



C-reactive protein concentrations as a marker of inflammation or infection for interpreting biomarkers of micronutrient status

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Background

C-reactive protein (CRP) is an acute-phase protein that serves as an early marker of inflammation or infection. The protein is synthesized in the liver and is normally found at concentrations of less than 10 mg/L in the blood. During infectious or inflammatory disease states, CRP levels rise rapidly within the first 6 to 8 hours and peak at levels of up to 350–400 mg/L after 48 hours (1–5). CRP binds to phosphocholine expressed on the surface of damaged cells, as well as to polysaccharides and peptosaccharides present on bacteria, parasites and fungi (6). This binding activates the classical complement cascade of the immune system and modulates the activity of phagocytic cells, supporting the role of CRP in the opsonization (i.e. the process by which a pathogen is marked for ingestion and destruction by a phagocyte) of infectious agents and dead or dying cells (1, 6). When the inflammation or tissue destruction is resolved, CRP levels fall, making it a useful marker for monitoring disease activity (2, 5).

CRP has been most widely measured using enzyme-linked immunosorbent assays (ELISA), immunoturbidimetry, or antibody-based nephelometric assays, which are typically sensitive to concentrations of 5–20 mg/L. Recent awareness of the utility of measuring CRP as a risk factor for cardiovascular disease has led to the development of high-sensitivity CRP (hs-CRP) assays to detect lower levels of CRP; these assays are sensitive to 0.5–10 mg/L (7, 8). CRP levels are unaffected by anaemia, protein levels, red blood cell shape or patient age or sex (9). However, in women, CRP concentrations tend to be higher late in pregnancy (5).

The varying levels of CRP in response to inflammation or infection have been compared against other acute-phase proteins, including serum ferritin and serum retinol – indicators of the body's iron and vitamin A status, respectively. Serum ferritin levels increase in response to any infectious or inflammatory process, whereas serum retinol levels decrease. Therefore, the presence of an inflammatory or infectious state can potentially result in an overestimation of vitamin A deficiency and an underestimation of iron deficiency.

Scope and purpose

This document aims to provide users of the Vitamin and Mineral Nutrition Information System (VMNIS) with information about the use of CRP as a marker of inflammation or infection for assessing changes in biomarkers of nutritional status, particularly serum or

plasma ferritin or retinol levels, during infection or inflammation. It is a compilation of the existing information on cut-off values obtained from various World Health Organization (WHO) consultations. WHO has previously compiled summaries on the use of serum ferritin and plasma retinol as indicators of a population's iron and vitamin A status, respectively (10, 11).

The information included in this summary is essential for correct interpretation of serum or plasma ferritin and retinol values during times of infection or inflammation and can serve as a reference for the previously released indicator summaries. Assessment of CRP, along with indicators of iron and vitamin A status, is useful for monitoring trends in the iron and vitamin A status of populations and evaluation of the impact of public health interventions.

Description of technical consultations

The use of CRP as a marker of inflammation has been addressed in the following two WHO documents:

[Assessing the iron status of populations](#), 2nd edition (12). This document was published in 2007 and is a report of a joint WHO and US Centers for Disease Control and Prevention (CDC) technical consultation in Geneva, Switzerland, 6–8 April 2004. 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 receptor, 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.

[Influence of infection and inflammation on biomarkers of nutritional status with an emphasis on vitamin A and iron](#) (13), a background paper prepared for a WHO consultation on [Priorities in the assessment of vitamin A and iron status in populations](#) (14). This document was published in 2012 and is based on a consultation held in Panama City, Panama, 15–17 September 2010. The background paper describes the use of meta-analyses to determine the mean effect of inflammation on retinol and ferritin in different stages of the infection cycle, and makes suggestions for the use of CRP in these situations.

Discussions and recommendations

The 2004 joint WHO/CDC technical consultation supported the use of serum ferritin as an indicator of depleted iron stores and as an assessment of iron-intervention programmes (12). However, because serum ferritin is an acute-phase reactant, there are challenges in the applicability of previously established cut-off values (12–15 µg/L)

for determining iron deficiency. In 2001, a proposal was made to increase the serum ferritin threshold to 30 µg/L in the presence of infection (15); however, as summarized in the 2004 consultation, there is a need to validate this threshold in all population groups.

The consultation further discussed the use of other acute-phase proteins to facilitate interpretation of serum ferritin levels. Increases in both serum ferritin and other acute-phase proteins could confirm either infection or inflammation and explain elevated serum ferritin levels even in an iron-deficient state. However, comparison of the levels of acute-phase proteins is not universally applicable, especially in malaria-endemic areas. Parasitic infection, most often by *Plasmodium* spp., may produce a chronic acute-phase response, even in asymptomatic individuals, causing increased serum ferritin concentrations without any obvious infectious or inflammatory state (12, 16). Parasitic worm infestations may also generate an acute-phase response and result in anaemia and iron deficiency due to blood loss (12). Therefore, careful attention must be given to establishing and applying new threshold values for serum ferritin and other acute-phase proteins.

An increase in serum ferritin levels has previously been shown to parallel the rise in CRP, particularly at the onset of infection or inflammation (17). CRP levels initially rise rapidly, but quickly fall, even as ferritin levels remain elevated (18, 19). Although CRP is the most frequently used marker of the acute-phase response, α-1-antichymotrypsin (ACT) and α-1-acid glycoprotein (AGP) have also been considered for their potential role in distinguishing iron deficiency from concurrent disease states. ACT concentrations rise quickly, similar to CRP, but remain at higher levels for longer than CRP, whereas AGP concentrations initially respond more slowly but remain at higher levels for longer than either CRP or ACT (18, 19). It was suggested that AGP may be a better indicator than CRP or ACT but that a meta-analysis is necessary to explore the possibilities of using acute-phase proteins to correct serum ferritin levels in the presence of infection or inflammation (12). A serum CRP threshold of less than 5 mg/L was suggested to define normal values when using a rapid test, or less than 3–10 mg/L when using immunoassays (e.g. ELISA) (12).

In contrast to serum ferritin, serum retinol levels fall during inflammation or infection. However, similar changes in CRP and AGP levels occur relative to changes in serum retinol concentrations from baseline. Serum retinol and CRP levels initially change rapidly, with CRP levels returning to baseline prior to the normalization of serum retinol levels (20). AGP levels rise more slowly in response to inflammation or infection and remain elevated longer than CRP levels (13). No comparison of serum retinol and ACT levels has been performed.

More research is needed on assessing the iron and vitamin A status of populations in the presence of an acute-phase response. Revised cut-off values for serum ferritin and serum retinol levels based on CRP and AGP levels were proposed at the 2010 WHO consultation on [Priorities in the assessment of vitamin A and iron status in populations](#) (14, 21, 22). However, no formal recommendation from WHO is currently available.

In addition to comparing the utility of acute-phase proteins for interpreting serum ferritin and retinol levels, international reference standards for ACT and AGP must be developed. In 1986, WHO supported the development of an international standard for CRP (85/506), held by the National Institute for Biological Standards and Control for use as a calibrant for CRP assays (23). This first international standard for human CRP serves as a reference source of defined biological activity expressed in an internationally agreed unit, being assigned a value of 0.049 mIU/ampoule, for use worldwide. Currently, reference ranges for ACT and AGP are specific to the commercial assay (12). Finally, data on the prevalence of infectious diseases, malaria parasitaemia and parasitic worm infections in the context of iron deficiency could also support further investigation of the relationship between specific infections and acute-phase proteins.

Summary of statement development

This summary contains information from two WHO publications and additional resources from the scientific literature. The first WHO document, [Assessing the iron status of populations](#), 2nd edition (12), was published in 2007 and includes the interpretation of indicators of iron status during an acute-phase response. These reviews were provided for a joint WHO and CDC technical consultation held in Geneva, Switzerland,

6–8 April 2004. The second document, [Influence of infection and inflammation on biomarkers of nutritional status with an emphasis on vitamin A and iron](#) (13), was prepared as a background paper for a WHO technical consultation on [Priorities in the assessment of vitamin A and iron status in populations](#) (14).

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](#) (22).

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