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Serum and red blood cell folate concentrations for assessing folate status in populations

WHO/NMH/NHD/EPG/12.1

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VMNIS | Vitamin and Mineral Nutrition Information System

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Background

Folate is the general term for a water-soluble B vitamin naturally found in foods such as leafy vegetables, legumes, egg yolks, liver and some citric fruits (1). This vitamin is essential for normal cell growth and replication, but the bioavailability of naturally occurring folate is less than that of folic acid, a synthetic compound that is used in supplements and in fortified foods (2). Folate and vitamin B₁₂ deficiencies have been acknowledged as the most common causes of macrocytic anaemia (3). In addition, poor folate status is associated with other negative health outcomes, for example, inadequate maternal folate status has been linked to abruptio placentae, pre-eclampsia, spontaneous abortion, stillbirth, preterm delivery, low birth weight (4), and serious congenital anomalies of the brain and spine, such as neural tube defects (5).

Increasing awareness of the significance of public health consequences of insufficient folate intake has emphasized the need for identification of accurate biomarkers for large-scale assessment of folate status. Laboratory methods for measuring folate status were first developed in the 1950s (6) and still form the basis for currently used assessment methods. Although folate is mainly stored in the liver, folate status can be assessed in urine, serum, plasma or the red blood cells using a variety of techniques including microbiological methods, radioisotope competitive binding, and enzyme-linked or chemiluminescence assays (7). Serum folate is considered an indicator of recent folate intake (8), and a single measurement cannot be used to differentiate between a transitory decrease in dietary folate intake and chronic deficiency states. However, repeated low values of serum folate within an individual over the course of a month are indicative of low folate status or folate depletion (9). Conversely, red blood cell folate concentrations respond slowly to changes in folate intake because the erythrocytes, which have a 120-day lifespan, accumulate folate only during erythropoiesis (8). Thus, red blood cell folate concentrations are useful to indicate long-term folate status.

Folate status tends to vary with age and gender. Data from different periods of the United States of America National Health and Nutrition Examination Surveys (NHANES) revealed that serum and red blood cell folate concentrations are considerably higher in women than in men and among older adults. For example, individuals older than 60 years were more likely to have higher serum and red blood cell folate concentrations than any other age group (10). This was true for folate status assessed both before and after the introduction of folic acid fortification of cereal grains.

Scope and purpose

This document provides users of the Vitamin and Mineral Nutrition Information System (VMNIS) guidance about the use of serum (or plasma) folate and red blood cell folate to assess the folate status in different populations. It summarizes the current World Health Organization (WHO) recommendations on the cut-off values used for defining folate status in populations as well as the chronology of their establishment.

Assessment of serum folate and red blood cell folate concentrations is useful for the monitoring of folate status trends and the evaluation of the impact of public health interventions.

Description of technical consultations

This document synthesizes the current WHO guidelines, published previously in the following four documents:

Nutritional anaemias (11): report of a technical consultation of a WHO scientific group, held in Geneva, Switzerland, on 13–17 March 1967. This consultation followed two other consultations held in 1958 and 1962 (12) and focused on the aetiology of nutritional anaemias and the feasibility of developing laboratory methods for field application. It was convened three years after the start of a multi-country collaborative study in India, Israel, Mexico, Poland, South Africa, the United Kingdom, the United States of America and Venezuela, which (i) investigated iron metabolism in pregnancy and the role of hookworm in anaemia during pregnancy, and (ii) further tested the procedures for

examining blood and serum. The 1967 consultation reviewed the overall progress of the study and also discussed the nutritional requirements for iron, folate and vitamin B₁₂.

Nutritional anaemias (13): report of a meeting of a group of WHO experts, held in Geneva, Switzerland, on 11–15 October 1971. The group examined the validity of parameters and concepts in the field of nutritional anaemia and reviewed the information that had become available since the 1967 meeting. The topics covered in this meeting included: standardization of techniques to measure folate status; studies on the availability and absorption of iron, folate and vitamin B₁₂; and prevalence studies and trials on preventive measures in population groups.

Control of nutritional anaemia with special reference to iron deficiency (14): report of a joint meeting of the International Atomic Energy Agency (IAEA), the US Agency for International Development (USAID) and WHO, held in Geneva, Switzerland, on 28 October – 1 November 1974. The purpose of the meeting was to: (i) update the state of knowledge with regard to the aetiology of nutritional anaemia and (ii) provide guidance on some public health interventions considered useful for its control.

WHO technical consultation on folate and vitamin B₁₂ deficiencies (15): report of a meeting of a group of WHO experts, held in Geneva, Switzerland, on 18–21 October 2005. The consultation aimed to: (i) review the global prevalence, causes and health consequences of folate and vitamin B₁₂ deficiency, with emphasis on the contribution of these deficiencies to the global burden of anaemia, adverse outcomes in pregnancy, child development and mental function, and cardiovascular disease; (ii) review the metabolism of folate and vitamin B₁₂; (iii) identify the best indicators for assessing folate and vitamin B₁₂ status at the population level and monitoring response to interventions; (iv) reach a consensus on cut-off values to define folate and vitamin B₁₂ deficiency; (v) define criteria for determining the severity of folate and vitamin B₁₂ deficiency at the population level that should trigger an intervention; and (vi) critically review current interventions (supplementation and fortification) to prevent folate and vitamin B₁₂ deficiencies and their potential side-effects.

Recommendations

Cut-off values for the assessment of folate status in all age groups using the folate serum or red blood cell concentrations were first proposed in 1968 (11) (Table 1). Values indicative of deficiency were based on the concentrations at which macrocytic anaemia is more likely to appear. These cut-offs were endorsed by subsequent WHO consultations in 1972 (13) and 1975 (14), although it was acknowledged that the correlation between folate concentration and

megaloblastic anaemia was not always strong. The consultation highlighted the urgent need for data on the clinical significance of low concentrations of folate and vitamin B₁₂ in non-pregnant individuals who have no evidence of other haematological changes, because studies at that time failed to detect any obvious impairment of health. It should be noted that folate levels defined as “elevated” were based on the assay’s upper limit capabilities without dilutions, and not on biological implications for health.

Table 1

Folate concentrations in serum and red blood cells for determining folate status in all age groups, using macrocytic anaemia as a haematological indicator

Serum/plasma folate levels ng/mL (nmol/L) ^{a, b}	Red blood cell folate level ng/mL (nmol/L) ^{a, b}	Interpretation
>20 (>45.3)		Elevated
6–20 (13.5–45.3)		Normal range
3–5.9 (6.8–13.4)		Possible deficiency
<3 (<6.8)	<100 (<226.5)	Deficiency

^aFolic acid conversion factor: 1 ng/mL = 2.265 nmol/L.

^bAssayed by *Lactobacillus casei*.

Source: Reference (11).

In 2005, the cut-off values were revised to reflect folate deficiency based on metabolic indicators (15) (Table 2). These cut-offs were based on NHANES III data on American men and women aged 30 years and older. The study assessed the relationship between homocysteine and plasma or red blood cell folate and identified the cut-off for folate deficiency at the folate concentration below which homocysteine concentrations start to rise (16). High levels of

circulating homocysteine are considered a functional indicator of folate deficiency and results from the inability of folate to donate the methyl group necessary to convert homocysteine to methionine (17). These values apply to all age groups, although the consultation recognized that the values may not be appropriate to assess the folate status in pregnant women, since folate concentrations typically decline during pregnancy (15).

Table 2

Cut-off values for determining folate deficiency in all age groups using homocysteine concentrations as the metabolic indicator

Folate indicator	Cut-off value indicating folate deficiency ng/mL (nmol/L) ^{a, b}
Serum/plasma folate level	<4 (<10)
Red blood cell folate level	<151 (<340)

^aFolic acid conversion factor: 1 ng/mL = 2.265 nmol/L.

^bMeasured by the radioimmunoassay. In this dataset, the measurements obtained by radioimmunoassay need adjustment to make them comparable with the microbiological assay (10).

Source: Reference (15).

Since 1968, the microbiological assay using *Lactobacillus casei* has been recommended for folate measurement. Regular monitoring and use of reference preparations is necessary to improve the accuracy of the results, particularly at lower concentrations, and in inter-laboratory comparisons (13, 18).

Summary of statement development

The main bibliographic sources used to prepare this summary were four WHO publications released between 1968 and 2008 (11, 13–15). All of these reports have contributed to building knowledge in this area. Briefly, folate deficiency cut-off values based on megaloblastic anaemia risk were first presented in the 1968 document (10). The cut-offs were revised at a consultation held in 2005, using homocysteine as metabolic indicator of deficiency (15).

Plans for update

The Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, WHO, is responsible for reviewing this document. It will be updated by 2013 if required, following the *WHO handbook for guideline development* (19) procedures.

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