Tidsskriftet Tidsskrift for Den norske legeforening

# What is optimal folate status?

FROM THE LABORATORY

ANNE-LISE BJØRKE-MONSEN

anne-lise.bjorke.monsen@helse-bergen.no
Anne-Lise Bjørke-Monsen, specialist in paediatrics and medical biochemistry, senior consultant in the Department of Medical Biochemistry and Pharmacology at Haukeland University Hospital and associate professor in the Department of Clinical Science at the University of Bergen. She is a board member of the Norwegian Society of Medical Biochemistry.
The author has completed the ICMJE form and declares no conflicts of interest.

RENATE RENSTRØM

Renate Renstrøm, specialty registrar in the Department of Medical Biochemistry and Pharmacology at Haukeland University Hospital.
The author has completed the ICMJE form and declares no conflicts of interest.

## Folate is essential for DNA synthesis and cell growth. Deficiency is particularly harmful in pregnancy and is associated with an increased risk of foetal malformations.

High concentrations of folate are present in vegetables and fruit, but the vitamin is unstable, and 50–80 % is lost in cooking. In the United States and some other countries, breakfast cereals and flour are fortified with synthetic folate, folic acid, which is reflected in the population's folate status. Median serum folate levels in American women of childbearing age are 39.0 nmol/l (1). Corresponding levels in Norwegian women in the same age group are 13.8 nmol/l (own data).

Folate requirements increase during periods of growth, pregnancy and breastfeeding. Maternal folate deficiency is associated with an increased risk of fetal malformations, and women are recommended to take 400 µg folate daily from one month before conception until the end of the first trimester to reduce

the risk of fetal neural tube defects. In countries where folic acid fortification has been introduced, the incidence of neural tube defects has fallen (2). This reduction has not been observed in Europe (3). There has been debate about whether folic acid fortification may increase the risk of cancer, but no change in the prevalence of cancer has been found in countries that have introduced this (4).

Additional intake of folate is often required throughout pregnancy and the breastfeeding period to prevent maternal deficiency (5). Folate levels in breastmilk remain high throughout the breastfeeding period, and serum folate levels are high in the first and second year of life. Folate deficiency is rare in young children (6).

It is sufficient to measure serum folate when investigating folate status. Serum levels are rapidly affected by changes in intake or absorption, which makes serum folate well-suited as a marker of nutritional status and intestinal function.

Along with cobalamin, folate is needed to remethylate homocysteine to methionine, and a deficiency in either of these two vitamins will increase homocysteine levels and reduce methionine levels. In older children and adults, homocysteine levels are primarily a folate marker, and they start to rise when serum folate levels fall below 25–27 nmol/l (Figure 1), as an indication of sub-optimal intracellular folate status. A daily intake of 300–400 µg folate in adults is associated with stable plasma homocysteine levels.

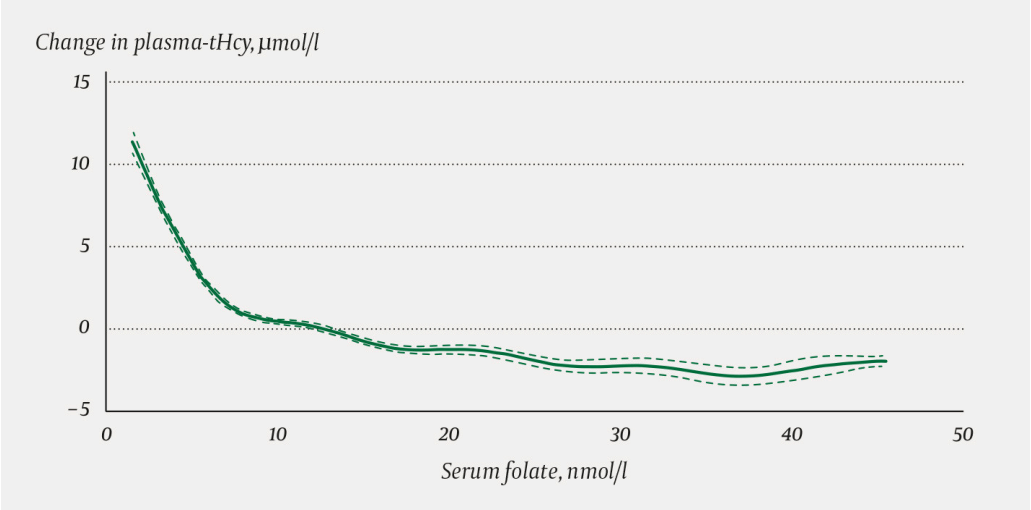


**Figure 1** Change in total homocysteine levels (tHcy) in plasma in relation to serum folate in adults aged over 16 years with glomerular filtration rate (GFR) > 60 ml/min/1.73 m2. The values on the y-axis indicate change from the mean tHcy. The dotted lines show the 95 % confidence interval. The figure is based on patient data (n = 12,988) from the Department of Medical Biochemistry and Pharmacology at Haukeland University Hospital.

In cases of severe folate deficiency, plasma homocysteine levels can increase to as much as 40–50 µmol/l. Individuals homozygous for the *C677T* polymorphism in the *MTHFR* gene (methylenetetrahydrofolate reductase) (prevalence 5–15 %), may develop higher homocysteine levels (up to 100 µmol/l) at low serum folate values, and serum folate levels > 15 nmol/l are advised in these patients (7).

The World Health Organization recommends a cut-off value for folate deficiency of <10 nmol/l (8). In women of childbearing age, serum folate levels should be > 25.5 nmol/l to prevent fetal malformations (9). This corresponds to the level of red blood cell folate that has been demonstrated in studies to provide increased genomic stability (10) and stable low plasma homocysteine levels in adults (Figure 1).

## REFERENCES


1. Nguyen B, Weiss P, Beydoun H et al. Association between blood folate concentrations and depression in reproductive aged U.S. women, NHANES (2011-2012). J Affect Disord 2017; 223: 209–17. [PubMed][CrossRef]

2. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC et al. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev 2015; nr. 12: CD007950. [PubMed] [CrossRef]

3. Khoshnood B, Loane M, de Walle H et al. Long term trends in prevalence of neural tube defects in Europe: population based study. BMJ 2015; 351: h5949. [PubMed][CrossRef]

4. Vollset SE, Clarke R, Lewington S et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 2013; 381: 1029–36. [PubMed][CrossRef]

5. Allen LH. Causes of vitamin B12 and folate deficiency. Food Nutr Bull 2008; 29 (Suppl): S20–34, discussion S35 - 7. [PubMed][CrossRef]

6. Monsen AL, Refsum H, Markestad T et al. Cobalamin status and its biochemical markers methylmalonic acid and homocysteine in different age groups from 4 days to 19 years. Clin Chem 2003; 49: 2067–75. [PubMed] [CrossRef]

7. Huang X, Qin X, Yang W et al. MTHFR gene and serum folate interaction on serum homocysteine lowering: Prospect for precision folic acid treatment. Arterioscler Thromb Vasc Biol 2018; 38: 679–85. [PubMed][CrossRef]

8. de Benoist B. Conclusions of a WHO Technical Consultation on folate and vitamin B12 deficiencies. Food Nutr Bull 2008; 29 (Suppl): S238–44. [PubMed][CrossRef]

9. Chen MY, Rose CE, Qi YP et al. Defining the plasma folate concentration associated with the red blood cell folate concentration threshold for optimal neural tube defects prevention: a population-based, randomized trial of folic acid supplementation. Am J Clin Nutr 2019; 109: 1452–61. [PubMed] [CrossRef]

10. Fenech M. Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity. Mutat Res 2012;

733: 21–33. [PubMed][CrossRef]

Publisert: 19 September 2022. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.19.0588