Inflammatory markers and the progression of IgA glomerulonephritis

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Abstract

Background. IgA glomerulonephritis (IgAGN) composes a variable prognosis with 15–40% of the patients eventually progressing to end-stage renal failure. Known risk factors for progressive course of IgAGN include hypertension, proteinuria and renal insufficiency. Although markers of inflammation such as serum or urinary interleukin-6 (IL-6) and serum albumin have predicted progression in some studies, sensitive CRP (hs-CRP) has not been directly linked to the progression of IgAGN.

Methods. A total of 174 (70 females) patients were invited for two visits 11 and 16 years (medians) after IgAGN was diagnosed in renal biopsy. All patients had been diagnosed at least 5 years before the first visit. Progressive disease was defined as cystatin-C exceeding normal limits and showing over 20% elevation between the visits, or kidney transplantation or start of dialysis. Cystatin-C and creatinine clearance, serum hs-CRP, s-albumin, s-IL-6 and white blood cell count (WBC) were available for analysis from 118 patients.

Results. IgAGN was progressive in 19.5% of the patients on the second visit. Hs-CRP, s-albumin and WBC of the first visit were significantly associated with the progression of IgAGN (P = 0.014; P = 0.0001; P = 0.023, respectively). S-IL-6 was not associated with the progression. All inflammatory variables correlated significantly with the concurrent level of kidney function. Possible study limitations are the relatively low number of outcomes in the study groups, and the lack of generally accepted definitions for disease progression.

Conclusions. Our results suggest that inflammatory markers hs-CRP, s-albumin and WBC are associated with the progression of IgAGN.

Keywords: albumin; hs-CRP; IgA glomerulonephritis; interleukin-6; white blood cell count

Introduction

The association between inflammatory variables and deteriorated renal function has been increasingly studied over the past years in both chronic renal insufficiency (CRI) and dialysis patients. Most of the reports have been performed in the dialysis population, while very little information exists on the role of inflammation and the progression of CRI of different aetiologies. The MDRD study, in which approximately 30% of the patients had a kidney disease of glomerular origin, did not find a significant association between the rate of decline in GFR and the level of CRP in a non-diabetic CRI population [1]. However, in a smaller Italian study, the inflammatory variables CRP and serum interleukin-6 (s-IL-6) were inversely related to creatinine clearance [2]. Stenvinkel and co-workers also found a strong association between atherosclerosis and inflammation (especially with CRP as a marker) along with malnutrition in Swedish predialysis patients [3]. In the CARE study, CRP and soluble tumour necrosis factor receptor II were independently associated with higher rates of kidney function loss [4]. In addition, in a study on community-based cohort of elderly individuals, inflammatory variables (higher WBC, CRP, fibrinogen and factor VII levels and lower s-albumin and haemoglobin) were significantly associated with the rise in creatinine in a multivariate model [5].

The course of IgA glomerulonephritis (IgAGN) is very variable with approximately 15–40% of the patients eventually progressing to end-stage renal failure. Hypertension, renal insufficiency and proteinuria are known risk factors for poor prognosis [6]. However, identification of other putative factors involved in the progression of IgAGN is a growing area of interest. Our previous results showed that insulin resistance may predict the progression of IgAGN [7]. Since inflammation is also a part of the insulin resistance syndrome [8], we examined the association between markers of inflammation (serum hs-CRP, s-albumin, s-IL-6 and WBC) and the progression of IgAGN in a cohort of biopsy proven patients.
Subjects and methods

Patients

A detailed description of the patient population has been given in our previous paper [7]. In short, the original population consisted of patients in whom IgAGN was diagnosed on the basis of renal biopsy in our institution (Tampere University Hospital) between 1 January 1980 and 31 December 1990 (223 patients). Thirty patients had died, 15 had moved away from the district and the rest of the patients were invited for physician’s appointment in 1996 (first visit) and approximately 6 years later (second visit). Of these 174 patients, 70 were females. A description of the protocol is shown in Figure 1. Altogether inflammatory variables and cystatin-C were available from 118 patients on both visits. None of the patients had a febrile infectious disease at the time when the laboratory values were obtained.

The median age on the first visit was 48.5 years (range 17–85) and the median follow-up time from the renal biopsy was 11 years (6–17). All patients had been diagnosed at least 5 years, 63% at least 10 years and 26% at least 15 years before that visit. By the time of the second visit, 10 (6%) patients had died, 114 (70% of the living ones) patients came for the visit, 30 (18% of the living ones) only filled and returned a questionnaire. At that point, the median age was 54 years (17–90), and the median follow-up time from the biopsy 16 years (7–24). A total of 97% of the patients were diagnosed at least 10 years and 63% at least 15 years before that visit. The causes of death were confirmed from the patient files or from the death certificates kept by Statistics Finland.

The study protocol was approved by the Ethics Committee of the Tampere University Hospital, Finland.

Clinical data

Clinical and laboratory variables were recorded during the visits. The criterion of hypertension was the use of antihypertensive medication, or systolic blood pressure (SBP) > 140 mmHg, or diastolic blood pressure (DBP) > 90 mmHg. The use of antihypertensive and lipid lowering medications increased between the visits. Four percent of the patients used lipid lowering medications and 49% antihypertensive medications on the first visit, compared to 19% and 60% on the second visit, respectively. Six patients had diabetes mellitus at the time of diagnosis, and during the follow-up 19 new diabetic patients were diagnosed, adding the amount of diabetic subjects to 25 by the time of the second visit.

The median body mass index (BMI) of the first and second visits were 26 kg/m² (range 18–45) and 27 kg/m² (18–43), respectively. Median SBP at the first visit was 140 mmHg (104–190) and at the second visit 142 mmHg (90–224), while median DBP was 89 mmHg (60–118) and 88 mmHg (52–120), respectively. Thirteen percent of the patient population smoked on the first visit and 16% on the second visit. The percentage of ex-smokers was 33% and 31%, respectively.

Kidney function was determined using serum cystatin-C and 24-h creatinine clearance, which were measured on both visits or obtained from the patient files. Progressive IgAGN during the follow-up was defined as an elevation of the cystatin-C above the normal level and over 20% elevation from the value of the first visit, or if the patient had had a kidney transplantation or was on dialysis. All transplantations were carried out after a period of dialysis treatment.

Laboratory measurements

Serum hs-CRP values and cystatin-C were analysed using immunoturbidometry methods with Cobas Integra 700, and Cobas Mira S, respectively (both provided by F. Hoffmann-La Roche, Basel, Switzerland). Cystatin-C values were considered normal if they were < 1.2 mg/l (age ≤ 50 years) or < 1.4 mg/l (age > 50 years). S-albumin was analysed by modified bromcresol green binding assay with Cobas Integra (F. Hoffmann-La Roche, Basel, Switzerland). The reference value for normal s-albumin was 36–50 g/l. S-IL-6 was analysed by an enzyme immunoassay method using a commercial PeliKine compact human IL-6 Elisa kit (Sanquin Reagents, Amsterdam, the Netherlands). Other laboratory variables were analysed in the laboratory of Tampere University Hospital using in-house routine methods. All blood samples were obtained after an overnight fast. Creatinine clearance was
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Table 1. Correlations between the inflammatory variables and kidney function of the first visit; correlations are either Spearman (rS) or Pearson (rP)

<table>
<thead>
<tr>
<th>Inflammatory variable of the first visit</th>
<th>Variable of the first visit</th>
<th>Correlation coefficient (rS or rP)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP</td>
<td>S-albumin</td>
<td>−0.328 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>S-interleukin-6</td>
<td>0.380 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>WBC</td>
<td>0.359 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>0.105 (rS)</td>
<td>0.177</td>
</tr>
<tr>
<td></td>
<td>S-cystatin-C</td>
<td>0.395 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance</td>
<td>−0.251 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td>S-Alb</td>
<td>S-interleukin-6</td>
<td>−0.249 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>WBC</td>
<td>−0.287 (rP)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>−0.136 (rS)</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>S-cystatin-C</td>
<td>−0.411 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance</td>
<td>0.381 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td>S-IL-6</td>
<td>WBC</td>
<td>0.209 (rS)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>−0.025 (rS)</td>
<td>0.747</td>
</tr>
<tr>
<td></td>
<td>S-cystatin-C</td>
<td>0.313 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance</td>
<td>−0.219 (rS)</td>
<td>0.005</td>
</tr>
<tr>
<td>S-WBC</td>
<td>Proteinuria</td>
<td>0.247 (rS)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>S-cystatin-C</td>
<td>0.307 (rS)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance</td>
<td>−0.214 (rS)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The number of patients varies (n = 122–168).

Determined by using venous blood for s-creatinine and a 24-h urine collection and the following formula: creatinine clearance = (urine concentration of creatinine × 24-h urine volume)/s-creatinine. Low-density lipoprotein cholesterol was calculated using the Friedewald formula providing that the triglyceride value was < 4.0 mmol/l.

Statistical analyses

The SPSS for Windows 11.5 package was used for statistical analyses (SPSS Inc., Chicago, USA), and the two-sided P value < 0.05 was taken as the level for statistical significance. The correlations between two continuous variables were calculated using Pearson (rP) bivariate correlations if both variables were normally distributed, and Spearman (rS) bivariate correlations if one or both variables were non-normally distributed. The associations between categorical variables and continuous non-normally distributed variables were calculated using the Mann–Whitney U-test or Kruskall–Wallis test depending on the number of the categories. The associations between categorical variables and normally distributed variables were analysed with Student’s t-test or one-way ANOVA depending on the number of categories. The relationships between categorical variables were analysed with the χ²-test. Odds ratios and 95% confidence intervals were computed using logistic regression (enter method) with adjustment for the presence of hypertension.

Results

Correlations between inflammatory variables and clinical and laboratory variables of the first visit

The different inflammatory variables correlated significantly with cystatin-C and creatinine clearance [Table 1]. Hs-CRP [mean 4.6 mg/l, standard deviation (SD) 8.8] showed significant correlations with various components of the metabolic syndrome: SBP (rS = 0.294), BMI (rS = 0.346), waist circumference (rS = 0.491), s-HDL-cholesterol (HDL) (rS = −0.282), s-triglycerides (TG) (rS = 0.288), s-insulin (rS = 0.358) and surate (rS = 0.309). However, the only metabolic syndrome component that significantly correlated with s-albumin (mean 41.2 g/l, SD 3.9) was SBP (rP = −0.248). S-IL-6 (mean 3.2 pg/ml, SD 3.3) correlated significantly with BMI (rS = 0.163), waist circumference (rS = 0.22), HDL (rS = −0.183), TG (rS = 0.192), insulin (rS = 0.249) and urate (rS = 0.261). WBC (mean 5.9 10E9/l, SD 1.5) correlated significantly with SBP (rP = 0.216), waist circumference (rP = 0.21), HDL (rP = −0.307), TG (rS = 0.270), insulin (rS = 0.331) and urate (rP = 0.195). S-albumin had a significant inverse correlation with overnight albumin excretion (rS = −0.161, P = 0.04), but instead did not have a significant correlation with 24-h protein excretion (rS = −0.136, P = 0.08).

Progression of IgAGN

IgAGN was progressive in 23/118 (19.5%) patients on the second visit, based on the definition presented in the Methods section. By the time of the second visit, end-stage renal failure had developed in 13/174 (7%) patients, and impaired kidney function (elevated cystatin-C value or post-transplant situation) in 26/118 (22%) patients including 7 patients with a kidney transplant. One of these patients had had two transplantations. Two patients had undergone a kidney transplantation between the visits. The median creatinine-C values were 0.77 mg/l (range 0.44–5.70) and 1.06 mg/l (0.59–2.93) and the median creatinine clearance values 1.76 ml/s/1.73 m² (0.01–3.68) and 1.55 ml/s/1.73 m² (0.01–2.98) on the first and the second visits, respectively.
Table 2. The comparison of various inflammatory variables on the first visit between the patients with progressive and stable disease (n = 118); the data are expressed as median values and the range is in parenthesis

<table>
<thead>
<tr>
<th>1st visit</th>
<th>Stable disease n = 95</th>
<th>Progressive disease n = 23</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-CRP (mg/l)</td>
<td>1.8 (0.1–21.1)</td>
<td>2.9 (0.3–64.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>S-IL-6 (pg/ml)</td>
<td>1.6 (0.1–14.3)</td>
<td>2.6 (0.7–17.0)</td>
<td>0.091</td>
</tr>
<tr>
<td>S-albumin (g/l)</td>
<td>42 (31–50)</td>
<td>39 (26–45)</td>
<td>0.0001</td>
</tr>
<tr>
<td>WBC (10E9/l)</td>
<td>5.4 (3.0–11.6)</td>
<td>6.4 (3.8–8.8)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

On the first visit the patients later designated as progressive had significantly (P = 0.0001) higher levels of cystatin-C compared to the stable group; 1.23 ml/s/1.73m² (0.03–2.10) versus 0.7 mg/l (0.44–2.45), and also lower levels of creatinine clearance; 1.23 ml/s/1.73m² (0.03–2.10) versus 1.88 ml/s/1.73m² (0.5–3.68) (P = 0.0001). Of note is the fact that neither group was heavily proteinuric, as the median amount of protein excretion for stable patients was 3.9g/24 h (0.14–5.38) (P = 0.009) on the first visit. The median for overnight urine excretion of albumin for stable patients was 34.4 µg/min (2.2–604.0), and for progressive patients 206.0 µg/min (2.2–2130.0) (P = 0.012).

The correlations between inflammatory variables obtained on the first and second visits were all statistically significant: Hs-CRP (rS = 0.503), s-albumin (rP = 0.445), WBC (rP = 0.475) (P = 0.0001 for all). IL-6 was not measured on the second visit.

Associations of inflammatory variables of the first visit with disease progression

Hs-CRP of the first visit was associated with the progression of IgAGN (P = 0.014), and the patients in the progressive group had higher Hs-CRP values than the stable group [Table 2]. S-albumin was also significantly associated with the progression of IgAGN (P = 0.0001), the progressive patients having lower s-albumin levels. S-IL-6 was not significantly associated with the progression (P = 0.091); however WBC did (P = 0.023), so that those with progressive disease had also higher WBC.

If the inflammatory variables were adjusted for the presence of hypertention in a multivariate analysis, the associations for hs-CRP (OR = 1.1, 95% CI = 0.99–1.2, P = 0.07), WBC (OR = 1.4, 95% CI = 0.99–1.9, P = 0.05) and IL-6 (OR = 1.1, 95% CI = 0.9–1.3, P = 0.2) were not significant, but the association with s-albumin was still highly significant (OR = 0.7, 95% CI = 0.6–0.9, P = 0.001).

Correlations between inflammatory variables of the first visit and laboratory variables measuring kidney function on the second visit

There was a significant correlation between hs-CRP and cystatin-C (rS = 0.227, P = 0.014). There was also a significant inverse correlation between s-albumin and cystatin-C (rS = −0.327, P = 0.0001), but no statistically significant correlation existed between s-IL-6 and cystatin-C (rS = 0.155, P = 0.096). Between WBC and cystatin-C (rS = 0.236, P = 0.011) there was a statistically significant correlation as well.

If kidney function was estimated by the use of creatinine clearance, the correlations with the inflammatory variables were as follows: Hs-CRP (rS = −0.207, P = 0.026), s-albumin (rP = 0.335, P = 0.0001), s-IL-6 (rS = −0.033, P = 0.727) and WBC (rP = −0.117, P = 0.211).

Two patients having undergone a kidney transplantation between the visits were excluded from these correlation analyses.

Discussion

This is the first report suggesting that inflammation, as evaluated using hs-CRP, is linked with the progression in IgAGN. Previous evidence has associated low s-albumin with a progressive course, and also in our study low s-albumin was strongly associated with CRI progression. There is virtually no previous data on WBC, but in our study it seemed to predict the progression as well. S–IL-6 was the only inflammatory variable studied that was not significantly associated with the progression. There have been doubts that the plasma level of cystatin-C is influenced by other factors than renal function, and one study has suggested that CRP may be independently associated with cystatin-C level even after adjusting for creatinine clearance [9]. Therefore, we assessed kidney function also by the use of creatinine clearance. Both cystatin-C and creatinine clearance as measures of renal function revealed that hs-CRP was significantly correlated with loss of kidney function along with low s–albumin.

So far, studies on the role of inflammation in the progression of IgAGN have produced negative results when based on the evaluation of CRP [10–12], although some other mediators of inflammation have been suggested as useful prognostic markers. Serum advanced oxidation protein products (AOPP) [11] and soluble vascular adhesion molecule-1 (VCAM-1) [10] were significantly correlated with the prognosis of IgAGN. The former study [11] consisted of 120 IgAGN patients with a mean follow-up of 5.4 years, and AOPP levels were significantly higher in those patients who reached the renal end point (halving of Ccr). However, hs-CRP levels were not statistically different between those who reached the end point and those who did not. The latter study [10] evaluated 51 IgAGN patients in a cross-sectional study design. VCAM-1 correlated significantly with several markers of renal function, out of which
cytostatin-C seemed to have the greatest correlation coefficient. Hs-CRP was significantly higher in IgAGN when compared with healthy controls. However, there was no significant correlation with renal dysfunction but rather a significant correlation with markers of vascular risk factors (BMI, smoking pack years, SBP and pulse pressure) in IgAGN.

A German study compared 56 IgAGN patients with a group of non-immune mediated renal disease patients and healthy controls. Although plasma CRP levels were significantly higher in both patient groups than in healthy controls, there was no statistically significant difference between the two patient groups. The progressive IgAGN patients had higher CRP values compared to stable patients, but the correlation of baseline CRP or the mean CRP of the first year with the 1/creatinine slope was not significant [12].

In the present study, hs-CRP associated and correlated significantly with the progression of IgAGN, whether kidney function was assessed using cytostatin-C or creatinine clearance. Also several components of the metabolic syndrome (SBP, BMI, waist circumference, HDL, TG, insulin, urate) correlated with hs-CRP, confirming previous observations from non-renal population in the IRAS study [8] and observations in IgA patients [10]. However, whether the observed minor elevations of hs-CRP in our study signify only inflammation is unclear. A recent review suggests that the presence of distressed cells rather than inflammation might be the stimulus for C-reactive protein production under several medical conditions [13]. The renal distressed cells could perhaps act in the same way causing minor elevations of serum CRP.

Significantly poorer renal survival rate has been reported with s-albumin < 35 g/l compared with ≥ 35 g/l in 151 IgAGN patients from New Zealand during a mean follow-up period of 5 years [14]. Similar results were obtained from a registry of 253 IgAGN patients from the United Kingdom [15]. In that report s-albumin < 40 g/l was independently predictive of poor outcome. However, a Chinese study showed a significant correlation of s-albumin with histological grading, but not with renal survival, in a cohort of 168 IgAGN patients with an average follow-up of 7.4 years [16]. In a Finnish report, low levels of s-albumin were associated with disease progression, which was thought to result from the strong correlation between s-albumin and proteinuria [17]. Our results showed a strong correlation between s-albumin and progression of IgAGN. However, proteinuria could not be the sole explanation for this, since s-albumin and 24-h proteinuria did not significantly correlate. As there was a significant inverse correlation between s-albumin and overnight albumin excretion, it is possible that increased proteinuria partly explains the low s-albumin in the progressive cases.

There are more reports on urinary than serum IL-6 levels, which have assessed the prognosis of IgAGN. A French group reported that serum cytokines had no correlation with the decline in GFR, although serum IL-6 levels were significantly higher in IgAGN compared to healthy controls, and decreased significantly after immunoglobulin therapy (29 IgAGN patients) [18]. Our findings support these results, as s-IL-6 was the only inflammatory variable studied that did not significantly associate with the progression.

There is virtually no previous data concerning the predictive value of WBC in the progression of IgAGN. In a community-based cohort of elderly individuals, higher WBC count was associated with a rise in creatinine during a follow-up of 4–7 years [5]. In the present study, WBC was significantly associated with IgAGN progression, if evaluation of kidney function was based on cytostatin-C. If creatinine clearance was used instead, WBC was not a significant variable anymore. The reason for this discrepancy is not clear.

With the limited amount of outcomes in our study, it is not possible to perform a thorough multivariate analysis including all of the inflammatory variables simultaneously with the known risk factors of progression. Instead, we performed an additional analysis by adjusting each inflammatory variable for the presence of hypertension. In this analysis, the association for s-IL-6 remained insignificant (P = 0.2), and for s-albumin was highly significant (P = 0.001), whereas the outcomes for hs-CRP and WBC were close to statistical significance (P-values 0.07 and 0.05, respectively). Altogether, a larger study population would be required to demonstrate by the use of multivariate analysis whether the inflammatory variables are dependent predictors of the progression of IgAGN.

In conclusion, our results show that several inflammatory variables are associated with the progression of IgAGN.

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Conflicts of interest. None declared.

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