Proteinuria and Hemoglobin Levels in Patients With Primary Glomerular Disease

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• ***Background:*** **Anemia in association with nephrotic syndrome has been described in small patient series and case reports. Whether nephrotic patients develop anemia has not been formally investigated.** ***Methods:*** **We undertook a retrospective cross-sectional study of patients with biopsy-proven primary glomerular disease, various degrees of proteinuria, and creatinine levels less than 2 mg/dL (<177 μmol/L). In addition to proteinuria, values for hemoglobin (Hb), age, body mass index (BMI), serum albumin and protein, and estimated glomerular filtration rate (eGFR) were derived from patient charts.** ***Results:*** **We studied 297 patients, 187 men and 110 women, aged between 16 and 81 years. Univariate analysis showed no correlation between Hb level and proteinuria in either sex. Stratification of women and men into quartiles according to proteinuria showed no differences in Hb levels among the 4 groups. Three of 52 non-nephrotic women (6%) were anemic (Hb < 12 g/dL [<120 g/L]) compared with 11 of 58 nephrotic women (19%; *P* = 0.047). Multiple regression analysis of all patients showed Hb level to have a correlation with sex (*P* < 0.001), BMI (*P* < 0.001), and eGFR (*P* = 0.005); negative correlation with age (*P* = 0.028); and borderline negative correlation with proteinuria (*P* = 0.054). In women, BMI showed a positive correlation with Hb level (*P* = 0.030). Proteinuria did not reach statistical significance (*P* = 0.093). In men, BMI (*P* = 0.001) and eGFR (*P* = 0.013) were associated positively and age (*P* = 0.031) was associated negatively with Hb level.** ***Conclusion:*** **These results indicate that nephrotic syndrome is not associated with anemia in men, but with a tendency to decrease Hb levels in women.** ***Am J Kidney Dis*** **46:424-431.**

INDEX WORDS: Anemia; nephrotic syndrome; proteinuria; glomerulonephritis; hemoglobin.

SEVERE PROTEINURIA exceeding 3.5 g/d of protein causes a number of symptoms and metabolic changes commonly called nephrotic syndrome. Patients with nephrotic syndrome show hypoalbuminemia and hypoproteinemia. Their cholesterol and triglyceride levels are markedly elevated. Other consequences are sodium retention and edema and increased risk for thromboembolic events and infection.[1] In addition, it was proposed that nephrotic syndrome may cause anemia.[2,3] As the main mechanisms, inappropriately low renal erythropoietin synthesis and urinary loss of erythropoietin have been postulated.[4] In addition, renal loss of transferrin and iron might cause anemia.[5,6] In patients with diabetic nephropathy, which is the most common cause of nephrotic syndrome, anemia develops early in the course of the disease.[7,8] The occurrence of anemia in patients with nephrotic primary glomerular disease has been described in only small groups of patients or case reports, but it is not yet clear whether anemia is a common feature of nephrotic syndrome.[2,9-12] Therefore, to formally study a possible association between urinary protein loss and anemia, we undertook a retrospective cross-sectional study of a larger number of patients with biopsy-proven primary glomerular disease, well-preserved renal function, and various levels of proteinuria.

METHODS

Patients

Patients were recruited at the 3 nephrology departments of Innsbruck Medical University, Feldkirch District Hospital, and Klinikum Kreuzschwestern Wels. All patients older than 16 years who had undergone a renal biopsy within the last 20 years and had a serum creatinine level less than 2 mg/dL

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(<177 μmol/L) were enrolled. Indications for biopsy were proteinuria with or without hematuria and, in some patients, isolated glomerular hematuria without significant protein excretion. Only patients for whom a primary glomerular disease was diagnosed were included in the study. Exclusion criteria were such systemic diseases as diabetes, lupus, vasculitis, or amyloidosis. Patients with other conditions that can cause anemia, such as malignancy, infectious disease, or recent blood loss, also were excluded from the study.

The following parameters were retrieved from patient charts: age, sex, body mass index (BMI), serum creatinine level, hemoglobin (Hb) level, hematocrit, serum protein level, and serum albumin level. Estimated glomerular filtration rate (eGFR/1.73 m^2) was calculated by using the Modification of Diet in Renal Disease 2 formula (eGFR = 183 × creatinine$^{-1.154}$ × age$^{-0.203}$ [× 0.742 if female]).[13] Of initially 516 patients eligible for the study, 219 patients were excluded because of incomplete data (mainly missing body weight, Hb level, or quantification of proteinuria). Of excluded patients, 75 were women and 144 were men. Mean age was 35 years, and renal function was similar to that of included individuals. Proteinuria was either derived from a 24-hour urine collection (281 patients) or a protein-creatinine ratio (16 patients), in milligrams per deciliter per milligrams per deciliter, was calculated from a single urine sample. For a subgroup of 90 patients, levels of serum iron, transferrin, and ferritin were available.

Statistical Analysis

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL) for Windows 12.0. Because reference values for Hb differ between the sexes, most calculations were performed separately for women and men. Differences in Hb levels between the diagnostic groups were calculated by means of analysis of variance. We calculated Spearman correlation coefficients between Hb levels and various other variables. In addition, to investigate nonlinear associations between proteinuria and Hb level, patients were stratified into 4 groups of almost equal size according to proteinuria per 24 hours: protein less than 1 g, 1 to 3.5 g, greater than 3.5 to 7 g, and greater than 7 g. Hb levels of those groups were compared by means of analysis of variance. The frequency of anemic individuals with and without nephrotic proteinuria was compared by using Fisher exact test. Multiple regression analysis was used to test the influence of the variables eGFR, BMI, age, serum albumin level, and proteinuria on Hb values.

RESULTS

Hb and Histological Diagnosis

A total of 297 patients, 110 women and 187 men, were included in the analysis. Mean age was 39.5 years (range, 16 to 81 years). Patients were divided into 6 groups according to histological diagnosis: minimal change nephropathy, focal segmental glomerulosclerosis, immunoglobulin A nephropathy, membranous nephropathy,

Table 1. Patient Demographic Characteristics and Laboratory Values

Diagnosis	No. of Patients	Age (y)	BMI (kg/m^2)	eGFR (mL/min/1.73 m^2)	Hb (g/dL)	Proteinuria (g/d)	Protein (g/dL)	Albumin (g/dL)
Women	110							
Minimal change nephropathy	26	36.19 ± 13.77	24.30 ± 4.41	83.38 ± 20.87	13.74 ± 1.53	5.23 ± 3.65	5.77 ± 1.15	2.87 ± 0.88
Focal segmental glomerulosclerosis	18	37.72 ± 11.39	25.28 ± 6.22	70.47 ± 24.45	13.64 ± 0.94	5.14 ± 5.14	6.54 ± 1.36	3.30 ± 1.26
Immunoglobulin A nephropathy	22	35.32 ± 11.10	25.10 ± 4.70	78.44 ± 24.10	13.63 ± 1.51	1.97 ± 1.42	7.04 ± 0.71	4.13 ± 0.38
Membranous nephropathy	24	43.46 ± 14.34	25.34 ± 3.59	75.74 ± 22.81	13.05 ± 1.53	6.54 ± 4.24	5.63 ± 0.98	2.80 ± 0.69
Membranoproliferative glomerulonephritis	5	47.40 ± 16.29	23.04 ± 1.44	58.96 ± 24.67	13.32 ± 1.09	4.30 ± 4.30	6.44 ± 1.05	3.43 ± 0.84
Others	15	36.80 ± 11.54	22.63 ± 2.93	68.26 ± 18.38	13.05 ± 1.7	2.85 ± 3.45	6.94 ± 1.01	3.74 ± 0.60
Men	187							
Minimal change nephropathy	20	33.35 ± 13.15	25.87 ± 4.22	88.23 ± 17.80	15.55 ± 1.33	6.93 ± 4.98	5.87 ± 1.45	2.78 ± 1.35
Focal segmental glomerulosclerosis	38	41.13 ± 5.11	26.10 ± 4.76	75.63 ± 25.85	14.86 ± 1.92	6.43 ± 5.99	6.55 ± 1.18	3.63 ± 1.05
Immunoglobulin A nephropathy	68	38.32 ± 14.78	26.06 ± 4.31	72.27 ± 22.84	14.84 ± 1.43	2.21 ± 2.56	7.03 ± 0.84	4.15 ± 0.66
Membranous nephropathy	35	49.09 ± 17.29	26.15 ± 3.64	81.30 ± 26.07	14.69 ± 1.65	5.91 ± 3.92	5.63 ± 0.97	2.99 ± 0.94
Membranoproliferative glomerulonephritis	8	38.50 ± 15.68	29.43 ± 8.05	69.23 ± 17.75	13.30 ± 1.89	5.13 ± 2.11	6.03 ± 0.92	3.38 ± 0.38
Others	18	41.72 ± 15.22	26.64 ± 3.74	67.91 ± 28.53	14.55 ± 1.51	3.65 ± 3.00	6.79 ± 1.30	3.69 ± 0.90

NOTE. To convert eGFR in mL/min to mL/s, multiply by 0.01667; Hb, protein, and albumin in g/dL to g/L, multiply by 10.