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Urinary IgG excretion as a prognostic factor in idiopathic membranous nephropathy

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Abstract. In membranous nephropathy it would be of great value to be able to identify in an early phase patients at highest risk for disease progression, since potentially toxic treatment could then be restricted to these patients only. We measured renal hemodynamics, serum proteins and urinary protein excretion in 22 patients with membranous nephropathy, nephrotic syndrome and normal renal function (endogenous creatinine clearance >85 ml/min). These patients were followed for a mean of 56 months. Renal function deteriorated in nine patients. When using univariate analysis, deterioration of renal function appeared to be associated with a low serum albumin and transferrin, high urinary transferrin, β -microglobulin, and IgG excretion, but not with renal hemodynamics. A step-up procedure, used for selecting variables associated with survival, showed that IgG excretion was independently associated with renal function deterioration. In patients with membranous nephropathy and normal renal function, the urinary excretion rate of IgG predicts future renal function outcome.

Key words: membranous nephropathy – proteinuria – renal insufficiency – urinary IgG excretion

Introduction

While membranous nephropathy is the most common cause of nephrotic syndrome in adults, its treatment is still a matter of debate [Lewis 1993]. Membranous nephropathy may be secondary to an underlying disease such as hepatitis B, systemic lupus erythematosus, malignancy, or occur as a side effect of drug treatment. In most cases, however, no underlying cause can be found. About a quarter of the patients with so-called idiopathic membranous nephropathy experience a spontaneous remission of proteinuria, which is a predictor for a favourable renal outcome [Ponticelli et al. 1992]. The remaining three quarters of the patients continue to have proteinuria, and half of these patients will progress to renal insufficiency, if left untreated [Donadio et al. 1988]. Treating all patients with methylprednisolone and cyclophosphamide or chlorambucil would unjustifiably expose up to 50% of the patients to these potentially toxic drugs. Identifying patients at the highest risk for disease progression would provide an opportunity to better direct immunosuppressive treatment. In a previous study we have demonstrated

that the urinary β_2 -microglobulin excretion can reasonably well predict renal outcome in patients with membranous nephropathy [Reichert et al. 1995]. In the present study we analyzed the results of precise measurements of renal hemodynamics and urinary excretion of different proteins to determine if these parameters improve our ability to identify patients at highest risk for subsequent renal function deterioration. Our data suggest that the urinary excretion of IgG may be a valuable parameter in this respect.

Subjects and methods

Patients

Twenty-two patients with a biopsy proven membranous nephropathy, a nephrotic syndrome (i. e. urinary protein excretion exceeding 3.5 g per day and/or a serum albumin \leq 25 g/l) and normal renal function (endogenous creatinine clearance >85 ml/min) were included in the study. Patients with secondary types of membranous nephropathy (malignancy, hepatitis, infection, positive tests for anti-DNA antibodies or the use of drugs that could induce membranous nephropathy) were excluded. During the study the patients were not treated with cytotoxic drugs. Until 1989 patients were treated with alternate day steroids. Since 1989 patients were randomized for treatment with prednisone on alternate days or only supportive treatment. No difference was noted in renal

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outcome with respect to prednisone treatment, which is in agreement with more recent studies [Cattran et al. 1989]. Diuretics and antihypertensive treatment were given if required. The study protocol was approved by the Hospital Ethics Committee. All patients gave informed consent.

Methods

During the baseline study patients were supine, except when voiding. During voiding they were in an upright or sitting position, to ensure complete emptying of the bladder. Glomerular filtration rate was measured using a continuous infusion technique. Blood and urine samples were taken at regular intervals. The renal clearances of Inutest (polyfructosan, Laevosan-Gesellschaft, Linz, Austria) and PAH (Para-aminohippurate) were used as markers for glomerular filtration rate and effective renal plasma flow respectively. Since β_2 -microglobulin is unstable in acidic urine (pH <6.0) all patients received four grams of sodium bicarbonate the evening before the measurements. Urine samples collected at short intervals during the renal hemodynamic measurements were used for the analysis of urinary proteins. The freshly voided urine samples were centrifuged and stored for at most one week at 4° C, or otherwise kept at -70° C. In blood and urine samples the concentrations of albumin, IgG and transferrin were measured by immunonephelometry using antibodies whose specificity was checked by Ouchterlony double immunodiffusion and immunoelectrophoresis. Details of the nephelometric procedure for the measurement of albumin have been described [Elving et al. 1989]. For the measurements of transferrin we have used a rabbit anti-human transferrin antibody (DAKO A120, Dakopatts, Glostrup, Denmark) which was diluted 300-fold in a diluent of phosphate-buffered isotonic saline (phosphate 5 mM, pH 7.4) containing 20 g/l of polyethylene glycol 4000 and 20 g/l polyethylene glycol 2000. For the measurements of IgG we have used a rabbit anti-human IgG (DAKO A090 or Q331), which was diluted 200-fold in a diluent containing 100 mM phosphate, 10 g of BSA and polyethylene glycol as described above. We have used a standard serum which was calibrated against the WHO 067-86 standard (for IgG) and against commercially available standards for albumin and transferrin (Behringwerke). Serum and urinary β_2 -microglobulin were measured by RIA (Pharmacia, Uppsala, Sweden). Inulin, PAH, and creatinine were measured using standard colorimetric methods.

Statistics

Values are given as means (SD) or medians (range) when appropriate. Statistical comparisons between groups

were made with the non-parametric two-sample rank sum test. Correlations were calculated using Spearman's rank correlation test. Possible factors associated with renal outcome were selected by univariate analysis. Subsequently, a step-up procedure was used for selecting variables independently associated with survival [Krall et al. 1975]. A p value less than 0.05 was considered significant.

Results

We have studied 19 male and 3 female patients. Mean age of the patients was 46 years (median 48.5 years, range 24–60 years), serum creatinine 95 μ mol/l (median 90 μ mol/l, range 70–145 μ mol/l), and creatinine clearance 123 ml/min (median 117 ml/min, range 87 to 210 ml/min). Total proteinuria averaged 8.0 g per day (median 6.45 g per day, range 2.8–20.3 g per day) and serum albumin was 21 g/l (median 18, range 7–32 g/l). Patients were studied 3 months (median 2, range 0 to 11 months) after renal biopsy. Patients were followed for at least 12 months after measurement of renal hemodynamics and protein excretion. Deterioration of renal function was defined as a doubling of serum creatinine at any time interval in all but one patient. In this patient immunosuppressive therapy was started already when his serum creatinine had increased by 25% within 3 months. Exclusion of this patient did not influence the statistical results. Dehydration and renal vein thrombosis as a cause of declining renal function were excluded on clinical grounds. The clinical characteristics and laboratory parameters of the patients divided according to final renal outcome are shown in Tables 1 and 2. No significant differences were noted between the groups with respect to age, time of diagnosis to start of the study, presence of hypertension or length of follow-up. We also did not find a significant difference in GFR or ERPF (Table 1). Although filtration fraction was numerically lower in the group of patients with future deterioration of renal function, the difference was not significant ($p = 0.09$). A scatter plot of the individual data confirms that there is a considerable overlap between the groups (Figure 1). From the data given in Table 1 it is evident that the simultaneously measured creatinine clearance considerably overestimates real GFR in this group of patients. The mean differences between calculated creatinine clearance and inulin clearance was 38 ml/min (95% confidence interval 24–52 ml/min; $p < 0.001$). Overestimation of GFR by using creatinine clearance was especially evident when GFR was reduced.

In blood and urine samples collected during the measurements of renal hemodynamics we measured the levels of different proteins. At the time of biopsy there was no significant difference in proteinuria between the groups. At the time of the renal function study there also

Table 1 Characteristics of the study patients at the start of the study

	Group 1 Stable renal function (n = 13)	Group 2 Deteriorating renal function (n = 9)
Sex (male/female)	10/3	9/0
Age at biopsy (range)	48 (36–57)	43 (24–60)
Serum creatinine ($\mu\text{mol/l}$)	89 ± 12	102 ± 24
Endogenous creatinine clearance (ml/min)	117 ± 24	132 ± 38
Inulin clearance (ml/min)	87 ± 28	82 ± 36
Effective renal plasma flow (ml/min)	551 ± 179	607 ± 185
Filtration fraction	16 ± 1.8	13.6 ± 4.4
Proteinuria at biopsy (g/day)	6.2 (3.2–20.3)	9.2 (2.8–15.0)
Hypertension	4	3
Follow-up (months)	57 (12–132)	48 (12–108)

Values are given as absolute number of patients, median (range), or means \pm SD. There are no significant differences

Table 2 Baseline values of serum and urinary proteins in patients without and with deteriorating renal function during follow-up

	Group 1 Stable renal function (n = 13)	Group 2 Deteriorating renal function (n = 9)
Serum albumin (g/l)	22.9 ± 5.0	17.2 ± 6.9^a
Urinary albumin excretion (mg/day)	4,634 (1,180–10,283)	9,410 (2,248–13,848)
Serum transferrin (g/l)	2.30 ± 0.56	1.60 ± 0.36^b
Urinary transferrin excretion (mg/day)	411 (104–916)	1,080 (127–1,182) ^a
Serum IgG (g/l)	5.3 ± 2.6	4.2 ± 2.1
Urinary IgG excretion (mg/day)	98 (52–528)	387 (73–785) ^a
Serum β_2 -microglobulin (mg/l)	2.30 ± 0.69	2.75 ± 1.13
Urinary β_2 -microglobulin excretion (ng/min)	174 (61–24,988)	1,020 (129–13,519) ^a
Selectivity index	0.16 (0.07–0.36)	0.23 (0.11–0.31)

Values are given as medians (range) or means \pm SD

^a $p < 0.05$ between the two groups

^b $p < 0.01$ between the two groups

was no significant difference in the level of albuminuria. However, urinary β_2 -microglobulin, transferrin, and IgG excretions were significantly elevated in the group of patients who subsequently developed renal insufficiency. Serum albumin and serum transferrin were significantly lower in this group. Although serum IgG was not significantly different, the fractional excretion of IgG was significantly higher in the group of patients with a poor

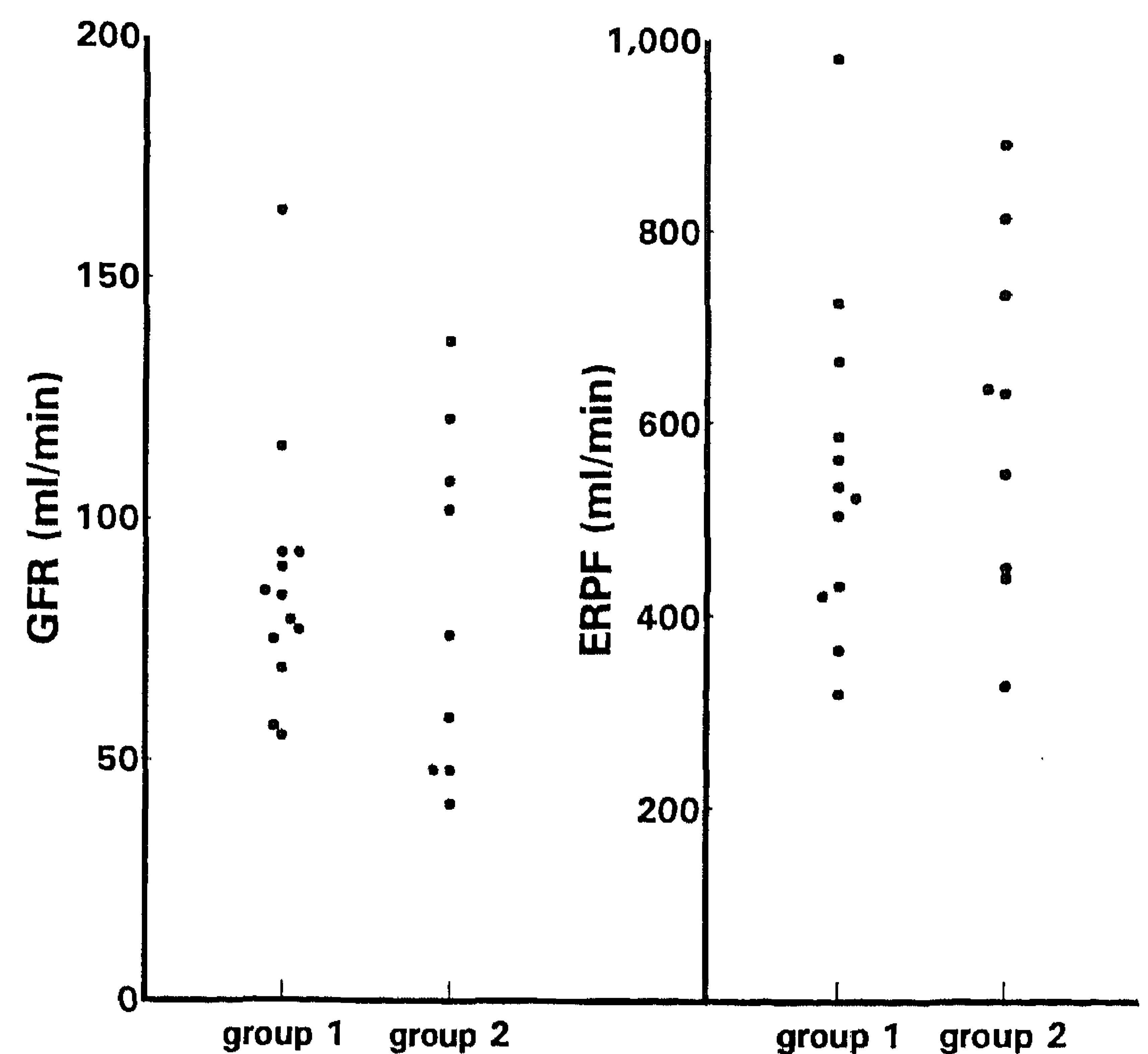


Fig. 1 Scatter plot of values of GFR and ERPF. Group 1 represents patients with stable renal function, group 2 with deteriorating renal function during follow-up.

renal prognosis (median 1.14 [0.08–2.42] vs 0.18 [0.06–2.05]; $p < 0.01$).

As could be expected there was a correlation between the excretion of different proteins. Spearman's correlation coefficient between urinary IgG and albumin excretion was 0.84, between IgG excretion and transferrin excretion 0.83, and between urinary transferrin and albumin excretion 0.92 (all $p < 0.001$). Using a step-up procedure for selecting variables associated with survival [Krall et al. 1975] only IgG excretion was associated with renal function deterioration as a significant explanatory variable ($p < 0.01$; Figure 2). A threshold of 250 mg/day proved most discriminative. Only two out of 10 patients with a value above 250 mg/day had stable renal function during follow-up. These two patients had a relatively short follow-up of 15 months. Only one patient out of 12 with an IgG excretion below 250 mg/day had a subsequent renal function deterioration. This patient had a very slow rise in serum creatinine during a period of 4 years of $10 \mu\text{mol/l/year}$. During the following year, his serum creatinine quickly doubled, after which he was treated with immunosuppressive therapy. Unfortunately, we did not repeat the measurements of IgG excretion in this patient. With these results a positive predictive value can be calculated of 80%, a negative predictive value of 92%, a sensitivity of 89% and a specificity of 85%. In view of our previous results [Reichert et al. 1995], we have analyzed more closely the relationship between urinary IgG and urinary β_2 -microglobulin excretion. Urinary β_2 -microglobulin could not be measured in one patient because of an urinary pH below 6.0. There was a strong correlation between the excretion of IgG and the

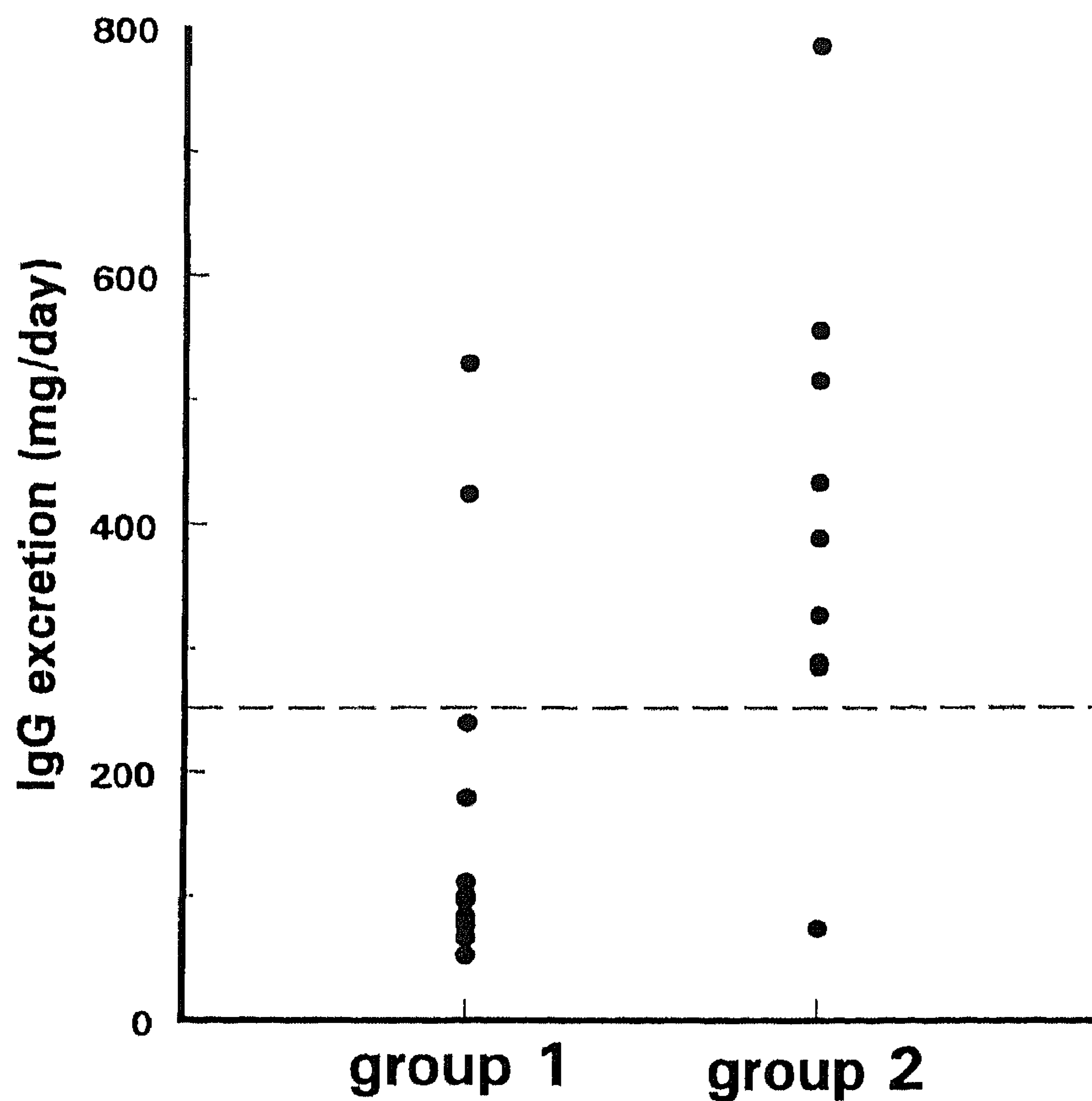


Fig. 2 Scatter plot of values of IgG excretion. Group 1 represents patients with stable renal function, group 2 with deteriorating renal function during follow-up. The threshold value of 250 mg/day is indicated by the dotted line. $p < 0.05$ between the two groups.

excretion of β_2 -microglobulin ($r = 0.80$). When using a threshold of 500 ng/min as discriminative value, only two patients out of nine with a urinary β_2 -microglobulin excretion > 500 ng/min had stable renal function during follow-up, whereas renal function deteriorated in only two out of twelve patients with a β_2 -microglobulin excretion ≤ 500 ng/min. With these results a positive predictive value can be calculated of 78%, a negative predictive value of 83%, a sensitivity of 78% and a specificity of 83%. The results of urinary β_2 -microglobulin and IgG excretion concurred in all but one patient. In this one patient urinary β_2 -microglobulin excretion was below the threshold of 500 ng/min, whereas the urinary excretion of IgG was above the threshold of 250 mg/day. In this patient renal function deteriorated during follow-up.

Discussion

Patients with membranous nephropathy may benefit from immunosuppressive therapy [Piccoli et al. 1994, Passerini et al. 1993]. However, in untreated patients membranous nephropathy runs a benign course in approximately half of the patients. Therefore, it has been advocated to limit therapeutic measures to patients with an unfavourable prognosis [Glasscock 1991]. Risk factors for the development of renal failure include male sex [Hopper et al. 1981], old age [Cameron 1979, Schieppati et al. 1993], decreased renal function at presentation

[Toth and Takebayashi 1994, Donadio et al. 1988], massive proteinuria [Honkanen et al. 1994, Cattran et al. 1992] and tubulointerstitial changes on biopsy [Wehrmann et al. 1989]. However, all these risk factors lack the sensitivity and specificity that is needed to reliably guide therapy. The present study was undertaken to investigate renal hemodynamics and the urinary excretion rates of different proteins and their relation with renal outcome in patients with membranous nephropathy and normal renal function. Only patients with a nephrotic syndrome at the time of renal biopsy were studied, because non-nephrotic proteinuria in membranous nephropathy usually carries a good prognosis [Schieppati et al. 1993]. In patients with renal function impairment at the time of diagnosis renal function usually continues to deteriorate, if left untreated [Davison et al. 1984]. These patients were treated with immunosuppressive drugs [Wetzels et al. 1989, Reichert et al. 1994] and also not included in this study.

When comparing the two groups of patients divided according to renal function outcome we did not observe a difference in renal hemodynamics (GFR and ERPF).

We observed marked differences in serum and protein levels between patients with and without renal function deterioration during follow-up. Patients with subsequent deterioration of renal function had lower serum albumin and transferrin levels, whereas the urinary excretion of transferrin, IgG, and β_2 -microglobulin was increased. Of note, the urinary excretions of total protein or albumin were not significantly different. By multivariate analysis, only IgG excretion was independently associated with renal function deterioration. Why is the urinary excretion of IgG a better predictor of prognosis than proteinuria, albuminuria or size selectivity? It is tempting to speculate that these differences point to mechanisms involved in the progression of renal disease in patients with proteinuria. It has been suggested that the progression of renal injury is related to the extent of glomerular injury and the development of glomerulosclerosis [Brenner et al. 1982]. In this hypothesis, proteinuria is considered to be a mere reflection of glomerular injury. It is important to realize that the extent and nature of glomerular injury is reflected not only by the level of proteinuria, but also by the size distribution of urinary proteins. Severe glomerular injury results in a loss of size selectivity of the glomerular basement membrane, with increased loss of proteins of higher molecular weight, such as IgG. In clinical practice such a loss of size selectivity is reflected in an increase of the selectivity index (i. e., clearance of IgG divided by the clearance of transferrin or albumin). Both the level of proteinuria and the selectivity index would be expected to predict renal function outcome. However, this is found in only a few studies [Collaborative Study of the Adult Idiopathic Nephrotic Syndrome 1979, Mallick et al. 1983]. We suggest that this can be explained by the fact that the level of proteinuria and size selectivity are not necessarily correlated.

IgG excretion may be a particular good marker of renal injury because it combines information on the level of proteinuria and the loss of size selectivity.

Admittedly, the role of glomerular injury in the progression of renal disease has been questioned. In recent years it has been demonstrated that the rate of deterioration of renal function is correlated more with tubulointerstitial injury than with glomerular injury [Bohle et al. 1990]. Proteinuria may play a central role in the induction of tubulointerstitial injury [Eddy 1994]. The mechanisms of proteinuria-induced tubular cell injury are still debated. It is clear, however, that albuminuria is not the most important in this respect. Tubulointerstitial injury is more frequently seen with non-selective proteinuria, suggesting that loss of higher molecular weight proteins, such as growth factors or complement components, may be involved in tubular cell damage. The excretion of IgG may then reflect urinary loss of these high molecular weight injurious factors. Tubular cell injury will lead to tubulointerstitial damage [Wehrmann et al. 1989]. Tubulointerstitial damage will impair the reabsorption of low molecular weight proteins such as β_2 -microglobulin excretion, thus explaining the increased excretion of β_2 -microglobulin in most of our patients at risk for renal function deterioration [Reichert et al. 1995]. In the present study we could identify one patient with subsequent renal function deterioration who initially demonstrated an increased IgG excretion but normal β_2 -microglobulin excretion. The data of this particular patient suggest that increased loss of high molecular weight proteins actually precedes tubulointerstitial injury. The present study thus confirms our initial findings that patients with an increased excretion of β_2 -microglobulin are at increased risk for renal function deterioration. However, the data suggest that the urinary excretion of β_2 -microglobulin is not an independent risk factor but rather closely correlates with the urinary excretion of IgG, which appears to be the primary risk factor.

Pei et al. have quantified the risk of developing renal insufficiency using proteinuria as a marker [1992]. Baseline proteinuria was of limited value in predicting prognosis; the duration of proteinuria was more reliable. Patients with a proteinuria of ≥ 4 g/day lasting for more than 18 months, ≥ 6 g/day for more than 9 months or ≥ 8 g/day for more than 6 months were found to have the greatest risk of renal function deterioration, with a positive predictive value ranging from 47 to 66% and a sensitivity ranging from 44 to 66%. Our values compare favourably with their results, not only with regard to the actual figures, but also because reliable predictions can be made without the need of following the course of proteinuria during a period of many months.

In conclusion: with the use of the urinary IgG excretion, which reflects the combination of selectivity and magnitude of proteinuria, we have a sensitive and simple tool for selecting patients with membranous ne-

phropathy at highest risk for disease progression. Measuring urinary IgG excretion may be of help in guiding the treatment of these patients. Future, larger, studies should enable us to further clarify the relationship between the excretion of IgG, β_2 -microglobulin, and other proteins and their role in renal function deterioration.

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