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The significance of folate supplementation

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ABSTRACT

Folates are pterin derivatives oxidised to various degrees, which exhibit the biological activity of folic acid. Physiologically, they act as coenzymes (cofactors) essential for ensuring normal metabolism, tissue renewal, and growth, particularly whenever any increasing demands arise due to accelerating cell division and metabolism. The importance of their role in organogenesis is widely recognised during pregnancy. The most common cause of folate deficiencies occurs when there are increased physiological demands for this compound, for instance: during pregnancy (especially in cases of having twins), gastrointestinal (GI) malabsorption of folate, congenital disorders of the GI tract, or if cytostatic medication has been given. Taking folate as a prophylactic measure also reduces rates of megaloblastic anaemia and neural tube defects.

KEY WORDS: folate, supplementation, prevention.

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INTRODUCTION

According to the ancient Greeks, the literal translation of the word diet is 'lifestyle' (i.e. *Δίαιτα diaita*). Nowadays the word is usually understood to mean a way of eating or nutrition. An adequate or normal diet should satisfy the body's daily requirements for most nutrients. Whenever there is an insufficient dietary intake of key nutritional components, then adverse metabolic processes will arise resulting in outcomes detrimental to health. In such instances, taking supplements or nutritional additives are thus indicated. The role of a supplement is to deliver those substances lacking in the body that are required for its normal functioning. Giving supplements depends on the nutritional status, of which nutritional components include: vitamins, minerals, herbs and/or other botanicals, amino acids, enzymes, and metabolites. The USA considers a dietary supplement to be any oral agent whose function is to supplement one's diet. Thus, according to USA law, dietary supplements can be orally taken either in isolation or as a supplement to one's daily diet, but they cannot be a substitute for eating complete meals. A dietary supplement can be given without any prescription, according to European law, and constitutes a substance that is safe to the body; both in quantity and quality [1]. Supplements should be tailored to the requirements of a patient's individual nutritional status. A normal diet covering the body's need for all nutritional components is, according to the literature, adopted by only a small proportion of the population, which is able to deliver the required dietary intakes of thiamine, riboflavin, niacin, and vitamins A, B_{12}, and C, but to a lesser extent for iron, calcium, zinc, and vitamins B_6, D, E, and folate [1-4]. Such outcomes are undoubtedly influenced by economic factors as well as cultural mores, those of significance being: low income, young age, smoking cigarettes, substance abuse, slimming, and frequently used elimination diets. A growing area of concern are the problems of baryophobia and eating disorders, often

arising from an emotion-based avoidance of certain foods. Of course, metabolic diseases should also be taken into account, as should other conditions such as any psychological reasons for making dietary changes. Supplementation with vitamins and minerals should be considered in circumstances of food allergy in women suffering from heavy menstrual periods, pregnancy, and women during childbirth and lactation, together with those engaging in sports, patients treated with certain medications (e.g. phenytoin), and high-risk health groups. It should, however, be remembered that such supplementation does not lessen the need to eat a normal diet [1-4]. Dietetic experts also emphasise that nutrient absorption can be altered by other factors: interactions can occur during digestion, absorption, transport, utilisation, and excretion of nutrients. Among those nutrients that are essential for normal body function are the essential folate compounds belonging to the water-soluble vitamin B group. They must therefore be delivered/taken from outside the body to ensure its normal functioning.

Folate (otherwise known as folacin or folic acid) is a pterin derivative oxidised to varying degrees, which is biologically active. Folate as a coenzyme is a key factor involved in metabolism, tissue renewal, and growth, as well as being in increasing demand during times when elevated cell division and metabolism occur. The role of folates in organogenesis reflects their importance in pregnancy [3-5]. Folate deficiencies are observed in people who rarely consume fruit, green vegetables, and cereal products, since these are rich sources of folate (e.g. spinach, broccoli, kale, legumes, avocado, kiwi, mango, oranges, as well as liver and yeast) [6, 7].

Studies have shown that many people are folate deficient, with a low daily intakes of around 0.2 mg. The most common cause of folic acid deficiency occurs whenever there are increased demands for the compound, such as in pregnancy (especially when having twins), folate malabsorption in the gastrointestinal tract, congenital gastrointestinal dysfunction, or if cytostatics are taken. Folate deficiency can be linked to conditions such as miscarriage, preterm delivery, and foetal growth retardation. Taking folate as a preventative measure reduces rates of megaloblastic anaemia and neural tube defects. Nevertheless, studies have not clearly shown any efficacy of taking folate in other obstetric-related conditions [4, 8, 9]. Because of the importance of folate in normal metabolism and organogenesis, it is vital that women, either planning or being pregnant, have a sufficient dietary intake of folate and a normal folate absorption. However, many pregnancies are unplanned, with dietary folate intake being insufficient, so the only way to ensure adequate intake in such circumstances is by taking folate supplements according to the recommendations that all women of childbearing age should have a diet containing appropriate amounts of folate. Strategies for raising folate intake include dietary changes, supplementation, and the fortification of food. As mentioned previously, those foods containing high folate levels are include raw, green, and leafy vegetables, grains, legumes, fruit (especially citrus), and cereals. The method of food preparation is also relevant because 50% to 90% of folates are degraded by cooking. Folic acid and its derivatives are involved in the syntheses of dopamine, adrenaline, and noradrenaline where any dietary deficiencies can lead the development of neuropsychiatric disorders, e.g. dementia, depression, and epilepsy. In addition, some central nervous system (CNS) dysfunctions may be related to high concentrations of homocysteine in the body; this being a metabolite of folate. Folate excess may contribute to atherosclerosis developing in the arteries supplying blood to the CNS, resulting in hypoxia of the brain and cerebral infarction. In contrast, folate deficiency may lead to megaloblastic anaemia which arises from abnormal nucleic acid synthesis in haematopoietic stem cells. Megaloblastic anaemia occurs, *inter alia*, in preterm newborn infants or twins, resulting from relatively small amounts received from the mother. Due to the intensive development of the child after birth and a depletion of folic acid, folate-related disorders most commonly arise between 2 and 17 months of age [4, 5, 7, 8].

Already alluded to several times is the key role of folate in growth and organogenesis where insufficient dietary intakes in the first weeks of pregnancy are linked to an increased risk of neural tube defects. The increased folate demand during pregnancy is associated with maternal erythropoiesis, uterine and breast growth, as well as foetal and placental growth. An increased folate demand, resulting in low serum folate levels, can lead to megaloblastic erythropoiesis and more rarely to megaloblastic anaemia [3-6]. Adequate intake of folate is vital at the moment when the neural tube closes during embryonic development.

Folate deficiency is thus linked to growth and developmental disorders, neurological problems, neural tube defects, neurodegenerative diseases, megaloblastic anaemia, and an abnormal/unbalanced metabolism of nucleic acids and amino acids, leading to physiological irregularities that manifest in the whole metabolic system. It is worth stressing that folate metabolism is not only affected by environmental factors but also by genetics. There are different polymorphic variants of genes coding for enzymes responsible for the metabolism of nucleic acids and amino acids, where different variants of the same gene can affect metabolic pathways by enhancing or diminishing the activity of these enzymes. The response of the human body to dietary components is individualised. There are ongoing studies being performed on the molecular mechanisms underlying folic acid effects on its deficiency symptoms and defects resulting thereof. In addition to both environmental factors and genetic predisposition, disorders in the methylation pattern caused by folate deficiency are also important. Polymorphisms

that control folate metabolism play an important role in determining the susceptibility to certain diseases. Some variants of polymorphic genes increase the risks of neural tube defects, developmental disorders, neurodegenerative diseases, cardiovascular disease, and cancer. An important role of folate in normal bodily function is due to its biological properties (instability, sensitivity to temperature), which is an argument for promoting its supplementation. Dietary supplements of folic acid are particularly recommended for pregnant women [10]. The beneficial effects of folic acid in preventing disorders of embryogenesis, particularly neural tube defects, has been repeatedly confirmed. Such defects, like many other disorders of foetal development, can be eliminated through providing proper health care before pregnancy and during pregnancy, especially in its early period. One of the important tasks during preconception is for women to be broadly aware of the importance of a normal diet and of supplementation with vitamins and minerals. It has been recommended for a long time previously in many countries, that all women likely to conceive should take 400 micrograms of folic acid to reduce/prevent the risk of spina bifida and other neural tube defects from happening. In making the decision to prescribe any medication it is important that a case history is properly collected and a physical examination undertaken. Routine laboratory testing may be useful for assessing nutritional status, particularly through measuring haemoglobin, haematocrit, and blood glucose levels.

Choosing any supplementation with minerals and trace elements should be based on risk factors assessed by interview, physical examination, and laboratory tests. Folic acid supplementation of 0.4-5 mg/day for women with children with confirmed defects reduces the risk of neural tube abnormalities by 72% in any subsequent children born. If, however, neural tube defects were absent in previous pregnancies, a prophylactic folic acid dose of 0.8 mg/day will reduce the risk of this defect by up to 93%. In light of recent studies on women planning a pregnancy, it is recommended that the diet be supplemented with folate at 0.4 mg/day for a month before the planned conception, as well as during the first trimester of pregnancy. In cases where high-risk factors are present for neural tube defects, then the folic acid dose should be increased to 4 mg/day during the entire period of pregnancy [4, 10, 11].

SUMMARY

Folic acid regulates growth and cellular function and is beneficial to the nervous system and brain, as well as being important for mental well-being. It prevents the so-called 'neural tube defects' from arising in the foetus and is advantageous for infant development. Maintenance of genetic material and the transmission and distribution of hereditary traits in cells is facilitated and regulated by folate. Other gainful effects of folate are in improvement in the function of the digestive system and in the formation of gastric juice, and ensuring healthy functioning of the liver, stomach, and intestines. It is also an anti-anaemic factor, stimulating haematopoiesis (i.e. red blood cell formation), and it affords the body some protection against cancer; particularly cancer of the uterus.

Consequences of folate deficiency and prophylaxis:

- Arrested cellular growth and recovery.
- Lowered red blood cell count; so-called megaloblastic anaemia (macrocytic).
- Fatigue and problems with concentrating.
- States of anxiety, fear, depression, and excessive irritability.
- Insomnia, being distracted, and impaired memory.
- Dysfunction in digestion and in nutrient absorption, malnutrition, diarrhoea, decreased appetite, weight loss, inflammation of the tongue and mucous membranes of the lips, headaches, palpitations, and premature grey hair.
- Growth retardation in children and adolescents.

Adequate intake of folic acid is essential for pregnant women, and in its supplements taken during pregnancy, *inter alia*, reducing the rates of foetal spina bifida; a serious backbone malformation which may arise at about the third week of pregnancy. To prevent neural tube defects in the foetus, taking a dose of 0.4 mg of folic acid daily is recommended from three months before any planned pregnancy until its twelfth week. In real life, however, due to the high numbers of unplanned pregnancies, it is recommended that all women of childbearing age continuously take oral supplements of folic acid at a dose of 0.4 mg per day. For those women who have already given birth to one child with neural tube defects, a preventive daily dose of 5 mg of folic acid is recommended [4, 6, 10, 11].

THE EFFECTS OF EXCESSIVE FOLATE

Elevated folic acid doses may result in insomnia, irritability, depression, gastrointestinal disturbances, allergic skin reactions (rash, redness, itching), and in rare cases, bronchospasm. If excessive folate doses are experienced during pregnancy then there is an increased risk of asthma to the child.

Absorption of folate by the body:

- Factors that improve folate absorption are as follows: vitamin B, vitamin B_6, vitamin B_{12}, p-aminobenzoic acid, vitamin H, and vitamin C.
- Factors impairing absorption are: light, drinking alcohol, high temperature, and contraceptives.

Folates take part, amongst others, in the following processes:

- Synthesis of nucleic acids, purine, and pyrimidine.
- Hydroxylation of long-chain fatty acids.
- Conversion of homocysteine to methionine in conjunction with vitamin B_{12}.
- Normal functioning of the haematopoietic system, nervous system, and the cardiovascular system.

- Regulation and maturation of red blood cells.
- Growth, development, and proliferation of all body cells.

Nutritional folate deficiencies in expectant mothers may cause such neonatal birth defects as anencephaly or a herniated spinal cord [4, 6, 10, 11]. Despite the high folate content in some food products, the bioavailability of folic acid can be low. It is recommended that a diet rich in folate is adopted, or one where it is replaced by synthetic folic acid in prophylactic doses of 400 mg daily. According to expert opinion, all women of childbearing age should consume at least 0.4 mg of folate daily to reduce the risk of neural tube defects. Women should also be made aware of the importance of diet for reducing the chance of defects in the foetus from occurring. In fact, all pregnant women should consider their eating habits in order to either improve diet or to take vitamin and mineral supplements. Taking 30 mg of iron (i.e. 150 mg of ferrous sulphate) is recommended in the second and third trimesters of pregnancy. Vitamin and mineral supplements are recommended during pregnancy for women not following an appropriate diet as well as of women in high-risk groups due to multiple pregnancies, smoking cigarettes, and alcohol and drug abuse. For pregnant women and those lactating, the recommended daily intake of iodine is 200 g; however, increasing the dietary salt intake is not recommended, and therefore products containing iodine are recommended only at a level of 200 μg/day [7, 10, 11]. According to the recommendations of the Polish Gynaecological Society the daily dose of folic acid for preventing CNS defects is 40 mg daily. In approximately 50% of women an enzymatic block occurs where there are reduced levels of the methylated active forms of folate that arise from various mutational variants in the gene coding for the methylene tetrahydrofolate reductase (MTHFR) enzyme. In women possessing this enzymatic block, the absorption of folic acid is reduced by 30% in 40% of such cases, whereas in 10% of these cases, this absorption is reduced by 70%. Recommended daily doses of 40 mg may therefore be ineffective in these women for preventing defects arising in the CNS. In such instances, it is advisable to fortify the supplements by introducing active folates. Numerous studies have demonstrated the potential benefits of supplementation with Metafolin or Actifolin. As an active substance, the former contains the calcium salt of L-5-methyltetrahydrofolate. Actifolin, however, contains the glucosamine salt of L-5-methyltetrahydrofolate, which exhibits a 10% higher bioavailability than the aforementioned calcium salt. Whenever the activity of the MTHFR enzyme becomes significantly reduced, taking Metafolin can deliver additional benefits in balancing out any perturbations in folate metabolism [12-14]. Folic acid and its active forms are recommended to women planning pregnancy for at least six weeks prior to, and also to the end of, the second trimester of pregnancy. In 1997 a team of experts, assembled for the 'Primary Prevention of Neural Tube Defects', recommended that 0.4 mg of folic acid should be provided daily to pregnant women. The folic acid demand for breast feeding mothers is, however, higher. After four months, dietary deficits of folic acid intake deplete its stocks in the body. The dose of folic acid must also be increased in women with a BMI > 30 as well as for treating megaloblastic anaemia and in women suffering from hyper-homocysteinaemia.

DISCLOSURE

Authors report no conflict of interest.

References

1. Strain JJ, Dowey L, Ward M, et al. B-vitamins, homocysteine metabolism and CVD. Proc Nutr Soc 2004; 63: 597-603.
2. Duthie SJ, Narayanan S, Sharp L, et al. Folate, DNA stability and colo-rectal neoplasia. Proc Nutr Soc; 63: 571-578.
3. Polish Pharmaceutical Society: Polish Pharmacopoeia IX. The Office for Registration of Medicinal Products, Medical Devices and Biocides, Warszawa 2011; 4574.
4. Czyżewska-Majchrzak Ł, Paradowska P. Skutki niedoboru i ryzyko suplementacji folianów w diecie [The effects of folate deficiency and its supplementation]. Now Lek 2010; 79: 457-463.
5. Kwas foliowy – karta substancji aktywnej (DB 00158) (ang.). DrugBank. Available from: http://www.heltechnic.pl/info_Kwas_foliowy (accessed: 4 December 2016).
6. Kwas foliowy. Karta charakterystyki produktu Sigma-Aldrich dla Stanów Zjednoczonych [Folic acid. MSDS Sigma Aldrich for the United States]. Available from: http://www.sigmaaldrich.com/catalog/product/usp/1286005?lang= pl&region=PL (accessed: 4 December 2016).
7. Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. JAMA 1988; 260: 3141-3145.
8. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol 2009; 170: 1486-1493.
9. MRC Vitamin Study Research Group. Prevention of neural tube defects; results of the Medical Research Council Vitamin Study. Lancet 1991; 338: 131-137.
10. Jägerstad M, Piironen V, Walker C, et al. Increasing natural food folates through bioprocessing and biotechnology. Trends Food Sci Tech 2005; 16: 298-306.
11. Finglas PM, de Meer K, Molloy A, et al. Research goals for folate and related B-vitamins in Europe. Eur J Clin Nutr 2006; 60: 287-294.
12. Seremak-Mrozikiewicz A. Zaburzenia metabolizmu folianów w etiologii poronień nawracających [Metabolism folate in the etiology of recurrent miscarriages]. Perinatol Neonatol Ginekol 2013; 6: 111-112.
13. Seremak-Mrozikiewicz A, Barlik M, Borowczak P, et al. The frequency of 677C>T polymorphism of MTHFR gene in the Polish population. Arch Perinatal Med 2013; 19: 12-18.
14. Dębski R, Paszkowski T, Wielgoś M. Stosowanie złożonych źródeł folianów w profilaktyce wad cewy nerwowej oraz innych

zaburzeń spowodowanych niedoborami folianów w okresie planowania ciąży i w ciąży – State of the Art 2015 [The use of complex sources of folate in the prevention of neural tube prevention of neural tube defects and other disorders caused by folate deficiency during planning pregnancy and pregnant – State of the Art 2015]. Available from: https://e-medycyna.pl/files/pdf/1.pdf (accessed: 4 December 2016).

AUTHORS' CONTRIBUTIONS

MPK prepared concept and design of the publication. GJB and MB collected data. MPK and GJB wrote the article and finally approved it.