# Quantitative data on the magnitude of the systemic inflammatory response and its relationship with serum measures of iron status

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**The present study aimed to quantify the magnitude of the systemic inflammatory response, measured by C-reactive protein (CRP) and albumin, and its relationship with common serum biochemical measures of iron status including total iron, transferrin, transferrin saturation, and ferritin. Retrospective interrogation of laboratory computer databases at 4 centers between 2006 and 2011 provided results from patients in which serum CRP and albumin had been measured together with iron studies (iron, transferrin, and transferrin saturation, n = 16,522) and ferritin (n = 7,226). Analyte results were categorized into groups according to CRP and albumin. When those groups with CRP <10 mg/L and albumin >35 g/L, CRP 11–80 mg/L and albumin 25-35 mg/L, and CRP >80 mg/L and albumin <25 g/L were compared, the median serum total iron was 15.0, 7.0, and 3.0 $\mu$mol/L, respectively ($P < 0.001$), an overall reduction of 80%. The median serum transferrin concentration was 2.6, 2.0, and 1.3 $\mu$mol/L respectively ($P < 0.001$), an overall reduction of 50%. The median transferrin saturation was 23%, 13%, and 10% respectively ($P < 0.001$), an overall reduction of 56%. The median serum ferritin was 77, 173, and 445 $\mu$g/L respectively ($P < 0.001$), an overall increase of 578%. The present study quantifies the impact of the systemic inflammatory response on serum measures of iron status. This association should be taken into account when measures of iron status are requested and interpreted to prevent misdiagnosis. (Translational Research 2016;176:119–126)**

**Abbreviations:** AGP = $\alpha$-1-acid glycoprotein; CRP = C-reactive protein; F = female; IL = interleukin; LOD = limit of detection; M = male; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; sTFR = soluble transferrin receptor; TIBC = total iron binding capacity; TSAT = transferrin saturation

## INTRODUCTION

The gold standard assessment of iron status is considered to be microscopy of a bone marrow trephine sample; however, this is a painful and invasive procedure.[1] There are a number of serum analytes proposed for the assessment of iron status. These include iron itself, proteins involved in its metabolism such as transferrin, ferritin, soluble transferrin receptor (sTFR), and zinc protoporphyrin, and derived values such as transferrin saturation (TSAT) and total iron binding capacity (TIBC).[2]

There is evidence that the presence of systemic inflammation is associated with decreased serum concentrations of iron and transferrin, which are negative acute phase reactants.[3] In contrast, ferritin is a positive

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## AT A GLANCE COMMENTARY

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### Background

The aim of the present observational study (n = 16,522) was to quantify the impact of the magnitude of systemic inflammation, as evidenced by C-reactive protein and albumin, on commonly measured serum biochemical measures of iron status.

### Translational Significance

The results of the present study show that serum measures of iron status, iron, transferrin, transferrin saturation, and ferritin are significantly and independently associated with CRP and albumin. A clear conclusion is that determining the iron status of patients with acute or ongoing systemic inflammation using these serum measures is problematic.

acute phase protein and its serum concentrations rise in the presence of systemic inflammation.[4] Indeed, current WHO guidance on assessment and interventions in iron status recommend that the presence of inflammation be considered when ferritin levels are measured in those who are apparently well.[5] However, the magnitude of the impact is not well quantified in patients.

There is increasing evidence that the presence of a systemic inflammatory response confounds the interpretation of a number of serum micronutrients.[6] Indeed, recent studies have quantified the impact of the systemic inflammatory response, as evidenced by both serum C-reactive protein (CRP) and albumin, on serum vitamins and micronutrients.[7,8] With reference to iron status, hepcidin is a key regulator of iron homeostasis, acting to reduce iron export and cause sequestration of iron through the inhibition of ferroportin.[9] It is thought that hepcidin synthesis is influenced by cytokines such as interleukin 6, which promotes iron uptake by cells of the innate immune system.[10] Similar to hepcidin, the synthesis of CRP by hepatocytes is driven by circulating interleukin 6.[11] In addition, albumin, although it is not directly involved in iron transport, is quantitatively the most important circulating binding protein and is itself a negative acute phase protein commonly measured in clinical practice.[12]

Therefore, the aim of the present study was to quantify the impact of the magnitude of systemic inflammation, as evidenced by CRP and albumin, on commonly measured serum biochemical measures of iron status. Furthermore, the study was carried out with the aim of developing local guidelines for the interpretation of serum measurements of iron status.

## MATERIALS AND METHODS

**Patients.** Details of all requests for iron studies (total iron, transferrin, and derived transferrin saturation) and ferritin were obtained from the biochemistry and hematology laboratory information systems of 4 Glasgow hospitals respectively for the period 1st August 2006 to 31st July 2011. These requests were made from secondary inpatient, secondary outpatient, and primary care health care providers. Iron study and ferritin results were matched to CRP and albumin results obtained on the same calendar day using electronic laboratory patient identifiers. Any iron study requests which were not accompanied by a CRP and albumin request were not included in the study. Where an individual had repeat measurements, only the first was included in the study.

Two groups were obtained: a large cohort of patients who had iron study measurement, including total iron and transferrin results (n = 16,522), and a smaller cohort of patients who had ferritin results (n = 7,226). The data set of ferritin results was not a subset of the larger iron study data set.

The audit was conducted with the intent of developing local guidelines and to aid in the interpretation of serum measurements of iron status and was approved by NHS Greater Glasgow and Clyde.

**Methods.** Serum total iron (chemically using ferene), transferrin (by the immunoturbidimetric method), CRP (by the immunoturbidimetric method), and albumin (chemically using Bromocresol purple) were measured using an automated analyzer (Architect, Abbot Diagnosis, Maidenhead, UK) in the routine biochemistry laboratories. Ferritin was analyzed using 2-step chemiluminescent microparticle immunoassay within the routine hematology laboratories. All sites used the same analytic materials and automated platforms. There were no sustained concerns regarding Internal Quality Control performance requiring investigation into the performance of the assays. The A, B, and C scores were within the EQA (NEQAS) targets during the study period. Transferrin saturation was calculated empirically from serum total iron and transferrin by each laboratory as (4 * [Fe] nmol/L)/(Transferrin mg/L) assuming 2 iron molecules bind to 1 transferrin molecule. Although the theoretical problems with this method are noted, this was the calculation used in all the laboratories during the study period.[13] Where a calculated transferrin saturation result was not available as either the iron or transferrin results were