REVIEW ARTICLE

Folic Acid And Deficiency Diseases
Tania Mirza¹, Kiran Qadeer¹, Sadia Hafeez¹, Kefi Iqbal² and Iqbal Ahmed¹

ABSTRACT
Folic acid is a water-soluble vitamin, which is involved in hematopoiesis and the synthesis of amino acids and DNA. It is widely used for the treatment of megaloblastic anemia. Tetrahydrofolic acid is the fully reduced form of folic acid and is the parent compound of a variety of coenzymes that serve as carriers of one-carbon groups in metabolic reactions. The daily use of supplemental folic acid periconceptionally significantly reduces the risk of neural tube defects. The genetic polymorphisms affecting the structure-function of folate-related enzymes have been associated with the increased risk of birth defects and chronic diseases including vascular diseases and different types of cancers. Therapeutic use of folic acid has been found to greatly reduce the prevalence of these diseases.

INTRODUCTION
Folic acid (N-[4-{[2-Amino-1, 4-dihydro-4-oxo-6-pteridinyl]methyl}amino]-benzoyl-L-glutamic acid) (I) was isolated in 1940s which led to its widespread therapeutic use in the treatment of megaloblastic anemia. During the last 50 years the basic aspects of folate metabolism and the biochemical functions have been investigated and the key role of folate coenzymes in carbon metabolism established. Since the early 1990s, research has centered on determining the links between the folate intake and birth outcome or chronic disease risk. One of the most important public health discoveries of this century has shown that daily supplemental folic acid taken periconceptionally significantly reduces a risk of neural tube defects (NTDs). The identification of genetic polymorphisms that affect the structure-function of folate-related enzymes and proteins has served as the catalyst for the ongoing search for links between these polymorphisms and increased risk for birth defects or chronic disease.²³

![Folic Acid Structure](image)

Folic acid has extensive clinical applications and is an ingredient of many proprietary preparations. It is a yellow to orange micro-crystalline powder and is very slightly soluble in water. The aqueous solution of folic acid is inactivated by ultra-violet light. The alkaline solutions are sensitive to oxidation and the acid solution is sensitive to heat. The molecule has three ionizable groups with pKa values of 4.7, 6.8 and 9.0. The normal daily dose is 2.5 to 20 mg. Folic acid preparations should be kept in a well closed container and protected from light to avoid potency loss.⁴⁶

Folate Group
Folate is a group of compounds that differ in the oxidation state of the molecule, the length of glutamate side chain and the specific one carbon units attached to the folate molecule, tetrahydrofolate (THF) is a form of folic acid in which the pteridine ring is fully reduced, and is derived from 5, 6, 7, 8-tetrahydro-pteroylglutamate. It is the parent compound of a variety of coenzymes that serve as carriers of one carbon groups in metabolic reactions. In the majority of naturally occurring folates, the number of glutamate units in the side chain varies from 5 to 8. The fully oxidized mono-glutamate form of the vitamin is referred to as folic acid and is the form used commercially in supplements and fortified foods.¹⁷⁹

Dietary Sources
Folate occurs naturally in the diet and is concentrated in selected foods such as orange juice, strawberries, dark green leafy vegetables, peanuts, black beans, kidney beans and liver (Suitor and Bailey, 2000). Folic acid is an added ingredient in a large number of food products including breakfast cereals, meal replacement

¹: Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Toli Plaza, Super Highway, Gajap Road, Karachi, Pakistan
²: Department of Material Science, Baqai Dental College, Baqai Medical University, Toli Plaza, Super Highway, Gajap Road, Karachi, Pakistan
and infant formulas and snack foods. In the United States, all "enriched" cereal grain products such as bread, pasta, flour, breakfast cereal and rice, are required by the Food and Drug Administration to be fortified with folic acid to reduce the risk of NTDs.\textsuperscript{10-11}

**Bioavailability**

The bioavailability of folate may be defined as the portion of nutrient that is physiologically available. It is influenced by several factors including the chemical form of folate, food matrix, the chemical environment in the intestinal tract and factors affecting the metabolic fate postabsorption.\textsuperscript{12,13} The estimate of folate bioavailability in humans is quite variable largely due to the differences between experimental approaches and analytical methodologies used.\textsuperscript{12,14} The average bioavailability of food folate is not more than 50% relative to folic acid intake alone in a fasting condition.\textsuperscript{15} The bioavailability of folic acid with light meal consumption is about 85% that of supplemental folic acid taken alone on fasting.\textsuperscript{16}

**DEFICIENCY DISEASES**

**Hematological Defects**

The folate deficiencies may lead to hematological abnormalities in the bone marrow that precede hypersegmentation of neutrophils in peripheral blood.\textsuperscript{17} Macrocycotic cells are produced in the bone marrow when folate supply becomes rate limiting for erythropoieses. Megaloblastic anemia is characterized by an increase in mean cell volume and reduction in RBC number that occurs slowly after the early stages of folate-deficient megaloblastosis. Impaired cell division is evident in reduced leukocyte number and impaired regeneration of rapidly dividing gastrointestinal epithelial cells, with clinical consequences.\textsuperscript{17}

**Abnormal Pregnancy**

Pregnant women need greater folate requirements to meet the demands for DNA synthesis and one carbon transfer reactions in rapidly dividing fetal and maternal cells.\textsuperscript{18}

When folate intake is restricted during pregnancy it may lead to preterm delivery, low infant birth rate and fetal growth retardation. Maternal hyperhomocysteinemia has been linked to increase habitual spontaneous abortion and pregnancy complications, with increased risk of low birth rate and preterm delivery.\textsuperscript{19} Randomized controlled trials with folic acid supplementation in women with high risk of pregnancy complications are required to determine a cause and effect relationship.\textsuperscript{1}

**Birth Defects**

Incomplete closure of the neural tube in the developing embryo result in a group of birth defects refers to as NTDs that vary in severity depending on the location and size of the defect. Marked geographical variations have been found in the prevalence of NTDs. For example, the prevalence at birth during 1980s was 0.8 per 1000 birth in the United States, 3.6 per 1000 in the republic of Ireland, 10.6 per 1000 in a Chinese province.\textsuperscript{20} Folic acid supplements taken periconceptionally has been found to significantly reduce the risk of NTDs, a major public health issue.\textsuperscript{21-22} The basis of folic acid-responsive NTDs appears to be due to both metabolic and genetic defect which impair normal maternal folate metabolism that restrict the delivery of adequate folate to the developing embryonic neural tube.\textsuperscript{23} In the United States, heart defects have been found to affect 1 in 110 newborns and account for a third of infant death due to birth defects, more than that of any other congenital anomaly including NTDs.\textsuperscript{24} The use of periconceptional folic acid supplements has been found to reduce the risk of congenital heart defects in some cases.\textsuperscript{25} The specific types of heart effects associated with periconceptional folic acid use include ventricular septal defects and some conotruncal defects, tetralogy of Fallot and D-transplantation of the great arteries.\textsuperscript{26}

**Chronic Diseases**

The elevated plasma homocysteine concentration has been found to be a significant risk factor for vascular disease.\textsuperscript{27} It has been estimated that a 25% reduction in plasma homocysteine concentration leads to an 11-16% decrease in risk for ischemic heart disease and a 19-22% decrease in risk for stroke.\textsuperscript{28} Folic acid supplementation has been found to lower plasma homocysteine concentration with the greatest effect in individuals with the highest pre-treatment homocysteine concentration.\textsuperscript{30} The magnitude of the reduction in homocysteine was about 25% for doses = 0.8 mg with 90% and 60% of this effect associated with lower doses (0.4 and 0.2 mg/day, respectively).\textsuperscript{30}

Poor folate status is associated with increase in the risk of cancer, with the strongest support for colorectal cancer and its precancerous lesion.\textsuperscript{31} The presence of MTHFR 677C-T (folate related candidate gene)
polymorphism has been associated with a significant reduction in the risk of colorectal cancer. It has been proposed that a reduction in MTHFR activity associated with the 677C-T polymorphism in the presence of adequate folate may lead to an increase in the 5, 10-methylene THF required for DNA synthesis and normal cell division.

Folate has been found to play a protective role against breast cancer, especially among alcohol users. In a health study, there has been a significant reduction in the risks associated with total folate as well as folate from supplements among women who consume alcohol (≥15 g/day). The increased breast cancer risk associated with this alcohol consumption can be significantly reduced by an increase in folate intake. Potential mechanisms by which folate status could modulate cancer risk include those that influence DNA stability or methylation. In a limited folate intake, dTMP synthesis is impaired leading to a nucleotide imbalance and misincorporation of uracil into DNA, i.e. associated with increased cancer risk. Excessive DNA uracil content in folate deficient human has been reversed with folic acid supplementation.

CONCLUSION
This article highlights the role of folate in one carbon metabolism and links between metabolic abnormalities affecting health related risks. The folate status in the body or folate-related polymorphisms has been found to influence the risk for developmental abnormalities in newborn and chronic diseases including vascular diseases and cancer. The use of folate preparations and supplements may significantly reduce the risk of neural tube defects and congenital heart defects in infants and chronic diseases including vascular abnormalities and colorectal and breast cancers.

REFERENCES
17. Lindenbaum, and J. Allen, R., Clinical spectrum and diagnosis of folate deficiency in Folate in Health and Disease, Bailey, L. B., ed., Marcel