# CLINICAL RESEARCH

## Assessment of iron stores in inflammation by assay of serum ferritin concentrations

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### Abstract

**A serum ferritin concentration of below 15 μg/l is accepted as indicating diminished iron reserves in an otherwise normal person. In patients with inflammatory disease this lower limit of normality may be inappropriate as inflammation may directly stimulate the production of ferritin protein. Results obtained in a survey of 150 patients with early inflammatory joint disease suggest that a ferritin concentration of 55 μg/l is a more appropriate lower limit of normality.**

### Introduction

Serum ferritin concentrations provide a reliable index of iron stores in normal subjects[1]; so also, however, do the haemoglobin concentration and red-cell variables, which therefore usually render estimation of ferritin concentration superfluous. In inflammatory conditions red-cell variables, serum iron concentrations, and transferrin concentrations do not serve as an index of iron stores. This is because iron is redistributed from the plasma and red-cell compartments to the stimulated reticuloendothelial cells and stored within the protein apoferritin as ferritin.[2] Serum ferritin concentration, which is thought to reflect intracellular ferritin concentrations, has been recommended as a suitable index by which to assess iron stores in rheumatoid inflammation.[3] "Ferritin" in this context, however, is a misnomer as all routinely used assays measure only the apoferritin concentration, apoferritin being a protein that contains variable quantities of iron.

Intracellular iron is not the only stimulus to production of apoferritin. Animal studies have shown that inflammation may induce synthesis of apoferritin independently of iron.[4] If this is true in man it implies that an iron-deficient subject, with stimulation by an inflammatory process, may develop a serum ferritin concentration within the normal range. This hypothesis has not been tested directly, nor the extent of this non-specific acute-phase response defined, yet it has considerable relevance to the investigation and treatment of aneamic patients with acute or chronic inflammatory diseases.

We examined this hypothesis in two ways: directly, by observing the effect of inflammatory synovitis on serum ferritin concentrations in patients known to have a serum ferritin concentration within the range indicating iron deficiency, and indirectly, by measuring serial ferritin concentrations in patients who presented with an acute inflammatory synovitis but whose disease settled rapidly and completely.

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### Patients, methods, and results

Serial serum ferritin concentrations were measured using a commercially available radioimmunoassay (iodine-125-labelled ferritin; Gammadab, Travenol Laboratories). Patients were excluded from the survey if they had received any preparation containing iron.

*Direct study*—In a prospective survey of 150 patients with early inflammatory arthritis eight patients were found to have a normal serum ferritin concentration (≥15 μg/l) at presentation (range 55–15 μg/l) but low concentrations (<15 μg/l) during follow-up (range 13-5 μg/l). In these eight patients further exacerbation of the disease was reflected by an increase in ferritin concentrations. The maximum serum ferritin concentration observed was 45 μg/l, but in none of the patients was the exacerbation of the disease severe. One further patient (a 60-year-old man) with severe rheumatoid disease was found to have no iron stores in the bone marrow. Serum ferritin concentration was 70 μg/l. Synovial fluid ferritin concentration, however, was 4000 μg/l, and biopsy of the inflamed synovial membrane confirmed the presence of large concentrations of apoferritin protein (stained with the immunoperoxidase technique) and an appreciable quantity of ferric iron (stained with Perls's reagent).

*Indirect study*—Among the same patient population 13 patients (11 women, two men) were found to be in total disease remission at six-month follow-up. Four of these had had a ferritin concentration below 15 μg/l at presentation (range 14–8 μg/l), but five more had low concentrations when in total remission (range 10–5 μg/l). In this population the maximum ferritin concentration that fell to less than 15 μg/l was 55 μg/l. This was in a 22-year-old woman with classical rheumatoid arthritis, which remitted spontaneously over six months. During this time the haemoglobin concentration rose from 8 to 13 g/dl and the IgM rheumatoid factor titre reverted from being strongly positive (Rose-Waaler titre 1/512) to being negative.

## Discussion

These observations suggest either that small quantities of iron may stimulate the production of large quantities of apoferritin or that production of apoferritin may occur independently of iron. A serum ferritin concentration greater than 55 μg/l, however, would appear to exclude appreciable iron deficiency in the presence of synovial inflammation. The difficulties in assessing total body iron stores from bone-marrow values are highlighted by the observation that iron may be redistributed to other active reticuloendothelial organs (synovial membrane). Thus the much greater fluctuations in serum ferritin concentrations observed during changes in inflammatory activity[5] probably reflect a fundamental disturbance in iron kinetics with a redistribution of iron from the plasma, red-cell, and bone-marrow compartments to any stimulated reticuloendothelial cell and not a non-specific production of apoferritin protein.

A teleological explanation for this phenomenon relates to the nutritional requirement of replicating bacteria for iron. The drop in serum iron concentration observed early during inflammation and infection may be seen as an attempt to deprive a potential pathogen of an essential growth factor. The need of reticuloendothelial cells to manufacture a suitable storage protein for this iron in advance is understandable in view of the known stimulatory effect of free iron on oxidative radical reactions.[6]

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# Prostacyclin and thromboxane in diabetes

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## Abstract

**Concentrations of the stable antiaggregatory prostacyclin metabolite 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) and of the proaggregatory thromboxane $A_2$ metabolite thromboxane $B_2$ were measured by radioimmunoassay in plasma from 53 diabetics. In 33 of these patients the ability of platelets to produce thromboxane $B_2$ during spontaneous clotting was also studied.**

**Plasma 6-keto-$PGF_{1\alpha}$ concentrations were higher ($p<0.05$) in the diabetics (mean 107·7±SE 7·6 ng/l) than in non-diabetic controls matched for age and sex (87·5±4·7 ng/l), and diabetics with microangiopathy (n=28) had higher ($p<0.01$) concentrations (124·3±10·8 ng/l) than those without microangiopathy (n=25; 89·2±9·3 ng/l). Plasma thromboxane $B_2$ concentrations were also higher ($p<0.01$) in the diabetics (mean 218·5±SE 25·3 ng/l) than in the controls (127·7±9·8 ng/l), but this increase was not related to microangiopathy. The ability of platelets to generate thromboxane $B_2$ did not differ between the diabetics (181·4±16·4 μg/l) and controls (195·8±11·8 μg/l). Platelets of diabetics with microangiopathy or taking oral hypoglycaemic agents (n=19), however, produced decreased amounts of thromboxane $B_2$ during clotting. Plasma concentrations of 6-keto-$PGF_{1\alpha}$ and thromboxane $B_2$ were not related to concentrations of glucose, haemoglobin $A_1$, high-density lipoprotein cholesterol, cholesterol, triglycerides, magnesium, or creatinine.**

**These results suggest that in diabetics with microangiopathy a balance between prostacyclin and thromboxane $A_2$ is shifted to dominance by prostacyclin.**


Dr Jorma Kaila died after this paper had been accepted.


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## Introduction

The increased adhesiveness and aggregability of platelets in diabetes mellitus may be related to the development of diabetic angiopathy, but the causes of these platelet abnormalities are not known.[1-3] Diminished production of potent antiaggregatory prostacyclin by the vascular wall[4] shown by some in-vitro studies in experimental[5,6] and human diabetes[7,8] has now been disputed.[9] Other studies have shown an increased generation of proaggregatory thromboxane $A_2$[10] by diabetic platelets in vitro.[11-13] Because the balance between prostacyclin and thromboxane $A_2$ rather than the absolute concentrations of these substances may be crucial in the interactions between platelets and blood-vessel walls,[14] we measured circulating concentrations of the stable hydration products of prostacyclin and thromboxane $A_2$—namely, 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) and thromboxane $B_2$[10,15]—in plasma from 53 diabetics and 53 controls matched for age and sex. We also studied the ability of platelets to produce thromboxane $B_2$ during spontaneous clotting of the blood.

## Subjects and methods

The 53 diabetics (21 men, 32 women) were aged 18–76 years (mean 53·1±SE 3·1 years) (table I). Fourteen had juvenile-onset diabetes and 39 adult-onset disease, and the duration of diabetes varied from two months to 33 years (mean 14·7±SE 1·3 years). Thirty-four were receiving once- or twice-daily subcutaneous insulin with a mean dose of 45·9±2·2 units/70 kg, and 19 were being treated with oral hypoglycaemic agents (glipizide in 12, metformin hydrochloride in four, and glibenclamide in three). No ketonuria was detected in any patient. Twenty-eight patients had diabetic microangiopathy, defined as