

# Serum transferrin receptor levels for the assessment of iron status and iron deficiency in populations

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## Inside

VMNIS | Vitamin and Mineral Nutrition Information System

**Background** 1

**Scope and purpose** 1

**Description of technical consultations** 2

**Discussions and recommendations** 2

**Summary of statement development** 3

**Plans for update** 3

**Acknowledgements** 3

**Suggested citation** 3

**References** 4

## Background

Transferrin is the main iron transport protein found in the blood and plays a role in maintaining cellular iron homeostasis through regulation of cellular iron intake. Each transferrin molecule has the ability to carry one or two iron ions before binding to a transferrin receptor on the cell membrane. The transferrin-iron complex enters the cell through endocytosis and the iron ions are released for metabolic functions. The transferrin receptor is recycled back to the cell surface and the transferrin molecule is released to re-enter the plasma transferrin pool.

Transferrin receptor in serum is largely derived from developing red blood cells. Cells can regulate their iron uptake by modulating the expression of the transferrin receptor on the cell surface and by storing excess iron as ferritin. Therefore, serum transferrin receptor levels reflect the intensity of red blood cell formation, or erythropoiesis, and the demand for iron. As the supply of iron to the tissues progressively declines, the expression of transferrin receptors increases (1). The opposite phenomenon is observed in the immune system, where increased cellular iron stores in macrophages raise transferrin receptor expression (2).

Assessment of serum transferrin receptor levels has been used to distinguish iron deficiency anaemia from anaemia of chronic disease because the receptors are generally unaffected by concurrent infection or inflammation. However, because serum transferrin receptor levels are affected by the rate of erythropoiesis from any cause, they cannot be used as the sole indicator of erythropoiesis due to iron deficiency. For example, serum transferrin receptor levels may be elevated in conditions with increased red cell production and/or turnover, such as thalassaemia and haemolytic anaemia, or decreased in situations of marrow hypoplasia, such as after chemotherapy (3–6). Therefore, serum transferrin receptor levels are an indicator of the severity of iron insufficiency only when iron stores are depleted and no other causes of abnormal erythropoiesis are known.

Combining the use of serum transferrin receptor concentrations with serum ferritin concentrations as the serum transferrin receptor/log ferritin ratio, also known as the serum transferrin receptor index, has also been proposed to increase the diagnostic sensitivity and specificity for diagnosing iron deficiency (7, 8).

## Scope and purpose

This document aims to provide users of the Vitamin and Mineral Nutrition System (VMNIS) with guidance about the use of serum transferrin receptor levels for assessing

the iron status of populations. It is a compilation of the current World Health Organization (WHO) recommendations on the topic and summarizes existing information on the population cut-off values for the prevalence of iron deficiency. The use of these prevalence cut-off values permits the identification of populations at greatest risk of iron deficiency and priority areas for intervention. It also facilitates the monitoring and evaluation of progress towards international goals of preventing and controlling iron deficiency.

## Description of technical consultations

This document synthesizes the current WHO guidance, published previously in the documents listed below:

[\*Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers\*](#) (9). This document was published in 2001 and is based on a consultation jointly organized by WHO, the United Nations Children's Fund (UNICEF) and the United Nations University (UNU) in Geneva, Switzerland, 6–10 December 1993. The purpose of this consultation was to provide scientists and national authorities with an updated review on iron deficiency anaemia and recently developed guidelines and recommendations. Furthermore, the consultation was aimed at helping national programme managers and policy-makers to identify and implement effective measures for fighting iron deficiency anaemia. The conclusions from the consultations were supplemented with additional data published between 1993 and 2000.

*Assessing the iron status of populations, report of a joint World Health Organization/Centers for Disease Control and Prevention technical consultation on the assessment of iron status at the population level*, 1st edition (10). This document was published in 2005 and is the report of a joint WHO and US Centers for Disease Control and Prevention (CDC) technical consultation in Geneva, Switzerland, 6–8 April 2004. The stated objectives of the consultations were:

(i) to review the indicators currently available to assess iron status; (ii) to select the best indicators to assess the iron status of populations; (iii) to select the best indicators to evaluate the impact of interventions to control iron deficiency in populations; and (iv) to identify priorities for research related to assessing the iron status of populations. A WHO/CDC working group met in January 2004 prior to the consultation, to review the literature on indicators for iron status and the interpretation of indicators of iron status during an acute-phase response.

[\*Assessing the iron status of populations\*](#), 2nd edition (11). This document was published in 2007 and is an updated version of the report published in 2005 (10). The document includes literature reviews on indicators of iron status, including red blood cell parameters, ferritin, free erythrocyte protophorphyrin, serum and plasma iron, total iron-binding capacity, transferrin saturation and serum transferrin receptors, and on the interpretation of indicators of iron status during an acute-phase response. These reviews were provided for the consultation as technical background on the measurement, biology, interpretation and diagnostic value of the indicators.

## Discussions and recommendations

Serum transferrin receptor levels, combined with measurements of serum ferritin concentrations, provide the most effective assessment of a population's iron status, as shown in Table 1. Unlike serum transferrin receptor levels, serum ferritin levels rise during inflammation, decreasing the utility of the indicator in areas where infectious disease is common. Therefore, in areas where inflammation is prevalent, assessing a population's iron status based on serum transferrin receptor levels is most appropriate. The proposed classification of iron deficiency based on serum ferritin and transferrin receptor levels awaits validation in population surveys (11).

Table 1

### Interpretation of serum ferritin and transferrin receptor concentrations in population surveys<sup>a</sup>

Percentage of serum ferritin values below threshold <sup>b</sup>	Percentage of serum transferrin receptor values above cut-off values <sup>c</sup>	Interpretation
<20 <sup>d</sup>	<10	Iron deficiency is not prevalent
<20 <sup>d</sup>	≥10	Iron deficiency is prevalent; inflammation is prevalent
≥20 <sup>e</sup>	≥10	Iron deficiency is prevalent
≥20 <sup>e</sup>	<10	Iron deficiency is prevalent

<sup>a</sup> Source: adapted from reference (11).

<sup>b</sup> Apply cut-off values by age group as described in reference (9).

<sup>c</sup> Apply cut-off values recommended by manufacturer of assay until an international reference standard is available.

<sup>d</sup> Less than 30% for pregnant women.

<sup>e</sup> 30% or higher for pregnant women.

Serum transferrin receptor levels are typically measured in serum or plasma by enzyme-linked immunosorbent assay (ELISA) or immunoturbidimetry. A summary of the characteristics, strengths and limitations of transferrin receptor levels as a measure of iron status is displayed in Table 2.

Table 2

### Characteristics, strengths and limitations of serum transferrin receptor levels as a measure of iron status<sup>a</sup>

Grade	Characteristics
Common method of analysis	Immunoassay (e.g. ELISA) or immunoturbidimetry
Units	µg/L
Indicator of	Balance between cellular iron requirements and iron supply
Advantages	Measure of the severity of iron deficiency even in the presence of inflammatory disorders
Disadvantages	Affected by the rate of erythropoiesis Standardization of assays not yet complete

<sup>a</sup> Source: adapted from reference (11).

At the time of the 2004 joint WHO and CDC technical consultation, there was no uniform standard for measuring serum transferrin levels or universally established reference values (9). Mean serum transferrin receptor levels tend to range from 5 mg/L to 8 mg/L in normal subjects, although the value is heavily dependent upon the commercial assay used (11). Recent efforts have focused on evaluating the use of recombinant soluble transferrin receptor as a new standard. WHO has supported the development of such material by the National Institute for Biological Standards and Control (NIBSC) (12). In 2010, WHO reference reagent 07/202 was released by NIBSC, with an assigned value of 21.7 mg/L (303 nmol/L) (13). It is hoped that this material will be used by manufacturers to standardize serum transferrin receptor immunoassay kits, which could then promote the establishment of internationally applicable cut-off values, similar to those developed for serum ferritin.

## Summary of statement development

This summary contains information primarily from three WHO publications. The first, [Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers](#) (9), was published in 2001 and reviews methods of assessing iron status in populations and strategies for preventing iron deficiency. The document discusses the strengths and limitations of serum transferrin receptor as an indicator for iron deficiency. The 2007 publication, [Assessing the iron status of populations](#), 2nd edition (11) was published in response to a joint WHO and CDC technical consultation in 2004 and is an updated version of the document published in 2005 (10). The document presents a method of interpreting the iron status of a population, based on measured values of serum ferritin and transferrin receptors. The literature

reviews included in the 2007 publication discuss the range of serum transferrin receptor values based on different assays, and the conditions for the use of serum transferrin receptor levels as an indicator of iron status.

## Plans for update

The WHO Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, is responsible for reviewing this document and, if needed, will update it by 2017, following the procedures of the [WHO handbook for guideline development](#) (14).

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## Suggested citation

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## References

1. Skikne BS, Flowers CH, Cook JD. Serum transferrin receptor: a quantitative measure of tissue iron deficiency. *Blood*. 1990;75:1870–6.
2. Ponka P, Lok CN. The transferrin receptor: role in health and disease. *Int J Biochem Cell Biol*. 1999;31:1111–37.
3. Cook JD, Dassenko S, Skikne BS. Serum transferrin receptor as an index of iron absorption. *Br J Haematol*. 1990;75:603–9.
4. Kohgo Y, Torimoto Y, Kato J. Transferrin receptor in tissue and serum: updated clinical significance of soluble receptor. *Int J Hematol*. 2002;76:213–8.
5. Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta*. 2003;329:9–22.
6. Dimitriou H, Stiakaki E, Markaki EA, Bolonaki I, Giannakopoulou C, Kalmanti M. Soluble transferrin receptor levels and soluble transferrin receptor/log ferritin index in the evaluation of erythropoietic status in childhood infections and malignancy. *Acta Paediatr*. 2000;89:1169–73.
7. Infusino I, Braga F, Dolci A, Panteghini M. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia. A meta-analysis. *Am J Clin Pathol*. 2012;138:642–9. doi:10.1309/AJCP16NTXZLZFAIB.
8. Angeles Vázquez López M, Molinos FL, Carmona ML, Morales AC, Muñoz Vico FJ, Muñoz JL et al. Serum transferrin receptor in children: usefulness for determining the nature of anemia in infection. *J Pediatr Hematol Oncol*. 2006;28:809–15.
9. UNICEF/UNU/WHO. Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers. Geneva: World Health Organization; 2001 (WHO/NHD/01.3; [http://apps.who.int/iris/bitstream/10665/66914/1/WHO\\_NHD\\_01.3.pdf](http://apps.who.int/iris/bitstream/10665/66914/1/WHO_NHD_01.3.pdf), accessed 6 June 2014).
10. WHO/CDC. Assessing the iron status of populations, 1st ed. Report of a joint World Health Organization/Centers for Disease Control and Prevention technical consultation on the assessment of iron status at the population level. Geneva: World Health Organization; 2005.
11. WHO/CDC. Assessing the iron status of populations, 2nd ed. Assessing the iron status of populations, 1st ed. Report of a joint World Health Organization/Centers for Disease Control and Prevention technical consultation on the assessment of iron status at the population level. Geneva: World Health Organization; 2007 ([http://apps.who.int/iris/bitstream/10665/75368/1/9789241596107\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/75368/1/9789241596107_eng.pdf), accessed 6 June 2014).
12. Thorpe SJ, Sharp G, Heath A, Worwood M, Cook J. Expert Committee on Biological Standardization, Geneva, 19 to 23 October 2009. WHO reference reagent for the serum transferrin receptor (sTfR). Geneva: World Health Organization; 2009 (WHO/BS/09.2104; [http://whqlibdoc.who.int/hq/2009/WHO\\_BS\\_09.2104\\_eng.pdf](http://whqlibdoc.who.int/hq/2009/WHO_BS_09.2104_eng.pdf), accessed 6 June 2014).
13. WHO reference reagent. Recombinant soluble transferrin receptor (rsTfR). NIBSC code: 07/202. Instructions for use (Version 1.0, Dated 23/03/2010). Potters Bar: National Institute for Biological Standards and Control; 2010 (<http://www.nibsc.org/documents/ifu/07-202.pdf>, accessed 6 June 2014).
14. WHO handbook for guideline development. Geneva: World Health Organization; 2012 ([http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf), accessed 5 June 2014).

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