World Health Organization

Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations

WHO/NMH/NHD/MNM/11.2

VMNIS | Vitamin and Mineral Nutrition Information System

Inside

Background

Iron stores in the body exist primarily in the form of ferritin. The ferritin molecule is an intracellular hollow protein shell composed of 24 subunits surrounding an iron core that may contain as many as 4000-4500 iron atoms. In the body, small amounts of ferritin are secreted into the plasma. The concentration of this plasma (or serum) ferritin is positively correlated with the size of the total body iron stores in the absence of inflammation. A low serum ferritin value reflects depleted iron stores, but not necessarily the severity of the depletion as it progresses.

Normal ferritin concentrations vary by age and sex. Concentrations are high at birth, rise during the first two months of life, and then fall throughout later infancy (*1*). At about one year of age, concentrations begin to rise again and continue to increase into adulthood (*2*). Beginning in adolescence, however, males have higher values than females; a trend that persists into late adulthood. Values among men peak between 30–39 years of age and then tend to remain constant until about 70 years of age. Among women, serum ferritin values remain relatively low until menopause and then rise (*2*).

Body ferritin levels, in contrast to haemoglobin, are not affected by residential elevation above sea level or smoking behaviour. However, ferritin is a positive acute phase response protein whereby concentrations increase during inflammation and thereby no longer reflect the size of the iron store. This makes the interpretation of normal or high serum ferritin values difficult in areas of widespread infection or inflammation (*3*). In the absence of inflammation or liver disease, high serum ferritin concentrations indicate iron overload.

Scope and Purpose

This document aims to provide users of the Vitamin and Mineral Nutrition Information System (VMNIS) with information about the use of serum ferritin for assessing iron status in populations. It is a compilation of the current World Health Organization (WHO) recommendations on the topic, and summarizes the cut-offs for describing iron stores and the chronology of their establishment.

Ferritin measurements and corresponding cut-offs facilitate the monitoring of iron deficiency trends and the assessment of the impact of health and nutrition interventions. Such assessments allow measurements of progress towards international goals to prevent and control iron deficiency and provide the basis for advocacy programmes for iron deficiency and anaemia prevention in vulnerable populations.

Description of Technical Consultation

This document compiles current WHO guidelines from two documents:

Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers (*3*), a document published in 2001, is mainly based on a consultation organized by WHO, UNICEF, and the United Nations University (UNU) held in Geneva, Switzerland, 6-10 December 1993. The purpose of this consultation was to provide scientists and national authorities with a timely and authoritative review of iron deficiency anaemia, and also to help managers of national micronutrient malnutrition prevention and control programmes to identify effective measures for fighting iron deficiency anaemia. The conclusions of the consultation were complemented with additional scientific literature that appeared before 2000.

Assessing the iron status of populations (*4*) is the report of a joint WHO and US Centers for Disease Control and Prevention (CDC) Technical Consultation held in Geneva, Switzerland, 6-8 April 2004, with the participation of 34 experts. With the ultimate goal of planning effective interventions to combat both iron deficiency and anaemia, the objectives of the consultation were to review the indicators currently available to assess iron status, to select the best indicators for assessing the iron status of populations, to select the best indicators to evaluate the impact of interventions to control iron deficiency in populations, and to identify priorities for research related to assessing the iron status of populations. This consultation was preceded by a short WHO/CDC working group meeting held in January 2004 to review the literature on indicators of iron status and to select indicators for discussion. In April 2004, the consultation was provided with four literature reviews on indicators of iron status, including red blood cell (RBC) parameters, ferritin, free erythrocyte protoporphyrin, serum and plasma iron, total iron binding capacity, transferrin saturation and serum transferrin receptor as well as a review on the interpretation of indicators of iron status during an acute phase response. These four reviews are available in the second edition, published in 2007.

Recommendations

A consultation held in Quito, Ecuador in 1987 by the International Nutritional Anaemia Consultative Group (INACG) concluded that at all ages a serum ferritin value of less than 10-12 µg/l was indicative of a depletion of iron stores (*5*).

These cut-offs were revised in 1993. Table 1 presents serum ferritin concentrations reflective of depleted iron stores. Separate cut-offs are provided for individuals less than five years of age and five years of age or older, for males and females, and for individuals less than five years of age with concurrent infection.

Table 1
Relative extent of iron stores on the basis of serum ferritin concentration

	Serum ferritin (µg/l)			
	Less than 5 years of age		5 years of age or older	
	Male	Female	Male	Female
Depleted iron stores	< 12	< 12	< 15	< 15
Depleted iron stores in the presence of infection	< 30	< 30	-	-
Severe risk of iron overload (adults)	-	-	> 200	> 150

The thresholds for adults are derived largely from the clinical literature, specifically from studies examining the highest ferritin concentration among patients with microcytic iron deficiency anaemia who also either show a therapeutic response to iron or who have no stainable iron in the bone marrow (*6*).

Infants, young children, and pregnant women usually have serum ferritin values near the cut-off reflective of depletion, though a value near the cut-off does not necessarily imply functional iron deficiency (*3*). Serum ferritin is of limited usefulness in diagnosing iron deficiency during pregnancy, as concentrations fall during late pregnancy, even when bone marrow iron is present (*3*).

In areas where inflammation is not prevalent, serum ferritin, along with soluble transferrin receptor, provide an approach to measuring the iron status of populations as transferrin receptor does not rise in response to inflammation (*4*). The interpretation of low serum ferritin and high transferrin receptor concentrations is presented in Table 2. However, the proposed classification still requires validation in population surveys (*4*).

Table 2
Interpretation of low serum ferritin and high transferrin receptor concentrations in population surveys

Percentage of serum ferritin values below cut-offs[a]	Percentage of transferrin receptor values above cut-offs[b]	Interpretation
Lower than 20%[c]	Lower than 10%	Iron deficiency is not prevalent
Lower than 20%[c]	10% or higher	Iron deficiency is prevalent; Inflammation is prevalent
20% or higher[d]	10% or higher	Iron deficiency is prevalent
20% or higher[d]	Lower than 10%	Iron depletion is prevalent

[a] Apply cut-offs by age group (Table 1)
[b] Apply cut-offs recommended by manufacturer of assay until an international reference standard is available.
[c] Lower than 30% for pregnant women
[d] 30% or higher for pregnant women

In areas of widespread infection or inflammation, defining iron deficiency using serum ferritin is difficult. If infectious diseases are seasonal, then the survey should be done in the season of lowest transmission; if they are permanent, then the concurrent measurement of two acute phase response proteins, C-reactive protein (CRP) and α_1-acid-glycoprotein (AGP), can aid in the interpretation of serum ferritin values. One method to account for the increase in ferritin values caused by inflammation is to raise the cut-off that defines deficiency, often to 30 µg/l (*4*). Another method is to exclude individuals with elevated concentrations of CRP or AGP from prevalence calculations based on ferritin. However, in areas and age groups where inflammation is nearly universal, such exclusion could artificially depress estimates of the prevalence of iron deficiency based on serum ferritin calculations. It is still a pending task to examine which acute phase proteins might be best to interpret serum ferritin data, with an ultimate goal of correcting rather than excluding data collected in such settings.

If the prevalence of iron deficiency in a population must be described with a single number, serum ferritin should be used and complemented with haemoglobin in all programme evaluations (*4*).

Ferritin is typically assessed in serum or plasma with enzyme-linked immunosorbent assays (ELISA) or enzyme immunoassays after venous blood collection; however dried serum spot samples can also be used to facilitate field collection (*5*). A summary of characteristics, strengths and limitations of ferritin as a measure of iron status is presented in Table 3.

Table 3
Characteristics, strengths and limitations of ferritin as a measure of iron status

Tissue of analysis	Serum or plasma
Common method of analysis	Immunoassay on immunnoturbidometry
Units	µg/l
Indicator of:	Size of iron stores
Advantages	Reflects iron status and responds to iron interventions
Disadvantages	Is an acute phase protein so concentration is increased in inflammatory disease and subclinical infection
	Limited usefulness during pregnancy

Summary Development

This summary is based on two expert consultations (*3,4*). A consultation held in December 1993 and convened by WHO and UNICEF, together with key partners, was the basis for *Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers*. This document provided serum ferritin cut-offs to define depleted iron status as well as iron overload. As described in the preceding section, the cut-offs for deficiency were largely based on clinical studies. The second consultation and resulting document, *Assessing the iron status of populations* reinforced these cut-offs and emphasized the utility of serum ferritin as an indicator of the iron status of populations.

Plans for Update

The WHO Micronutrients Unit, Department of Nutrition for Health and Development, is responsible for reviewing this document and if needed will update it by 2014, following the newly adopted *WHO Handbook for guideline development* (*7*) procedures.

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