The impact of sex in primary glomerulonephritis

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Abstract

Background. Studies comparing the impact of sex in primary glomerular disease have reported conflicting results. Methods. We analysed 395 membranous (MGN), 370 focal and segmental glomerulosclerosis (FSGS) and 542 IgA nephropathy patients to determine the impact of the patients’ sex on outcome. We assessed initial and follow-up blood pressure, proteinuria, anti-hypertensive and immuno-suppressive therapy, rate of renal function decline and survival from renal failure or a 50% decrease in creatinine clearance (combined event).

Results. Women accounted for one-third of the cohort. At presentation they were on average 2 years younger than men, and over follow-up received no more immunosuppression or anti-hypertensive agents than their male counterpart. Their mean arterial pressure (MAP) overall was 2 mmHg lower. Proteinuria at presentation and during follow-up in women compared to men was 50% and 30% lower in MGN and FSGS, while no differences were seen in IgA nephropathy. The rate of renal function decline and outcome favoured women over men in MGN (hazard ratios of a combined event of 0.63, 95% CI 0.40–1.00, \( P = 0.05 \)) and in FSGS (HR 0.67, 95% CI 0.48–0.95, \( P = 0.02 \)) but not in IgA nephropathy. These differences were not independent of blood pressure and proteinuria, indicating that these sex-dependent risk factors accounted for most of the hazards seen in men. However, the quantitative effect of proteinuria on the rate of progression was distinct and modified by sex in MGN and FSGS with higher proteinuria levels having less impact on progression rate in women. This interaction was independent of blood pressure.

Conclusions. Women have a better outcome than men in MGN and FSGS but not in IgA nephropathy. These benefits are mostly mediated through both lower proteinuria and blood pressure, although females did have an independent advantage at higher levels of proteinuria.

Keywords: focal and segmental glomerulosclerosis; IgA nephropathy; membranous nephropathy; progression risk factors; sex

Short summary

We assessed the impact of sex on disease progression in 1307 patients with primary glomerulonephritis. Women had a better outcome than men in MGN and FSGS but not in IgA nephropathy. These benefits are mostly mediated through both lower proteinuria and blood pressure, although females did have an independent advantage at higher levels of proteinuria.

Introduction

Although many studies in primary glomerular disease have reported that women have a more favourable outcome than men [1–5], other investigators have found either no sex differences or have observed women to be at greater risk of progressive loss of renal function [6–8]. None of these studies have systematically addressed the relationship between sex and known major determinants of outcome such as proteinuria or blood pressure. Additionally, a wide variety of renal diseases were included in these studies so the impact of a specific histology could not be assessed [4,9]. Whether the sex of the individual does influence progression, either independently or through modulation of other known risk factors, is important to elucidate, since the outcome in these primary glomerular diseases is quite variable and reliable predictors of outcome are needed to ensure that the risks of potentially toxic therapy are balanced by the selection of patients at high risk of progressive loss of kidney function.

We sought to determine the influence of sex on blood pressure, the level of proteinuria, the rate of renal function decline and survival in patients with the three most common histologic variants of progressive primary glomerulonephritis membranous nephropathy (MGN), focal and segmental glomerulosclerosis (FSGS) and IgA nephropathy.
Methods

Setting and participants
All primary MGN, FSGS and IgA nephropathy patients from the Toronto Glomerulonephritis Registry were considered for this study. This database began in 1974 and includes all biopsy-proven cases of glomerulonephritis from the Toronto area.

Patient information at onset is compiled using a standard form and registrars perform a periodic prospective assessment of the patient’s clinical status, medication and laboratory results [10]. This study focuses on patients older than 16 years at presentation, with at least 12 months follow-up and no known secondary cause for their renal disease. We considered only patients with classic pathological findings for each of the three histologic categories.

Parameters collected and definitions
Demographics were age and body mass index (BMI) at onset, sex and ethnicity. Asian descent included India, China, Japan, or Pacific Rim. Parameters prospectively collected included both initial and follow-up information on systolic and diastolic blood pressure, weight, serum creatinine and 24-h urine protein and creatinine measurements. Also recorded were exposure to immunosuppressive agents and antihypertensive medications including the angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) classes of drugs.

Creatinine clearance (CrCl) values were calculated using the Cockcroft–Gault method [11]. Proteinuria and CrCl were adjusted for body surface area (BSA) using the Dubois and Dubois equation [12] to account for different body size between sexes. In 28% of patients, the height was not available and BSA was estimated using the Boyd and Lowe equations [12]. The glomerular filtration rate was also estimated using the MDRD equation and the results of the analysis were the same, in terms of relative importance of predictors in determining the outcome. Renal failure was defined as a CrCl ≤15 ml/min/1.73 m², the start of dialysis or a renal transplantation. Mean arterial pressure (MAP) was defined as the diastolic pressure plus one-third of the pulse pressure. For each patient, an average MAP and proteinuria was determined for each 6-month period of follow-up. Time-average MAP and proteinuria represents the average of every period’s mean. Delta proteinuria was defined as the last minus first proteinuria measured. The proportion of subjects with MGN and FSGS without a partial or complete remission in proteinuria was also determined [13–15]. This group was used as a surrogate for a poor prognosis as previously established. Immunosuppressive treatment is reported as intent to treat regardless of the duration of therapy. MGN patients are categorized as having received no, mono or dual immunosuppressive therapy [13,16] and FSGS treated with either low- or high-dose prednisone (the latter defined as ≥0.7 mg/kg or ≥50 mg daily) and/or other immunosuppression [14]. We reported any exposure to immunosuppression for IgA nephropathy patients. Therapy with ACEi or ARB class of drugs is presented as any exposure.

Statistical analysis
Normally distributed variables were expressed as mean ± standard deviation and compared between men and women using Student’s t-test or the Pearson test. Non-parametric variables were expressed as median and range and compared using the Mann–Whitney test. Categorical variables were expressed in percentage and compared using the chi-square test.

The rate of renal function decline (slope) was determined by fitting a straight line through the calculated CrCl using the principle of least squares. This was plotted and visually examined in each patient. Periods of reversible acute renal failure defined as a rapid reduction and recovery in CrCl of ≥40% within a month were censored. Univariate analysis followed by multivariate linear regression was used to determine the impact of sex on slope. The assumption of linearity was verified by plotting standardized residuals against standardized estimates of the dependent variable (i.e. slope) [17]. A random pattern confirms the absence of nonlinearity. Since proteinuria distribution was skewed, we considered both log and non-transformed proteinuria in our regression analyses [4,9,18–20]. Finally, models including interaction terms of clinically relevant variables were also studied. We evaluated whether sex modifies the quantitative effect of (1) proteinuria, (2) blood pressure and (3) age on the rate of renal function decline (slope) in each of the three histologic groups.

Survival analysis was performed to test the association between each parameter collected and a combined event (renal failure or a 50% decrease in renal function). Univariate comparisons of renal survival were done by the Kaplan–Meier curves and the log-rank test. A Cox proportional hazard model was constructed to determine independent variables associated with this outcome. All P-values were two-tailed and values <0.05 were considered statistically significant. Analyses were carried out using SPSS software (version 11, SPSS Inc., Chicago, IL, USA).

Results
There were 1307 patients older than 16 years of age at presentation with a diagnosis of idiopathic MGN, FSGS or IgA nephropathy who were prospectively followed for >12 months in the Toronto Glomerulonephritis registry from 1974 to the end of June 2005. Exclusions are listed in Table 1.

At baseline, women accounted for 34, 38 and 38% of MGN, FSGS and IgA patients, respectively. Baseline characteristics for each sex and type of glomerulonephritis are shown in Table 2. Women presented 2 years earlier in all categories but this was significantly different only in IgA nephropathy. BMI was lower in females in both MGN and IgA nephropathy. Presenting corrected CrCl was similar between sexes in FSGS and MGN but higher in women compared to men with IgA nephropathy (difference in IgA nephropathy 8 ml/min/1.73 m², P = 0.004).
Changes over time

Comparisons by sex, in blood pressure, proteinuria, therapy and rate of progression in each histologic group are summarized in Table 3. Blood pressure was 2 mmHg higher in men ($P < 0.001$ for the entire cohort) despite a higher exposure to anti-hypertensive medication ($P = 0.003$). Use of renin–angiotensin blockade also tended to be higher in men although this reached statistical significance only in MGN (Table 3).

Table 2 Baseline characteristics of patients according to sex in MGN, FSGS and IgA nephropathy

<table>
<thead>
<tr>
<th></th>
<th>MGN</th>
<th>FSGS</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>$P$</td>
</tr>
<tr>
<td>$N$</td>
<td>134</td>
<td>261</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 ± 18</td>
<td>48 ± 14</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Ethnicity (%)a</td>
<td>84/10/5</td>
<td>91/4/4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>BMI</td>
<td>25 (16–40)</td>
<td>26 (15–53)</td>
<td>0.02</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>100 ± 14</td>
<td>103 ± 13</td>
<td>0.06</td>
</tr>
<tr>
<td>No of BP meds</td>
<td>0 (0–2)</td>
<td>0 (0–3)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>CrCl (ml/min/1.73 m²)</td>
<td>82 ± 32</td>
<td>77 ± 29</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Proteinuria (g/1.73 m²/d)</td>
<td>4.6 (0.6–14.3)</td>
<td>5.9 (0.3–27.6)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

aCaucasian/African American/Asian.

Table 3: Follow-up, therapy and rate of renal function decline according to sex in MGN, FSGS and IgA nephropathy

<table>
<thead>
<tr>
<th></th>
<th>MGN</th>
<th>FSGS</th>
<th>IgA</th>
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<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>$P$</td>
</tr>
<tr>
<td>$N$</td>
<td>134</td>
<td>261</td>
<td></td>
</tr>
<tr>
<td>Length FU (mo)</td>
<td>56 (12–327)</td>
<td>63 (12–400)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Proteinuria (g/1.73 m²/day)</td>
<td>2.7 (0.3–16.4)</td>
<td>4.1 (0.2–21.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time average-BSA</td>
<td>−2.9 ± 4.4</td>
<td>−2.7 ± 5.8</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Δproteinuria-BSA</td>
<td>19</td>
<td>33</td>
<td>0.003</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>98 ± 10</td>
<td>101 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>No of BP meds</td>
<td>0.3 (0.0–3.2)</td>
<td>0.7 (0.0–3.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Immunotherapy (%)</td>
<td>Mono: 37</td>
<td>Mono: 43</td>
<td>0.05</td>
</tr>
<tr>
<td>ACEI or ARB (%)</td>
<td>30</td>
<td>42</td>
<td>0.02</td>
</tr>
<tr>
<td>Slope (ml/min/1.73 m²/year)</td>
<td>−2.6 ± 7.8</td>
<td>−4.3 ± 8.3</td>
<td>0.05</td>
</tr>
</tbody>
</table>
that these sex-dependent risk factors for progression accounted for the hazards seen in men. The blood pressure and proteinuria adjusted hazard ratios were 1.1 in MGN and 0.9 in FSGS in females, \( P > 0.1 \). Similar findings were found with multivariate linear regression. No difference was seen in the outcomes between sexes in IgA nephropathy (Table 3 and Figure 1(c)).

**Interactions between risk factors of progression and sex**

We analysed potential interactions between quantitative proteinuria, blood pressure, age and sex on outcome in each of the histologic categories. We first examined whether the quantitative impact of proteinuria on slope was modified according to sex. We conducted a linear regression with the covariates sex, proteinuria and the interaction term (sex times proteinuria). This term was significant in MGN (\( P = 0.004 \)) and FSGS (\( P = 0.03 \)). This means in these two glomerular disease types that at identical levels of proteinuria, there is a more rapid deterioration in renal function in men than women but only in the higher ranges of proteinuria (>7 g/day, Figure 2). Similar results were obtained with regression models using untransformed rather than log-transformed proteinuria. Normality and linearity plots supported both methods. These findings were independent of blood pressure in both histologic groups. In IgA nephropathy, however, no interaction between proteinuria, sex and decline in function was seen (Figure 2(c)). Figure 2 illustrates this interaction in MGN and FSGS patients with high grade proteinuria.

We also examined whether the deleterious impact of blood pressure on the rate of renal function decline was modified according to sex but found no interaction in any of the three histologic categories (data not shown). Finally, we examined the effect of age by sex on the outcome and found in MGN that the slower progression and higher survival seen in women was clinically and statistically significant only in the youngest half of the cohort (data not shown). In contrast, no relationship to age was seen in either FSGS or IgA nephropathy.

Finally, we examined patients with no clinical information recorded since June 2002, 3 years prior to end of the study (loss to follow group) to assess potential bias. Their median duration of observation was 61 months and their rate of function decline was markedly slower than in remaining cohort (\(-2.8 \pm 7.2\) compared to \(-7.9 \pm 9.0\) ml/min/1.73 m\(^2\)/year, \( P < 0.001 \)). The proportion of women in this group was identical to the remaining cohort suggesting no sex selection bias. This remained true for each of the three histologic types of glomerular disease studied.

**Discussion**

Differences in progression rate and outcome between sexes in glomerular disease are a subject of debate [1–4, 6–8]. Much of the historical data comes from studies that did not specifically focus on sex and reported differences as a secondary outcome. Confounding variables such as type of glomerular disease, severity of proteinuria and hypertension were not systematically addressed [1,4,9]. We sought to determine the influence of sex on blood pressure, proteinuria, the rate of renal function decline and survival in patients with the most common types of progressive primary glomerulonephritis. We determined that in MGN and FSGS, women had a more favourable outcome than men.
A significant proportion of this benefit was attributable to lower initial and follow-up proteinuria and blood pressure found in females. However, even after adjusting for these two factors, female sex does contribute to a slower rate of progression in MGN and FSGS at high levels of proteinuria. In contrast in IgA nephropathy, no difference by sex in the baseline and follow-up proteinuria was found and patient sex did not influence progression.

This retrospective study on prospectively gathered data spans over three decades, and new and more effective treatments have evolved during this time. Lower blood pressure goals, renin–angiotensin blockade and newer immunosuppressive regimens were neither available nor adopted until the nineties and many patients in our study predated these practices. This explains the overall higher than ideal achieved mean blood pressure and the lower percent of patients exposed to the ACEi/ARB class of agents compared to the current recommendations. Although this study was observational and patients received various forms of therapy, the data were collected prospectively and do not indicate that greater treatment was given to females, making this an unlikely explanation for the differences observed. The possibility that the ‘lost to follow-up’ group would bias against men also seems unlikely, since this group had a median of 5 years of observation, a similar proportion of men and a significantly slower rate of progression compared to the remainder of the cohort.

We used two different outcomes (slope and survival from renal failure or a 50% reduction in renal function) to analyse our data. We used a combined outcome for survival to increase the number of events and enhance our statistical power. We adjusted our CrCl data for BSA since unadjusted values would favour men given their larger body size [21]. Adjusting proteinuria for BSA is unusual in adults although it is standard practice in the paediatric population [21]. Since women in general as well as in this cohort experienced less proteinuria, the strongest predictor of progression, it was essential to demonstrate that this represented a true sex difference in primary glomerular disease and not an artefact of smaller kidneys and lower number of nephrons in women.

We studied three potentially important clinical interactions with sex. We chose proteinuria and blood pressure as they are well-known risk factors for progression. We also studied age because although limited information is available in the glomerular diseases, differences between sexes in other disorders such as essential hypertension are more pronounced in younger patients [22]. The interaction between proteinuria and sex on the rate of progression was significant but only of clinical relevance at high levels of proteinuria. The slower progression rate in women was mostly mediated through both lower initial and sustained proteinuria and blood pressure and confirms that these risk factors should remain the main indicators for therapy in patients with primary glomerular disease, regardless of sex. The exception may be MGN patients where a longer observation prior to initiating immunosuppressive treatments may be warranted, given the independent protective benefits of sex especially in young women.

Studies like MDRD, REIN-2 and others have used a log transformation of proteinuria to predict the rate of renal function decline since the variable distribution is highly skewed [4,9,18–20]. Our normality and linearity plots support the use of either untransformed or log-transformed proteinuria. However, Figure 2 illustrates how the true relationship between proteinuria and the rate of renal function decline is more complex (nonlinear) and markedly influenced by the underlying histology; at equal levels of proteinuria, the rate of renal function decline in comparison to MGN was greater in FSGS and greatest in IgA nephropathy.

Compared to men, women have lower proteinuria in primary kidney disease and are less hypertensive whether or not they have underlying chronic kidney disease [2,22]. Interestingly, a recent patient-level meta-analysis of randomised controlled trials in non-diabetic renal disease found women to be significantly more hypertensive and at a greater risk of progression than men [8]. In that study, however, the baseline creatinine was identical in men and women because the entry criteria in many of the trials included dictated equal creatinines at entry regardless of patient sex. This meant that the women selected for inclusion would have had lower GFR than the men and therefore more likely to have advanced disease at entry [21]. Additionally, the majority of women in this analysis were post-menopausal, a period of time commonly associated with higher systolic blood pressure. The authors correctly pointed out in their review these important limitations of the data.
Sex differences in proteinuria per se in specific histologic types of primary glomerular diseases have seldom been reported. The better outcome we found in females with MGN is consistent with most [23–29] although not all of the published studies [30–32]. In FSGS, two large studies also found a better outcome in females by univariate but not multivariate analysis after they adjusted for proteinuria [33, 34]. Others smaller studies reported no statistical differences, although most showed a trend that favoured women [35–40].

We found no sex difference in proteinuria, rate of renal function decline or in survival from a combined event in IgA nephropathy. This is consistent of with multiple studies in this type [41–48] but is in contrast with a large meta-analysis [1]. The referenced studies used in the latter reported the impact of sex as a secondary analysis and quantitative outcomes were given only when significant differences were found. Hence, negative studies were excluded as differences were not specified. Furthermore, many of the cited studies used a level of creatinine as an outcome of chronic kidney disease and this would inevitably bias against males for the reasons discussed earlier [49–54]. Nevertheless, a few large reviews using either CrCl or renal failure as an outcome still observed a significant benefit in females in IgA nephropathy [55–57], although it is worth noting that gender was not the focus of the latter publications.

Experimental studies have suggested mechanisms responsible for gender differences in progression. We and others have noted differences for instance in the activity of the renin-angiotensin system and in nitric synthase activity by sex [58–60]. Given the epidemiological nature of our study we cannot define the specific quantitative contributions of sex nor answer the question of whether these findings will lead to new treatment options. However, by a greater understanding of risk factors for progression and by improved predictive algorithms using these factors, we may begin to tailor therapy and be in a better position to consider newer and more novel forms of treatment in the highest risk of progression group, as well as avoid unnecessary and potentially toxic interventions in low-risk patients.

In conclusion, women with MGN and FSGS have a slower rate of progression and better renal survival than men. These benefits are mostly mediated through both lower initial and sustained proteinuria and blood pressure in females. In addition, females do have a substantial additional benefit compared to males, but only at high levels of proteinuria. None of these benefits related to sex exist in females with IgA nephropathy.


Conflict of interest statement. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We have no conflict of interest to declare.

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Received for publication: 1.10.07
Accepted in revised form: 6.12.07