function was also seen in those without folate deficiencies.[104] Despite earlier reports on the benefits of folate and vitamin B complex in the maintenance of cognitive function, Castillo et al. reported that folic acid supplementation was not beneficial for cognitive function in the elderly. Low folate serum levels may lead to cognitive impairment and the combination of high levels of folic acid and low levels of vitamin B12 may lead to further deterioration. Therefore, it was suggested that fortification of food with folic acid should be re-examined to maximize benefits and to limit potential risks.[105]

Childhood asthma

The high morbidity and increasing prevalence of childhood asthma has made it a critical public health problem in recent years, therefore interest into research on the impact of nutrition and other exposures during pregnancy on this issue has increased. A study suggested that supplementation of high-dose folic acid during pregnancy might increase the risk of childhood asthma.[106] Crider et al. however reported in a meta-analysis that there were no evidences of the association between maternal folic acid supplement use (compared with no use) in the prepregnancy period through the first trimester and risk of asthma in childhood. However, additional research in this area is needed because of the limited number and types of studies found in the literature.[107]

Conclusion

The increasing pool of evidence supporting the health-promoting effects of folic acid suggests the possibility of its future role in the prevention and the treatment of diseases. Folic acid is used as a supplement in most cases but is increasingly being used as medication especially in trials as an anti-cancer medication. Although the effect of folic acid supplementation during the pre-conception period to reduce the incidence of neural tube defects (NTDs) is well established, its effect on other diseases yielded many contradictory results. Therefore, research into its effect on these diseases warrant further investigations. Most of the published studies were observational studies and a lesser proportion was conducted on cell lines and animals. Supplementation and medicinal benefits of folic acid in some diseases should only be recommended when its beneficial effects are well established in humans.

Acknowledgement

The author would like to thank Sheba D. Mani from the Language Department of the International Medical University for the language editing of this manuscript.

Resumo

Ácido fólico e doenças – suplementá-lo ou não?

Introdução: ácido fólico é uma vitamina solúvel em água produzida sinteticamente e encontrada em alimentos e suplementos enriquecidos. O folato é encontrado naturalmente em plantas, como vegetais folhosos verde-escuros. O folato não é sintetizado *de novo* por seres humanos; portanto, as necessidades diárias são satisfeitas a partir da ingestão de suplementos de ácido fólico ou alimentos ricos nessa vitamina. A deficiência de folato pode levar a inúmeros problemas de saúde comuns. Hiper-homocisteinemia e a possibilidade de desenvolver malignidades são as consequências a longo prazo desse déficit, ainda que os resultados sejam contraditórios sobre essas afirmações.
Métodos: os artigos incluídos nesta revisão tratam de relatórios recentes atualizados com base em provas e metanálises sobre a associação entre o folato/ácido fólico e várias doenças encontradas globalmente.
Resultados: o benefício da suplementação de ácido fólico no período de pré-concepção para a prevenção de defeitos do tubo neural (DTN) foi bem estabelecido e foi sugerido que sessões de aconselhamento devem ser providas às mulheres com gravidezes anteriores afetadas por DTN. No entanto, os benefícios da suplementação de ácido fólico e os efeitos medicinais no tratamento de outras doenças são contraditórios e pouco claros.
Conclusão: investigações mais detalhadas sobre os benefícios do ácido fólico são necessárias antes que a suplementação seja recomendada para tratamento ou prevenção de algumas das doenças discutidas nesta revisão.

Palavras-chave: ácido fólico, homocisteína, classificação de doenças, suplementos dietéticos.

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