Serum ferritin levels are increased in patients with glomerular diseases and proteinuria

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Abstract

Background. Ferritin is a high molecular weight protein which reflects body iron stores, but may also rise in the case of an acute phase response. Recently, ferritin has been identified as a predictive factor in the development and progression of atherosclerosis. This is the first report on serum ferritin levels in patients with proteinuria.

Methods. We have analysed the data of 142 male patients with a glomerular disease, and proteinuria exceeding 1 g/day. In all patients, we measured various parameters related to proteinuria, serum ferritin and serum iron. Serum β₂-microglobulin and the Modification of Diet in Renal Disease (MDRD) equation were used as measures of the glomerular filtration rate (GFR).

Results. Mean age (±SD) was 46±15 years, MDRD-GFR 57±25 ml/min/1.73 m² and median proteinuria 8.0 g/day [interquartile range (IQR) 3.6–13]. Serum albumin (29±9 g/l) and transferrin levels (1.7±0.5 g/l) were low, and cholesterol levels were elevated (median 7.3, IQR 5.9–9.5 mmol/l). Median serum ferritin was 148 μg/l (IQR 89–282), and exceeded 280 μg/l, the upper limit of normal, in 36 patients (25%). Elevated serum ferritin levels could not be explained by an acute phase response as determined by C-reactive protein, or haemochromatosis (DNA analysis). Regression analysis showed an independent relationship between ferritin levels and serum cholesterol, GFR and serum transferrin.

Conclusions. Serum ferritin levels are elevated in patients with overt proteinuria. The independent negative relationship between serum ferritin and transferrin points to a specific process and suggests that increased production of ferritin may compensate for the loss of the iron-binding protein transferrin, thus reducing the amount of free iron. Further studies are needed to elucidate the role of ferritin in patients with proteinuria, especially because of the suggested association between ferritin and atherosclerosis.

Keywords: ferritin; glomerulopathy; iron; proteinuria

Introduction

In patients with proteinuria, disturbances in iron metabolism may occur as a consequence of the increased urinary excretion of the iron-binding protein transferrin. The resultant losses of iron may deplete body iron stores. Indeed, iron-deficient anaemia can develop in patients with a nephrotic syndrome, although only a few cases have been clearly documented [1]. Alternatively, the urinary loss of transferrin may harbour the risk of iron-mediated toxicity. Free iron is able to catalyse the generation of reactive oxygen species, specifically hydroxyl radicals. In urine with a pH <6.5, iron will be released from transferrin and may cause tubular cell injury. Indeed, it has been suggested that iron plays a role in the progression of renal insufficiency in patients with proteinuria [2]. Decreased serum transferrin levels may contribute to elevated levels of free, non-transferrin-bound iron in the serum, which could give rise to free radical-mediated lipid peroxidation and ensuing injury of the vascular endothelial cells [3]. Within cells, iron is stored in complexes with ferritin. Serum ferritin levels are supposed to reflect body iron stores. Elevated levels of ferritin may signal iron overload, as seen in patients with haemochromatosis. The potential role of free iron-mediated endothelial cell injury has received more attention due to recent studies that have incriminated serum ferritin as an independent predictor of coronary artery disease [4].

Recently, we observed unexpectedly high serum ferritin levels in some of our patients with normal
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renal function and proteinuria. This observation resulted in the present study. In a cohort of male patients, we have examined the relationship between proteinuria and serum ferritin levels. Our data indicate that proteinuria is associated with increased levels of serum ferritin. To obtain insight into the mechanisms involved, additional studies were performed.

Patients and methods

In our centre, patients with proteinuria are evaluated using a standard protocol as part of a large cohort study. For this study, we analysed data obtained in patients with proteinuria who visited our out-patient clinic in the period between December 1995 and February 2000. We included all patients with a glomerular disease and proteinuria >1 g/day. We analysed the data of male and female patients separately because of the unpredictable effects of the menopausal state in women on iron metabolism.

Study protocol

Patients come to the ward after an overnight fast. Patients are instructed to take 4000 mg of sodium bicarbonate on the evening before to ensure that urinary pH exceeds 6.0, which is mandatory for the measurement of urinary β2-microglobulin. Upon arrival, 375–500 ml of tap water is given to enforce diuresis. The patients remain supine for 2 h except for voiding. Blood pressure measurements take place using an automatic device (DINAMAP, Criticon, Tampa FL). Timed urine samples are collected, and in the middle of the collection period a blood sample is drawn. In addition, 24 h urine samples are collected.

Serum ferritin levels were measured in a control group of male patients with renal disease and proteinuria <1.0 g/day, who visited the out-patient clinic in the period between November 2003 and January 2004. Because of the relationship between severe atherosclerosis and inflammation, we excluded patients with severe atherosclerotic renal disease (renal artery stenosis).

Laboratory measurements

Blood samples were used for the determination of creatinine, urea, β2-microglobulin, albumin, transferrin, IgG, cholesterol, ferritin, iron, iron-binding capacity and haemoglobin. In the timed urine samples, albumin and transferrin were measured. Total proteinuria was determined in 24 h urine samples. The concentrations of creatinine, urea, cholesterol and urinary total protein were measured with standard automated techniques. The concentrations of albumin and transferrin in serum and urine were measured by immunonephometry on a BNII nephelometer (Behring, Marburg, Germany) using antibodies whose specificity was checked by Ouchterlony double immunodiffusion and immunoelectrophoresis (Dako, Glostrup, Denmark). β2-Microglobulin was measured by enzyme-linked immunosorbent assay (ELISA) as described before [5]. Ferritin was measured on an Immulite 1 (DPC, Los Angeles, CA) using beads coated with monoclonal antiferritin and an alkaline phosphatase polyclonal conjugate.

Our reference values are based on those given by the manufacturer (Abbott Diagnostics) of the Immulite, which were found to be similar to those measured by the Immulite. This means that the upper value of the normal range is 280 μg/l in males and 80 μg/l in pre-menopausal women. Iron and total iron-binding capacity (TIBC) were both measured on the Hitachi 747 (Roche, Almere, The Netherlands) using the ferrozine colour reaction. The TIBC is calculated from the iron plus the unsaturated iron-binding capacity. The percentage transferrin saturation is calculated as serum iron/TIBC.

High sensitivity C-reactive protein (CRP) concentrations were determined with a BNII nephelometer (Behring, Marburg, Germany) using the N High Sensitivity CRP assay (Dade-Behring).

HFE-genotyping of patients was performed using a previously described PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method [6].

Calculations and statistics

The creatinine clearance was calculated according to the Cockcroft and Gault formula [7]. We also used the Modification of Diet in Renal Disease (MDRD) equation 7 as a measure of the glomerular filtration rate (GFR) [8]. We used the following equation: estimated \( \frac{GFR}{[\text{serum creatinine}]^{0.999} \times [\text{age}]^{-0.176}} \times \begin{cases} 0.762 & \text{if patient is a female} \\ 1 & \text{if patient is a male} \end{cases} \times \begin{cases} 0.170 & \text{if patient is a female} \\ 0.176 & \text{if patient is a male} \end{cases} \ \times \begin{cases} 1 & \text{if patient is a female} \\ 0.85 & \text{if patient is a male} \end{cases} \ \times \text{[serum albumin]}^{0.318} \). Mean arterial pressure was the average of the last six blood pressure measurements in a sequence of 10 measurements. For the comparison of means, the Student t-test (two groups) or ANOVA (multiple groups) was used for parameters with normal distribution, and the Mann–Whitney U-test or Kruskall–Wallis test were used in the case of non-parametric distribution. Correlations were made using the Spearman test. Linear regression analysis was performed to define independent parameters related to serum ferritin. In the multiple regression model, we entered factors that proved significant in univariate analysis. The analysis was repeated substituting the various markers of the GFR (see Results). In a subgroup of patients showing remission of proteinuria, parameters before and after remission were compared using the paired t-test or Wilcoxon signed rank test. Results are given as means ± SD, or medians with interquartile ranges (IQRs) when appropriate. A P-value <0.05 was considered significant. All statistics were performed using SPSS software, version 11 (SPSS Inc., Chicago, IL).

Results

During the study period, we evaluated 142 male patients with a proteinuria >1 g/day. The underlying renal diseases were: minimal change nephropathy \( n = 12 \), focal glomerulosclerosis \( n = 29 \), membranous nephropathy \( n = 50 \), IgA nephropathy \( n = 33 \), Henoch–Schönlein purpura \( n = 2 \), mesangiocapillary glomerulonephritis \( n = 3 \), extracapillary glomerulonephritis \( n = 2 \), diabetic nephropathy \( n = 1 \), unspecified glomerulonephritis \( n = 5 \), post-infectious glomerulonephritis \( n = 1 \), amyloidosis \( n = 2 \) and Alport’s syndrome \( n = 2 \). The baseline characteristics of the patients are summarized in Table 1. In 36 of the patients (25%), levels of ferritin exceeded the upper...
limit of normal (>280 μg/l). Patients with elevated ferritin levels were older, had more severe impairment of renal function, higher proteinuria, higher cholesterol levels, and lower serum albumin and serum transferrin levels (Table 1). Serum haemoglobin levels were not different between the groups. Two patients were treated with iron supplements, and one of them was also treated with erythropoetin. They both had normal ferritin levels. Thirty-five patients were treated with lipid-lowering drugs, 22 (21%) in the group with normal ferritin levels and 13 (36%) in the group with elevated ferritin levels. Thirty-five patients were treated with lipid-lowering drugs, 22 (21%) in the group with normal ferritin levels and 13 (36%) in the group with elevated ferritin levels (NS).

In univariate analysis, serum ferritin correlated significantly with serum β2-microglobulin ($r = 0.31$, $P < 0.001$), MDRD-GFR ($r = 0.31$, $P < 0.001$), serum albumin ($r = -0.39$, $P < 0.001$), serum transferrin ($r = -0.47$, $P < 0.001$), cholesterol ($r = 0.35$, $P < 0.001$), urinary transferrin excretion ($r = 0.33$, $P < 0.001$), urinary albumin excretion ($r = 0.33$, $P < 0.001$), proteinuria ($r = 0.38$, $P < 0.001$) and TIBC ($r = -0.45$, $P < 0.001$), and more weakly with the creatinine clearance calculated by the Cockcroft and Gault formula (ECC) ($r = -0.19$, $P = 0.02$), serum iron ($r = -0.19$, $P = 0.02$), haemoglobin ($r = -0.28$, $P = 0.001$) and age ($r = 0.23$, $P = 0.007$). Serum ferritin was not significantly correlated with serum creatinine ($r = 0.16$, $P = 0.054$).

Multivariate analysis

Eight variables with the highest correlation coefficient in the univariate analysis were included in the multiple linear regression analysis. Since TIBC is almost similar to serum transferrin, this parameter was not included. Only serum cholesterol ($P < 0.0001$), serum β2-microglobulin ($P < 0.0001$), serum transferrin ($P = 0.005$) and transferrin excretion ($P = 0.025$) were independently related to serum ferritin (Figure 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of patients with proteinuria</th>
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<tbody>
<tr>
<td>Total</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
</tr>
<tr>
<td>ECC (ml/min/1.73 m$^2$)</td>
</tr>
<tr>
<td>MDRD (ml/min/1.73 m$^2$)</td>
</tr>
<tr>
<td>S. creatinine (μmol/l)</td>
</tr>
<tr>
<td>Serum β2-microglobulin (mg/l)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
</tr>
<tr>
<td>Ferritin (μg/l)</td>
</tr>
<tr>
<td>Transferrin (g/l)</td>
</tr>
<tr>
<td>Fe (μmol/l)</td>
</tr>
<tr>
<td>TIBC (μmol/l)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
</tr>
<tr>
<td>Hb (mmol/l)</td>
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<tr>
<td>Proteinuria (g/day)</td>
</tr>
</tbody>
</table>

Overall data are presented as well as data for the patients with normal ferritin levels (<280 μg/l) and high ferritin levels (>280 μg/l). Data are given as means±SD or median (interquartile range).

MAP = mean arterial pressure; TIBC = total iron-binding capacity; ECC = creatinine clearance calculated by the Cockcroft and Gault formula; MDRD = GFR by MDRD equation 7 [8].

$P$-value: patients with high ferritin levels compared with patients with normal ferritin levels.

Serum β2-microglobulin is a marker of the GFR, and we observed a high correlation between serum β2-microglobulin and MDRD-GFR ($r = -0.862$, $P < 0.001$). To document that the GFR was independently associated with serum ferritin, we repeated the multiple regression analysis by including in separate analyses two markers of GFR. If serum β2-microglobulin was omitted, the MDRD-GFR proved a significant independent factor. Both serum β2-microglobulin and MDRD-GFR performed better than ECC or serum creatinine.
To illustrate the impact of proteinuria and hypoalbuminaemia on serum ferritin, we have performed a subanalysis of the data dividing patients according to the level of proteinuria and hypoalbuminaemia (Table 2). As depicted in Figure 2, serum ferritin levels were significantly higher in patients with the most severe proteinuria (i.e. nephrotic syndrome). Results were similar if we limited the analysis to patients with the best preserved renal function (MDRD-GFR above the median; Table 2). The differences are even more pronounced if we compare the data with serum ferritin levels in a control group of chronic renal failure patients without proteinuria. In this control group, 36 male patients were included with a mean age of 49 ± 15 years, mean serum creatinine of 128 ± 52 μmol/l, and median proteinuria of 0.1 g/day. None of these patients was treated with iron supplements or erythropoetin. Underlying renal diseases were membranous nephropathy (n = 4), IgA nephropathy (n = 10), Henoch-Schönlein purpura (n = 1), tubulo-interstitial nephritis (n = 3), solitary kidney (n = 5), polycystic kidney disease (n = 9), unspecified renal disease (n = 2) and post-infectious glomerulonephritis (n = 2). In these control patients, serum ferritin levels were 99 (IQR 63–185), which was significantly lower compared with serum ferritin in the 142 patients with proteinuria (P = 0.007).

Additional studies were done to formally exclude that elevated ferritin levels were the result of an acute phase response. Therefore, CRP levels were determined in 35 patients with elevated ferritin levels (one patient was omitted because there was not enough serum available to perform the additional CRP determination), and in 32 patients matched for age and GFR included in the group with normal ferritin levels (Table 3). CRP levels were not significantly different, arguing against an acute phase response. To document the possibility of having included patients with hereditary haemochromatosis, DNA analysis was performed in 13 patients fulfilling the criteria of haemochromatosis, i.e. the presence of both a serum ferritin level > 280 μg/l and a serum transferrin saturation > 45%. No patient was homozygous for the Cys282Tyr mutation and only one was heterozygous. The latter was also heterozygous for the His63Asp mutation; however, such compound heterozygoty rarely leads to iron deposition. The results of the gene analysis argue against HFE-related primary haemochromatosis as a cause of the laboratory abnormalities.

To document the relationship of proteinuria and serum ferritin further, we have analysed the data of patients in whom measurements were repeated during their follow-up. Specifically, we have selected all patients with proteinuria > 3.5 g/day and elevated ferritin levels at baseline, in whom proteinuria was

### Table 2. Serum ferritin and other laboratory parameters in patients in groups according to the level of proteinuria

<table>
<thead>
<tr>
<th></th>
<th>Uprot &lt;3.5 g/day</th>
<th>Uprot ≥3.5 g/day</th>
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<tbody>
<tr>
<td></td>
<td>S.alb &gt;30 g/l</td>
<td>S.alb ≤30 g/l</td>
</tr>
<tr>
<td>n</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45±13</td>
<td>47±15</td>
</tr>
<tr>
<td>MDRD-GFR (ml/min/1.73 m²)</td>
<td>58±25</td>
<td>53±25</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>2.2 (1.6–2.8)</td>
<td>5.5 (4.1–8.4)</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>108 (69–189)</td>
<td>122 (72–268)</td>
</tr>
<tr>
<td>MDRD-GFR ≥55 ml/min/1.73 m²</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±12</td>
<td>43±16</td>
</tr>
<tr>
<td>MDRD (ml/min/1.73 m²)</td>
<td>78±18</td>
<td>81±17</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>2.4 (1.9–2.9)</td>
<td>6.3 (4.2–8.2)</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>97 (62–161)</td>
<td>89 (67–240)</td>
</tr>
</tbody>
</table>

Data are given as means±SD or median (interquartile range). Uprot = proteinuria per day. MDRD-GFR = GFR by MDRD equation 7 [8]. The upper part of the table represents data of all patients and the lower part represents data of patients with values of GFR above the median.

*P* < 0.05 vs patients with Uprot <3.5 g/day.
Table 3. Comparison of CRP levels in patients with high serum ferritin levels (>280 µg/l) vs age-matched patients with normal ferritin levels (<280 µg/l)

<table>
<thead>
<tr>
<th></th>
<th>Normal ferritin (n = 32)</th>
<th>High ferritin (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 12</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>MDRD-GFR</td>
<td>44 (38–66)</td>
<td>39 (28–52)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>29 ± 8</td>
<td>25 ± 9*</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>8.1 (6.9–180)</td>
<td>9.6 ± 3.5</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>119 (307–517)**</td>
<td>344 (307–517)**</td>
</tr>
<tr>
<td>Transferrin (g/l)</td>
<td>1.8 ± 0.4</td>
<td>1.4 ± 0.4**</td>
</tr>
<tr>
<td>Serum β2-microglobulin (mg/l)</td>
<td>4.8 ± 2.2</td>
<td>5.4 ± 2.8</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>8.1 (3.8–13)</td>
<td>11.2 (5.6–15)*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>2.8 (0.9–4.3)</td>
<td>2.1 (1.0–5.6)</td>
</tr>
</tbody>
</table>

Data are given as means±SD or median (interquartile range).

MDRD-GFR = GFR by MDRD equation 7 [8].

#P = 0.05, *P < 0.05 and **P < 0.01 compared with patients with normal ferritin levels.

Table 4. Effects of >50% reduction of proteinuria on serum levels of ferritin in 12 patients showing (partial) remission of proteinuria during follow up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Proteinuria (g/day)</td>
<td>11.4 (10–16)</td>
<td>0.9 (0.5–1.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum ferritin (µg/l)</td>
<td>402 (330–896)</td>
<td>212 (143–260)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>22 ± 7</td>
<td>39 ± 3</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum transferrin (g/l)</td>
<td>1.3 ± 0.5</td>
<td>2.1 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>11.1 ±4.9</td>
<td>5.2 ± 1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum β2-microglobulin (mg/l)</td>
<td>6.0 ±2.3</td>
<td>3.0 ± 1.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are given as means±SD or median (interquartile range).

Our data clearly indicate that serum ferritin levels are increased in patients with overt proteinuria. This observation is new and may seem somewhat unexpected in view of the reports that patients with a nephrotic syndrome are predisposed to iron deficiency because of the continued losses of the iron-binding protein transferrin. Further studies are warranted, in particular in view of recent data suggesting a relationship between cardiovascular morbidity/mortality and elevated ferritin levels.

We have limited the analysis to male patients, since pre-menopausal blood loss and the widespread variable use of iron supplements in women may influence serum ferritin levels. In male patients, regular blood loss is unlikely, although we did not formally test patients for occult blood loss.

We found that cholesterol, β2-microglobulin and transferrin were independently related to serum ferritin. Based on these results, three likely explanations for the increases of serum ferritin in patients with proteinuria must be considered.

The first relationship, between serum ferritin and serum cholesterol, suggests that the increased ferritin levels may result from an increased non-specific hepatic protein synthesis. In patients with a nephrotic syndrome, such an increased non-specific synthesis rate has been reported previously for various proteins such as albumin, transferrin, fibrinogen and low-density lipoprotein (LDL)-APO B100 [9–11]. The increased synthesis of the latter protein is held responsible for the elevated levels of LDL-cholesterol in patients with a nephrotic syndrome [9]. In the latter study, a correlation was observed between serum cholesterol and albumin synthesis rate, thus suggesting that serum cholesterol can be used as a marker of hepatic protein synthesis rate. The increased hepatic synthesis cannot fully compensate the losses of the smaller proteins albumin and transferrin, thus explaining the hypoalbuminaemia and hypotransferrinaemia in patients with proteinuria [11]. However, levels of very large proteins such as fibrinogen and α2-
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macroglobulin will rise as a result of the increased production [10,12]. As ferritin is also a large molecular weight protein (480 kDa), it is likely that serum levels will rise as the production by the liver increases. Admittedly, as far as we know, thus far no studies have documented ferritin production rates in patients with a nephrotic syndrome.

The second independent relationship was between ferritin and well known markers of GFR such as serum β2-microglobulin or MDRD-GFR [8,13]. In univariate analysis, we observed a relationship between ferritin and ECC; however, in the multiple regression analysis, serum β2-microglobulin or MDRD-GFR proved the best predictor, clearly reflecting the weakness of ECC as a measure of GFR. High ferritin levels have been observed in patients with chronic renal insufficiency, in particular in patients on haemodialysis. Interpretation of the data in the latter patients is hampered by the fact that many patients on haemodialysis have received blood transfusions, or are being treated with erythropoetin and iron supplements. In haemodialysis patients, there is evidence that changes in ferritin levels are a reflection of the malnutrition inflammation complex syndrome, which explains the negative correlation of serum ferritin with serum albumin or serum transferrin in these patients [14,15]. In haemodialysis patients, there is also evidence of an acute phase response [14,16]. In non-dialysed patients with chronic renal failure (range of serum creatinine 651–1118 μmol/l), ferritin levels were in the normal range. In contrast, patients with acute renal failure (range of serum creatinine 528–1725 μmol/l), in whom an acute phase response is often present, all had markedly increased ferritin levels [17].

From our data, it is evident that the high ferritin levels in patients with proteinuria cannot be attributed to an acute phase response. Using a high sensitivity CRP assay, we observed no difference in CRP levels between patients with a high ferritin level and patients with normal ferritin levels. Normal CRP levels have been reported before in patients with nephrotic syndrome [18]. Thus, we have no likely explanation for the observed association between serum ferritin levels and renal function.

The third independent relationship that we found was between ferritin and loss of transferrin as reflected by low serum transferrin levels and high urinary transferrin excretion rates. We hypothesize that serum ferritin levels increase to accommodate elevated free (non-transferrin-bound) serum iron, an important mediator of free radical damage [2]. There is some evidence available that expansion of the free iron pool can stimulate ferritin synthesis both intracellularly and in serum [19]. In patients with a nephrotic syndrome, intestinal iron absorption may be increased as a result of the low transferrin levels. In this respect, there is a parallel with an experimental model of genetic hypotransferrinaemia in mice. In these mice, both the mucosal uptake of iron and iron transfer to the tissues (liver parenchym) were enhanced [20]. This increased transport of iron may be associated with increased amounts of non-transferrin-bound iron in the circulation. Also, increases of ferritin as observed in our patients with nephrotic syndrome have been reported in children with familial hypotransferrinaemia, a rare genetic disorder [21].

Although hypercholesterolaemia and hypotransferrinaemia (both correlated with serum ferritin) are the result of proteinuria, we found only a rather weak correlation between serum ferritin levels and proteinuria. In fact, proteinuria was not identified in the multivariate analysis as an independent predictive factor. Two explanations can be put forward. First, we suggest that the loss of individual proteins such as transferrin is more important than total proteinuria. Secondly, proteinuria is a poor reflection of glomerular protein loss, and partly dependent on tubular protein metabolism. Glomerular protein losses may be more closely linked to hepatic protein synthesis. Other investigators indeed have observed that proteinuria was not correlated with the hepatic albumin synthesis rate in patients with a nephrotic syndrome [10].

We can only speculate about the consequences of the increased ferritin levels in patients with proteinuria and hypotransferrinaemia. Ferritin levels may be a marker of the free iron load and ensuing damage. In the past few years, several studies that addressed the development and progression of atherosclerosis have identified serum ferritin as a strong predictor for carotid and coronary atherosclerosis [4]. The associations between ferritin and progression of carotid atherosclerosis as well as between ferritin and cardiovascular disease or death were stronger if hyperlipidaemia was also present. Changes in body iron stores modified the risk of atherosclerosis, with a beneficial effect of relative iron depletion. The most likely underlying pathophysiological mechanism is stimulation of lipid peroxidation and oxidative stress by ferrous ions that have been released from ferritin [3]. The above-mentioned data suggest that high ferritin levels may be indicative of iron-mediated cell injury, which may contribute to the development of atherosclerosis in patients with a persistent nephrotic syndrome.

In conclusion, serum ferritin levels are elevated in patients with nephrotic range proteinuria. We hypothesize that the increase of ferritin is partly the result of an increased non-specific hepatic protein synthesis. Furthermore, we suggest that ferritin production is increased to compensate for the loss of iron-binding transferrin, and to accommodate otherwise unopposed free iron. Further studies are needed to test our hypothesis and to evaluate the consequences of elevated ferritin levels in patients with the nephrotic syndrome, particularly because of the suggested relationship between ferritin and risk of cardiovascular morbidity.

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