Urinary iron loss in the nephrotic syndrome—an unusual cause of iron deficiency with a note on urinary copper losses

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Summary

Two patients with long-standing nephrotic syndrome are described in whom urinary iron losses may have contributed towards an iron deficiency state. Seven other nephrotic patients were also studied. Increased urinary iron excretion was found in six out of nine patients and increased urinary copper excretion in all eight patients in whom it was measured. Trace metal losses in the urine in nephrotics may be important clinically.

KEY WORDS: anaemia, ferritin, glomerulonephritis.

Introduction

There have been isolated case reports of iron deficiency anaemia in patients with the nephrotic syndrome which have been attributed to excessive urinary losses of transferrin and iron (Heilmeyer *et al.*, 1966; Hancock, Onstad and Wolf, 1976; Ellis, 1977). We report two patients with nephrotic syndrome where excessive urinary iron loss probably contributed to iron deficiency. Studies on a further seven patients with nephrotic syndrome including excretion of iron and copper are reported.

Case reports

Case 1

A white male, aged 56 years, presented with nephrotic syndrome in 1977. At presentation, the urine protein excretion was 9.5 g/24 hr and the plasma albumin 20 g/l. The ^{51}Cr EDTA clearance was 83 ml/min. A renal biopsy showed membranous glomerulonephritis. A search for an associated neoplasm was negative and investigations included a normal chest X-ray, barium meal and barium enema.

Tests for carcinoembryonic antigen were negative and a full blood count was normal. The patient was treated with frusemide and followed regularly in out-patients. Blood counts remained normal until 1981 when the mean corpuscular haemoglobin (MCH) fell to 25 pg although the haemoglobin concentration and mean cell volume (MCV) were normal. The serum ferritin was $<5 \mu\text{g/l}$ on two occasions. Three stool specimens were negative for occult blood in November 1981 and a further three specimens were negative in December 1981. A further barium meal and barium enema were again normal. The ^{51}Cr EDTA clearance had fallen to 31 ml/min. The urine protein excretion at this time was 11.4 g/24 hr with a transferrin excretion of 0.7 g/24 hr and a urinary iron excretion of $8.0 \mu\text{mol/24 hr}$. The plasma albumin was 36 g/l. The patient was treated with oral iron (Feospan 1 bd) and over the next 3 months the MCH and serum ferritin levels returned to normal.

Case 2

An Asian female, aged 46 years, presented with nephrotic syndrome in 1979 when the urine protein excretion was 2.6 g/24 hr and the plasma albumin 25 g/l. The ^{51}Cr EDTA clearance was 98 ml/min. A renal biopsy showed membranous glomerulonephritis. There was no evidence of an associated neoplasm. A chest X-ray and barium meal were normal. In 1982, an anaemia was noted with a haemoglobin of 9 g/dl, MCH 26 pg and an MCV of 85 fl. The ^{51}Cr EDTA clearance had fallen to 23 ml/min. Menstruation was regular and considered to be normal. Three stool specimens for occult blood were negative. A barium meal and follow-through examination were normal. A bone marrow aspirate showed reduced iron in macrophages and no iron in developing erythroblasts. The direct Coombs test was negative. The sickle

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test was negative. Serum and red cell folate and serum vitamin B₁₂ levels were normal. Dietary assessment indicated adequate intakes of iron, vitamin B₁₂ and folates, but with a high fibre and phytate diet which could interfere with the absorption of iron. A double isotope Schilling test was normal. The serum ferritin was $<5 \mu\text{g/l}$. The urine protein excretion at this time was 8 g/24 hr with a transferrin excretion of 0.52 g/24 hr and a urinary iron excretion of $2.6 \mu\text{mol/24 hr}$. The plasma albumin was 25 g/l. The patient was treated with oral iron (ferrous gluconate 300 mg tds) and over the next 3 months the MCH and serum ferritin levels returned to normal. The patient still had a normochromic normocytic anaemia presumably due to the chronic renal failure.

Further studies

Methods

Seven other patients with nephrotic syndrome were studied and 24 hr urine collections made for determination of urine protein, transferrin, iron and copper. Blood samples were taken for estimation of plasma iron, ferritin, transferrin, albumin and copper. The urine collection containers were cleaned before use by soaking in 10% (v/v) nitric acid and then extensively rinsed with deionized water. They were subsequently shown to be essentially iron and copper free. Serum albumin was measured on a Technicon 'Quantachem', serum and urine transferrin by immunonephelometry and total urine protein by the biuret reaction after trichloroacetic acid precipitation. Serum iron was measured by an 'Auto-Analyser' procedure using 2, 4, 6, -tri-(2'-pyridyl)- 1, 3, 5, -triazine (TPTZ), urine iron was measured by a manual procedure using ferene-S, serum and urine copper were measured by atomic absorption spectroscopy. Serum ferritin was measured by radioimmunoassay.

Results

Details of the patients including age, sex, underlying renal diagnosis and duration of nephrotic syn-

drome are shown in Table 1. Five patients were considered to have idiopathic membranous glomerulonephritis, two had minimal change glomerulonephritis, one had membranous glomerulonephritis secondary to penicillamine treatment for rheumatoid arthritis and one had idiopathic focal glomerulosclerosis.

The results of plasma and urine estimations are shown in Tables 2 and 3. The plasma albumin was below normal in six out of nine patients at the time of the study. The plasma transferrin was reduced in one out of five in whom it was measured. There was a significant negative correlation between the plasma transferrin and urine transferrin excretion ($P<0.005$). Plasma iron was reduced in 2/8 patients. Plasma copper was reduced in 1/6. Urine iron excretion was raised in 6/9 patients and urine copper excretion raised in all eight patients. Both urinary transferrin excretion ($P<0.001$) and urinary copper excretion ($P<0.001$) were significantly correlated with urinary protein excretion. With the exception of case 1 and case 2, none of the other seven patients had any evidence of iron deficiency. The serum ferritin was normal in three of the seven patients and raised in one patient.

Discussion

Increased urinary excretion of iron in the nephrotic syndrome has been reported by a number of workers. Wiltink *et al.* (1972) recorded mean urinary iron losses of 1.3 and $5.4 \mu\text{mol/24 hr}$ in two nephrotic patients compared with a mean of $0.06 \mu\text{mol/24 hr}$ in normal controls. These authors doubted whether an iron deficiency anaemia could be produced by such relatively small losses. Urinary iron loss was also considered to be of minor importance with regard to iron deficiency anaemia by Jensen *et al.* (1968) who from turnover studies of radioiodinated transferrin in seven nephrotic patients calculated urinary iron losses varying from 1.4–8.5 $\mu\text{mol/24 hr}$. Increased urinary excretion of transferrin and iron were reported in two patients with nephrotic syndrome by

TABLE 1. Clinical details of patients

Patient	Sex	Age (years)	Diagnosis	Duration of nephrotic syndrome
Case 1	M	56	Membranous GN	5 years
Case 2	F	46	Membranous GN	4 years
A	M	40	Membranous GN	5 months
B	M	70	Membranous GN	7 months
C	F	49	Membranous GN	12 years
D	F	58	Penicillamine-induced membranous GN	3 months
E	F	32	Minimal change GN	2 months
F	M	64	Focal glomerulosclerosis	3 months
G	M	55	Minimal change GN	3 months

GN = glomerulonephritis.

TABLE 2. Results of plasma estimations

Patient	Albumin (g/l)	Transferrin (g/l)	Iron (μ mol/l)	Ferritin (μ g/l)	Copper (μ mol/l)
Case 1	36	—	—	<5	—
Case 2	25	2.5	6	<5	—
A	33	—	21	22	16.0
B	25	1.2	5	138	10.0
C	35	2.1	15	—	16.0
D	29	1.9	11	27	16.6
E	25	—	14	—	13.6
F	22	—	17	492	—
G	40	2.8	22	—	23.0
Normal range	35-45	1.8-3.3	11-32	10-200 F 10-300 M	12-20

TABLE 3. Results of urine (24 hr) estimations

Patient	Total protein (g)	Transferrin (g)	Iron [μ g(μ mol)]	Copper (μ mol)
Case 1	11.4	0.7	446(8.0)	—
Case 2	8.0	0.52	145(2.6)	1.9
A	2.5	0.24	89(1.6)	1.3
B	29.5	1.21	440(7.9)	4.2
C	5.8	0.2	172(3.1)	2.5
D	3.4	0.12	94(1.7)	1.5
E	3.3	0.1	156(2.8)	1.1
F	12.3	0.8	1099(19.7)	3.3
G	3.1	0.14	111(2.0)	2.0
Normal range	—	—	—	<1.0

Normal values from Dagg *et al.* (1966). Nine normal males, mean 69 μ g/24 hr (s.d. $\pm$ 19.2) or 1.25 μ mol/24 hr $\pm$ 0.34; 13 normal females, mean 74 μ g/24 hr (s.d. $\pm$ 22.6) or 1.33 μ mol/24 hr $\pm$ 0.40.

Rifkind *et al.* (1961). Dagg, Smith and Goldberg (1966) in an extensive study of the urinary excretion of iron reported a mean urinary excretion of 1.25 μ mol/24 hr ($\pm$ 0.34 s.d.) in nine normal males and a mean of 1.33 μ mol/24 hr ($\pm$ 0.40 s.d.) in 13 normal females. In 12 patients with proteinuria, including 10 with the nephrotic syndrome, they demonstrated a considerable increase in urinary iron losses varying from 1.25-17.8 μ mol/24 hr. A significant positive correlation between the urinary excretion of iron and β -globulin was demonstrated and a less significant positive correlation between the urinary excretion of iron and total urinary protein, supporting the finding of Rifkind *et al.* (1961) that urinary iron loss in nephrotic syndrome is due to urinary loss of transferrin. Dagg *et al.* (1966) also suggest that urinary iron losses may have contributed to the iron deficiency anaemia in one of their patients.

In the present study, urinary iron losses were raised above the normal values reported by Dagg *et al.* (1966) in six out of nine nephrotic patients. There was however no significant correlation between urinary iron excretion and urinary protein excretion. In the two patients reported it seems likely that the urinary iron losses may have contributed in part at least to an

iron deficiency state. The duration of the nephrotic syndrome may well be relevant. Both patients had had nephrotic syndrome for several years. Six of the seven other patients had only had nephrotic syndrome for several months although the remaining patient had no evidence of iron deficiency despite having had nephrotic syndrome for 12 years. There is evidence of increased urinary losses of other metals in the nephrotic syndrome. Increased urinary losses of zinc have been reported (Lindeman *et al.*, 1978; Temes-Montes *et al.*, 1980). In the present study, urinary copper excretion was raised in all eight patients in whom it was measured and there was a significant positive correlation between the urinary copper excretion and the total urine protein excretion. The plasma copper concentration was reduced in only one of the six patients. It is known however that plasma copper concentration gives a poor indication of total body copper (Osiki, 1970; Klein, Metz and Price, 1972). The significance of urinary losses of trace elements such as zinc and copper in patients with long-standing nephrotic syndrome is not known, but it is possible that signs of clinical deficiency of these trace elements may be produced including anaemia (Aggett, 1979). Mahajan *et al.* (1983) have studied zinc metabolism in the nephrotic syndrome. These authors found low plasma zinc levels which they attributed to a combination of increased urinary zinc losses and to a decreased zinc intake. The zinc deficiency in their patients was associated with evidence of hypogeusia. In long-standing nephrotic syndrome, urinary iron losses may contribute however towards an iron deficiency state.

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