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Early prediction of IgA nephropathy progression: Proteinuria and AOPP are strong prognostic markers

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Background. Inflammation and oxidative stress have been incriminated in the pathogenesis of IgA nephropathy (IgAN). The aim of the present study was to assess whether markers reflecting these pathophysiologic processes, namely C-reactive protein (CRP) and advanced oxidation protein products (AOPP), would allow—in conjunction with clinical and histopathologic parameters—to predict disease progression.

Methods. Between 1994 and 1997, 120 adult patients with biopsy-proven IgAN were included in a prospective cohort study, and followed until the end of 2002 or start of dialysis. In every patient, we determined plasma levels of CRP and AOPP. These parameters were included, together with clinical data, in a multivariate Cox proportional hazard regression analysis, with halving of baseline creatinine clearance as the primary renal end point.

Results. A total of 51 patients reached the renal end point, including 30 who had to start dialysis. With multivariate analysis, the most potent independent risk factors of poor renal outcome were proteinuria ≥1 g/day [proportional hazard risk (HR) = 23.7, $P = 0.0001$], hypertension (HR = 8.13, $P = 0.008$), and AOPP plasma level (HR = 1.09 per 10 μmol/L, $P = 0.042$), whereas angiotensin II inhibitors were protective (HR = 0.19, $P = 0.001$).

Conclusion. Our data support the role of oxidative stress in the pathogenesis of IgAN and suggest that patients with proteinuria ≥1 g/day should be eligible for early implemented antioxidant and/or anti-inflammatory therapeutic strategies, with AOPP plasma level as a surrogate marker to evaluate their effects.

Immunoglobulin A nephropathy (IgAN), or Berger's disease, is the most common type of primary glomerulonephritis worldwide [1]. Although it was initially thought to be a benign condition, more recent studies with long-term follow-up have revealed that development of progressive renal failure is frequent, and IgAN now appears to be the leading cause of end-stage renal disease (ESRD) among primary glomerulonephritides in industrialized countries, especially in Japan [2, 3].

However, IgAN outcome is highly variable between individuals. End-stage renal failure may occur within 5 years of presentation, or conversely, more than 20 years later [2–6]. Therefore, identification of factors predictive of subsequent outcome at the time of presentation should be of great interest, particularly if such factors can be altered by treatment [6, 7]. Clinical and histologic parameters have been identified as independent risk factors for progression toward renal failure, especially heavy proteinuria [2–4, 7, 8], arterial hypertension [2, 4], reduced renal function at diagnosis [3, 8], and glomerular sclerosis or tubulointerstitial scarring at renal biopsy [2, 4, 8]. However, severe histologic lesions, heavy proteinuria, and/or elevated serum creatinine actually characterize already advanced renal failure rather than reflect the progression rate of renal disease. Thus, indices that may allow prediction of progression at an earlier stage of the disease should be of great interest.

Recent studies of the pathogenetic mechanisms of IgAN have stressed the presumptive role of mediators of inflammation, notably cytokines and oxidative stress (reviewed in [1]). This was supported by the encouraging results of therapeutic trials using corticosteroids [9, 10] or antioxidants such as fish-oil extracts in both experimental [11] and human IgAN [1]. Recently, advanced oxidation protein products (AOPP) emerged as relevant markers of oxidative stress and novel mediators of inflammation in renal diseases [12]. In a previous study, we found that AOPP plasma concentrations increased with the progression of chronic renal failure in uremic patients with a variety of chronic renal diseases, both glomerular and nonglomerular. Moreover, AOPP were closely

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correlated with markers of monocyte activation [13], thus suggesting that they may by themselves contribute to the inflammatory process associated with chronic renal failure.

The present study, performed in a large cohort of IgAN patients, was aimed at evaluating whether proteinuria, hypertension, and histologic scores could predict the subsequent progression of IgAN, and whether elevated levels of AOPP and C-reactive protein (CRP) were associated with a higher rate of progression of renal disease in IgAN patients.

METHODS

Study population

All 120 consecutive adult patients with biopsy-proven primary IgAN cared for at our institution between September 1994 and October 1997 were included in an observational cohort study after giving informed consent. Excluded from the study were patients with Henoch-Schönlein purpura, cirrhosis, or systemic lupus erythematosus, and patients aged less than 15 years at the time of renal biopsy.

Design

A single starting time (i.e., when plasma AOPP and CRP concentrations were determined) was used in every patient. The follow-up was extended until October 2002 so that it might last at least 5 years for each patient of the cohort. In every patient, we recorded the demographic and clinical data, including age, gender, blood pressure, urinary protein excretion (g/24hr), and serum creatinine (μmol/L) at entry in the study (baseline data). Existence or absence of at least one documented episode of macroscopic hematuria at any time in the course of the disease was also recorded. Proteinuria was categorized as <1 g/24hr or ≥1 g/24hr. Hypertension was defined as a systolic blood pressure (BP) ≥150 mm Hg and/or a diastolic BP ≥90 mm Hg, or current antihypertensive therapy; current treatment with angiotensin II (Ang II) inhibitors [angiotensin-converting enzyme inhibitors (ACEIs) or Ang II receptor antagonists] was also recorded.

Renal function was evaluated by the level of creatinine clearance (Ccr) according to the Cockcroft-Gault formula [14], normalized for body surface area and expressed as mL/min/1.73 m^2. The primary renal end point was taken as halving of baseline Ccr. Patients who exhibited a decrease in Ccr less than 50% at end of follow-up were classified as group I, and patients whose decline in Ccr was 50% or more were classified as group II. The rate of progression of renal failure was expressed as the yearly rate of decline in Ccr (ΔCcr, mL/min/1.73 m^2/year) between entry in the study and end of follow-up or start of dialysis. A progression rate <3 mL/min/1.73 m^2/year defined slow progressors, whereas a progression rate ≥3 mL/min/1.73 m^2/year was considered a fast progression.

Kidney biopsy samples were reviewed and semiquantitatively scored by one investigator (LHN). Glomerular score (range 0 to 8) was the sum of mesangial proliferation (none = 0, focal = 1, diffuse = 2), cellular crescents, segmental fibrosis, and global glomerular sclerosis (for each, none = 0, <50% = 1, ≥50% = 2). Interstitial score (0 to 4) included interstitial fibrosis and cellular infiltrate (for both none = 0, <50% = 1, ≥50% = 2). Vascular score (0 to 2) included sclerosis of arterioles and of interlobular arteries (for both none = 0, presence = 1).

Laboratory determinations

CRP and AOPP were determined at baseline in all patients. Ultrasentitive CRP, detection limit ≥0.5 mg/L, normal range 0.5 to 2 mg/L) was determined in the serum by enzyme-linked immunosorbent assay (ELISA) (Dade Berhing, Marburg, Germany) as described previously [15]. AOPP were determined in the plasma using the semiautomated method previously devised in our laboratory [12]. Briefly, AOPP are measured by spectrophotometry on a microplate reader (Model MR 5000; Dynatech, Paris, France), and are calibrated with chloramine-T (Sigma Chemical Co., St Louis, MO, USA) solutions, which, in the presence of potassium iodide, absorb at 340 nm. In test wells, 200 μL of plasma diluted 1:5 in phosphate-buffered saline (PBS) is placed on a 96-well microtiter plate (Becton Dickinson Labware, Lincoln Park, NJ, USA), and 20 μL of acetic acid is added. In standard wells, 10 μL of 1.16 mol/L potassium iodide (KI, Sigma Chemical Co.) is added to 200 μL of chloramine-T solution (0 to 100 μmol/L), followed by 20 μL of acetic acid. The absorbance of the reaction mixture is immediately read at 340 nm on the microplate reader against a blank containing 200 μL of PBS, 10 μL of KI, and 20 μL of acetic acid. The chloramine-T absorbance at 340 nm, being linear within the range of 0 to 100 μmol/L, AOPP concentrations are expressed in μmol/L of chloramine-T equivalents.

Statistical analyses

Data are expressed as mean ± SD unless otherwise specified. Differences in frequencies were determined by chi-square analysis. Comparison of groups was done by Student *t* test or analysis of variance (ANOVA). Gender, urinary protein excretion (UPE, < or ≥1.0 g/day), hypertension (yes/no), macroscopic hematuria (yes/no), treatment with Ang II inhibitors (yes/no), were used as categorical variables. The primary renal end point was taken as halving of baseline Ccr. The Kaplan-Meier method was applied to estimate survival proba-

bilities, and the log-rank test was used to determine their significance.

A first univariate Cox analysis was performed, including the parameters related to prognosis from baseline to renal end point. The following variables were considered: gender, age, proteinuria, macroscopic hematuria, hypertension, Ccr, CRP, and AOPP levels. Because kidney biopsy was performed at the time of study in only 56 patients, histologic scores were not entered in the Cox analysis.

Stepwise multivariate Cox proportional hazard regression with a maximum of five terms in subset (including the intercept) was then applied to determine the independent relationship of all unadjusted significant variable ($P < 0.10$) predictors of renal end point forced into the model. The subset selection was proceeded using a hierarchical forward algorithm with switching, taking into account interactions between the different variables. Variables were considered significant for $P \leq 0.05$ after adjustment for all variables, and after the maximum subset size has been reached.

All tests were performed using NCSS 2000 software (Jerry L. Hintze, Kaysville, UT, USA).

Table 1. Baseline demographic, clinical, histologic, and laboratory characteristics of IgAN patients who reached (Group II) or did not reach (Group I) the renal end point (halving of Ccr) at end of follow-up

Characteristic	Group I	Group II	*P* value
Number of patients	69	51	
Sex ratio (M/F)	2.6	4.1	0.39
Age *years*	36.2 ± 14.5	44.9 ± 15.7	0.0022
Urine protein excretion *g/day*	0.59 ± 0.62	2.67 ± 1.28	<0.0001
Proteinuria ≥1 g/day %	18.8	96	<0.0001
Macroscopic hematuria %	53.6	31.4	0.0168
Hypertension %	40.6	96.1	<0.0001
Treatment with Ang II inhibitors %	37.7	74.5	<0.0001
Plasma creatinine *μmol/L*	97 ± 22	297 ± 220	<0.0001
Creatinine clearance *mL/min/1.73m²*	79.5 ± 16.4	35.6 ± 20.2	<0.0001
Follow-up duration *years*	5,72 ± 2.46	4.89 ± 2.55	0.76
Δ Ccr *mL/min/1.73m²/year*	1.19 ± 0.72	5.18 ± 3.02	<0.0001
Δ Ccr≥3 mL/min/1.73m²/year %	2.9	90	<0.0001
CRP *mg/L*	2.05 ± 2.93	2.11 ± 2.45	0.93
AOPP *μmol/L*	35.2 ± 26.1	69.9 ± 41.2	<0.0001
Number of kidney biopsies	40	16	
Glomerular score	3.12 ± 1.45	4.37 ± 1.98	0.0049
Interstitial score	1.01 ± 0.99	2.44 + 0.73	<0.0001
Vascular score	1.28 ± 0.72	1.37 ± 0.88	0.68

RESULTS

Clinical and laboratory data

Of the 120 patients (96% Caucasian), 91 were males and 29 were females (sex ratio 3.1:1). Mean age at entry in the study (baseline) was 39.9 ± 15.5 years. The overall mean duration from baseline to end of follow-up was 5.4 ± 2.5 years (range 1.2 to 7.9).

By the end of the observation period, 51 patients (43%) reached the renal end point (i.e., halved Ccr), including 30 patients who reached ESRD and were started on maintenance dialysis. Table 1 compares baseline clinical and laboratory data in the 69 group I patients who retained a preserved renal function (group I) and in the 51 patients who reached the renal end point (halved Ccr, group II).

The sex ratio did not significantly differ between the two groups, but age of patients was significantly higher in group II than in group I. Urinary protein excretion and the proportion of patients with proteinuria ≥1 g/day were strikingly higher in group II than in group I. Many more patients were hypertensive and more patients were treated with Ang II inhibitors in group II than in group I. Conversely, macroscopic hematuria was less frequent in group II than in group I. Mean plasma creatinine was higher, and accordingly, mean Ccr was significantly lower in group II than in group I patients.

CRP level did not significantly differ between group I and group II. In contrast, AOPP level was significantly higher in group II than in group I.

In the 56 patients with kidney biopsy contemporary with AOPP and CRP determinations, vascular scores were not discriminant between the 40 patients who retained a preserved renal function and the 16 who reached renal end point, whereas both glomerular and interstitial scores were significantly higher in group II than in group I (Table 1).

Rate of IgAN progression

The rate of decline in Ccr (ΔCcr) was strikingly higher in group II than in group I. In group II, 46/51 patients (90%) were fast progressors with a ΔCcr ≥ 3 mL/min/1.73m²/year, whereas in group I, 67/69 patients (97%) had a slow progression rate with a ΔCcr < 3 mL/min/1.73m²/year. When analyzed in terms of slow or fast progressors groups, distribution of urinary protein excretion, hypertension, Ccr, CRP, and AOPP values was very similar to that observed between group I and group II patients stratified with respect to renal end point (data not shown).

There was a close relationship between ΔCcr and urinary protein excretion and AOPP level (Fig. 1).

Renal survival

By univariate Cox regression analysis (Table 2), age, proteinuria, hypertension, use of Ang II inhibitors, Ccr, and AOPP levels were significantly associated with

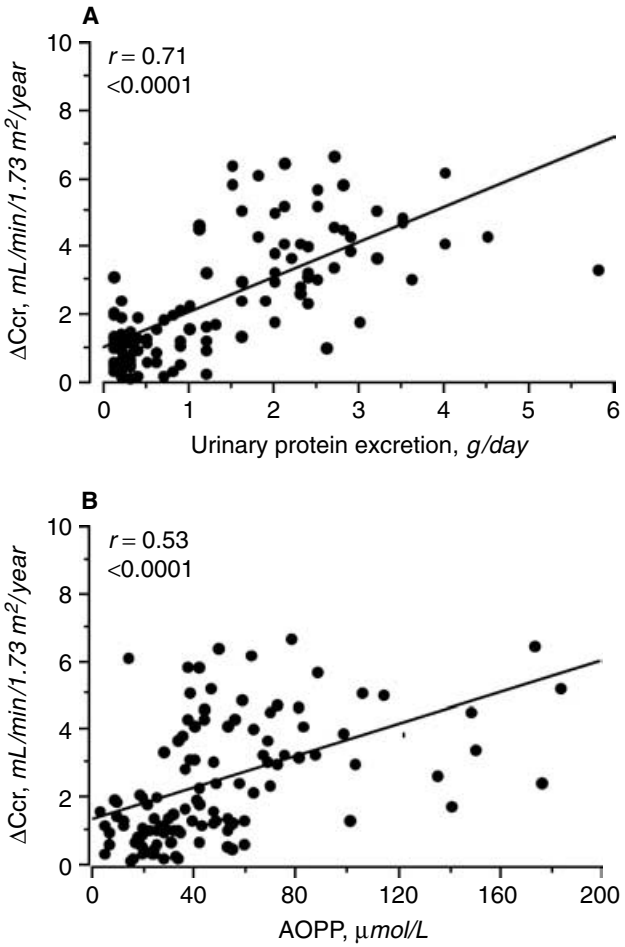


Fig. 1. Relationships between ΔCcr and urinary protein excretion (*A*) or advanced oxidation protein products (AOPP) plasma level (*B*) at entry in the study, in 120 IgA nephropathy (IgAN) patients. Ccr, creatinine clearance.

Table 2. Predictors of loss of renal function determined by univariate Cox regression analysis

Risk factors	HR (95%CI)	*P* value
Gender (male)	1.84 (0.69–3.83)	0.10
Age (per 1 year)	1.02 (1.01–1.04)	0.0028
Macroscopic hematuria *yes*	0.71 (0.37–1.33)	0.2817
Proteinuria ≥1 g/day *yes*	16.41 (3.97–67.84)	0.00001
Hypertension *yes*	18.2 (4.40–75.23)	0.0001
Ccr (per 1mL/min/1.73 m^2)	0.93 (0.91–0.95)	0.00001
Treatment with angiotensin II inhibitors *yes*	0.50 (0.28–0.96)	0.038
CRP (per 1 mg/L)	0.97 (0.89–1.06)	0.5133
AOPP (per 10 μmol/L)	1.42 (1.28–1.58)	0.00001

renal outcome. These factors were first entered in a multivariate adjusted Cox regression model (Table 3). In this model Ccr, proteinuria, and AOPP were significantly associated with renal end point. Because of the close correlation between Ccr at baseline and at end of follow-up ($r = 0.91$, $P < 0.0001$), we performed a second Cox regression analysis without including Ccr. In this model, proteinuria, hypertension, and AOPP were significant independent predictors associated with poor renal outcome, whereas anti-Ang II use was protective. Overall, these four factors explained 48% of the variance.

Table 3. Proportional hazard ratios for reaching renal endpoint determined by multivariate Cox regression analysis

Prognostic variables	HR (95%CI)	*P* value
First model (with Ccr included)		
Ccr (per 1 mL/min/1.73 m^2)	0.94 (0.92–0.97)	0.0000
Proteinuria ≥1 g/day *yes*	7.78 (1.81–33.4)	0.0057
AOPP (per 10 μmol/L)	1.11 (1.02–1.21)	0.0305
Second model (without Ccr included)		
Proteinuria ≥ 1g/day *yes*	23.7 (5.35–104.8)	0.0001
Hypertension *yes*	8.13 (1.72–38.5)	0.008
Angiotensin II inhibitors *yes*	0.19 (0.09–0.44)	0.001
AOPP (per 10 μmol/L)	1.09 (1.00–1.18)	0.042

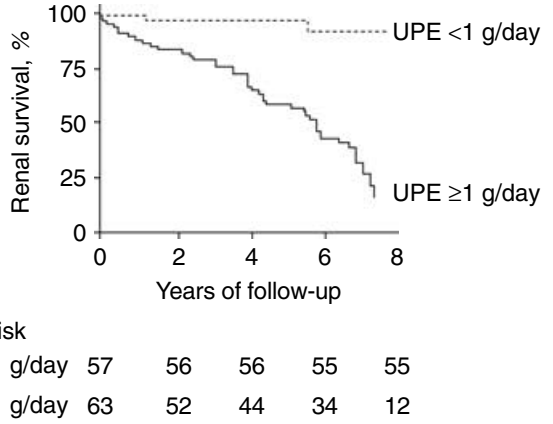


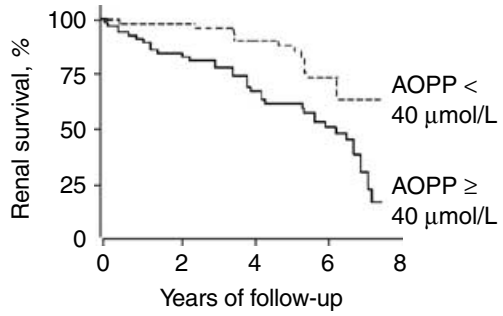
Fig. 2. Renal survival in IgA nephropathy (IgAN) patients with urinary protein excretion (UPE) <1 g/day ($N = 63$) or ≥1 g/day ($N = 57$) at entry in the study. Difference between Kaplan-Meier curves is highly significant (log-rank test, chi-square = 31.8, $P < 0.00001$).

The renal survival curves from baseline to renal end point highly significantly differed between patients with proteinuria <1 g/day or ≥1 g/day at baseline ($P < 0.0001$) (Fig. 2), and between patients with baseline plasma AOPP level lower or higher than the median value of 40 μmol/L (Fig. 3).

DISCUSSION

Our main conclusion is that in IgAN patients, the combination of proteinuria in excess of 1 g/day, hypertension, and disproportionate AOPP plasma level, as a marker of oxidative stress, is predictive of progressive renal disease.

In most published studies, multivariate analysis based on renal survivorship identified elevated serum creatinine and heavy proteinuria at presentation as the main predictors of poor outcome in adult patients. In particular, impaired renal function at the time of renal



No. at risk					
AOPP <40 µmol/L	56	55	53	49	46
AOPP ≥40 µmol/L	64	50	44	33	23

Fig. 3. Renal survival in IgA nephropathy (IgAN) patients with advanced oxidation protein product (AOPP) plasma level <40 µmol/L ($N = 84$) or ≥40 µmol/L ($N = 36$) at entry in the study. Difference between Kaplan-Meier curves is highly significant (log-rank test, chi-square = 24.7, $P < 0.0001$).

biopsy was found to be the most powerful predictive factor in a number of studies [3–5, 8, 17–21]. In these studies, impaired renal function was defined on the basis of variable threshold levels for serum creatinine ranging from 1.2 mg/dL [4, 5, 17, 22] to 1.4 to 1.5 mg/dL [2, 3, 18, 21, 23], or even as high as 1.7 mg/dL [8, 24]. However, all such levels of serum creatinine correspond to a markedly impaired renal function, with a Ccr already below 60 mL/min/1.73 m^2 in most cases. Therefore, as renal failure, once established, usually relentlessly progresses toward ESRD, the finding that impaired renal function at presentation is predictive of impaired renal failure at follow-up, as reported in most studies, is somewhat tautologic. It would be much more relevant to detect patients at risk of developing progressive renal failure at an earlier stage of the disease, when Ccr is still normal or nearly normal, and when therapeutic intervention has the best chances of stopping the progression [1]. Proteinuria universally appears to be the most significant, independent clinical factor predictive of a progressive course of IgAN. The most generally accepted risk threshold is a protein excretion ≥1 g/day [4, 5, 8, 25], although other authors used a higher threshold such as 2 g/day [18, 19, 22, 26]. Urinary protein excretion in excess of 2 g/day is undoubtedly a strong marker of a progressive course, but such a heavy proteinuria is infrequently present at clinical onset of IgAN or at biopsy [5, 27]. Therefore, a proteinuria ≥ 1 g/day at presentation appears to be a more sensitive risk factor. In our cohort, proteinuria ≥1 g/day was found by multivariate analysis to constitute the most powerful predictive clinical factor of poor outcome. Of note, proteinuria was already ≥1 g/day at clinical onset of IgAN in virtually all of our patients with such a urinary protein excretion at the time of study.

Hypertension has been reported to be associated with progressive forms of IgAN [2, 17, 24]. This was confirmed in our patients, and Ang II inhibitors were shown to have a protective effect. A beneficial influence of Ang II inhibitors on the course of IgAN has also been observed by other authors. In a short-term prospective study, ACEIs were shown to significantly reduce urinary protein excretion [28]. In a retrospective study of 115 IgAN patients with baseline proteinuria ≥1 g/day, hypertensive patients treated with ACEIs had a slower rate of decline in renal function and a higher percentage of remission in proteinuria than those who received other antihypertensive drugs [29]. Likewise, in a series of chronic nondiabetic nephropathies, including a subset of IgAN patients, ACE inhibition conferred renoprotection [30, 31].

High histopathologic scores have been proposed as predictive of poor outcome [2–4, 7, 8]. In our patients having had kidney biopsy at the same time as AOPP and CRP determinations, both glomerular and interstitial (but not vascular) scores were higher in patients with poor renal outcome.

A salient finding with regard to markers of inflammation and oxidative stress is that, while CRP level was not found to reflect the severity of the disease, elevated AOPP level was predictive of a poor renal outcome and remained an independent risk factor in multivariate analysis. This is in keeping with our previous reports in chronic renal failure patients showing that AOPP are not only markers of oxidative stress, but also affect the progression of renal failure, and by themselves act as potent mediators of monocyte activation [13].

In our present study, patients with progressive forms of IgAN (group II) had a lower Ccr level at baseline than those with slow progression, and this could account for their higher AOPP plasma concentration [13]. However, AOPP level in fast progressors was higher than could be expected from the Ccr reduction by itself, and thus was disproportionately elevated. In our cohort, 65 patients had a baseline Ccr ≥60 mL/min, and were, thus, expected to have AOPP levels within the normal range [13]. Among them, the 14 patients with a proteinuria ≥1 g/day had a faster progression rate than the other 51 with proteinuria <1 g/day, and while the mean Ccr level was close to 83 mL/min/1.73m^2 in both groups, baseline AOPP level was significantly higher in the former than in the latter (49 ± 40 µmol/L vs. 29 ± 18 µmol/L, $P = 0.009$).

The finding that high plasma AOPP levels closely reflect progressive forms of IgAN strongly suggests the role of oxidative stress in the pathophysiology of IgAN, and is in support of the beneficial effects of therapeutic strategies aimed at reducing oxidative stress and inflammation. As a matter of fact, in rat experimental models of IgAN, alpha tocopherol was shown to blunt the severity of oxidative stress [32], and fish-oil to reduce the proteinuria and the development of mesangial lesions [11].

In IgAN patients, randomized trials with fish oil extracts conducted in a large number of patients for a long time also showed beneficial effects in terms of slowed progression of renal failure, especially in patients who initially had a mild or moderate degree of renal dysfunction [16, 33]. Alternatively, corticosteroids have been proposed in the treatment of IgAN, especially in severe forms with active crescentic glomerular lesions, because of their anti-inflammatory and immunosuppressive properties. They were shown to lower proteinuria [10], and in some studies to also slow progression in IgAN patients with a low initial serum creatinine level ($\leq$120 μmol/L) [9]. A trial is underway to evaluate the effects of combined corticosteroids and azathioprine [34], but no trial to date has examined the effects of a recently proposed antioxidant (N-acetylcysteine) [35] or an association of antioxidants and corticosteroids.

CONCLUSION

The results of the present study validate the major predictive value of proteinuria on the renal outcome of IgAN patients, and strongly support the role of oxidative stress in the pathogenesis of IgAN. They also highly suggest that IgAN patients with proteinuria $\geq$1 g/day and inappropriately elevated plasma AOPP at the early stage of the disease may be identified as being at high risk for progression and should be considered for active therapy. Long-term prospective randomized studies involving a large number of IgAN patients with still preserved or mildly impaired renal function will allow the assessment of whether serial determination of AOPP may be used as a surrogate marker for evaluating the effect of therapeutic strategies.

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