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# Gender-related differences in IgA nephropathy; an eleven-year experience according to revised Oxford classification

Rohollah Valizadeh[1], Muhammed Mubarak[2], Raha Manouchehrian[3,4], Azar Baradaran[5*]

[1]Department of Biostatistics and Epidemiology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[2]Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan
[3]Nickan Research Institute, Isfahan, Iran
[4]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[5]Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran

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## ABSTRACT

*Introduction:* IgA nephropathy (IgAN) is a common glomerular disease characterized by dominant or co-dominant granular IgA deposits in the glomerular mesangial areas.

*Objectives:* This study aimed to determine the possible gender-related differences in IgAN at a single center in Iran.

*Patients and Methods:* All renal biopsy-proven cases of IgAN during the last 11 years (2009-2020) were studied. All kidney biopsies had two samples for immunofluorescence and light microscopy. Renal biopsies were reviewed using the recently revised Oxford classification of IgAN. In addition to Oxford-MEST morphologic variables, other data consisting of age, gender, serum creatinine and level of proteinuria within 24 hours at the time of biopsy were collected. The data were analyzed in SPSS version 21.0.

*Results:* This study included 246 biopsy-proven cases of IgAN patients with a mean age of 38.23 ± 13.71 years and a male prevalence of 67.1% (n=161). The mean ± SD values of serum creatinine and 24-hour proteinuria were 1.47 ± 1.06 mg/dL and 1753.63 ± 1049.418 mg/d, respectively. Analysis regarding age, serum creatinine, the quantity of 24-hour proteinuria, the number of sclerotic glomeruli, and the percent of interstitial fibrosis showed only serum creatinine to be significantly higher in males than females ($P=0.017$). Moreover, 24-hour proteinuria was higher in males than females ($P=0.047$). Our study showed that males have more segmental sclerosis ($P=0.023$) and more significant IgM deposits than females ($P=0.003$). The mean scores of IgA, IgG, and C3 deposited immunological reactants were not substantially different between males and females ($P>0.05$).

*Conclusion:* Our study showed that serum creatinine and proteinuria were significantly higher in males. Males also had higher segmental sclerosis on biopsies. Larger-scale research is needed to confirm our results.

*Implication for health policy/practice/research/medical education:*
Studies on gender-related differences in clinical, paraclinical, and morphologic variables of Oxford classification of IgA nephropathy (IgAN) are scarce. We studied gender-related differences in 246 renal biopsy-proven cases of IgAN - over 11 years. Serum creatinine and proteinuria were significantly higher in males. Males had more segmental sclerosis compared to females on renal biopsies. The male IgAN patients present with worse clinicopathologic features than female patients. However, more extensive studies with extended follow-up are needed to corroborate these findings.

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## Introduction

End-stage renal disease (ESRD) is a major public health problem, affecting one in 1000 individuals. One significant worldwide cause of ESRD is immunoglobulin A nephropathy (IgAN), the most common type of primary glomerulonephritis. Over 20 years, about 40% of people with IgAN will develop ESRD. The prevalence of this disease ranges from less than 10% in the United States to 30%-40% in Asia (1-3). Immunoglobulin A nephropathy is a highly heterogeneous disease with a wide range of

*Corresponding author: Prof. Azar Baradaran,
Email: azarbaradaran@yahoo.com, azarbaradaran@med.mui.ac.ir

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clinical, laboratory, and morphological presentations (4). Clinically, this condition is represented by gross or microscopic hematuria, varying degrees of proteinuria (sometimes nephrotic in type), and frequently high blood pressure (systolic blood pressure ≥130 mm Hg and diastolic blood pressure ≥90 mm Hg). Occasionally, the disease first manifests as chronic kidney disease (CKD). Patients may also be asymptomatic as well (5-9).

Morphologically, the disease can range from normal histology on light microscopy to a spectrum of morphologic abnormalities such as mesangial proliferation, endocapillary and extra-capillary hyper-cellularity, segmental sclerosis, and fibrinoid necrosis (10,11). Significant mesangial IgA deposits, detectable by immunofluorescence (IF) microscopy, are used to diagnose (12,13).

The probability of CKD and ESRD is not accurately predictable. However, male gender, amount of proteinuria, systolic hypertension, and the presence of kidney insufficiency at the beginning of the disease are some factors that worsen the prognosis (14).

## Objectives

In this study, we sought to determine the possible gender-related differences in IgAN patients at a renal pathology laboratory in Iran.

## Patients and Methods

### *Study design*

This cross-sectional study was conducted at a single pathology laboratory in Isfahan, Iran, over 11 years (2009 to 2020) by consecutive sampling. We first extracted biopsy-proven IgAN cases among 2000 renal biopsies, of which 246 were reported as primary IgAN. Primary IgAN was detected by the absence of other diseases like diabetes mellitus, amyloidosis, alcoholism, or liver diseases, associated with significant mesangial IgA deposits and lack of C1q depositions in renal biopsies (3,4).

All renal biopsies consisted of two cores of renal tissue, one for light and one for immunofluorescence microscopy. Accordingly, IgA mesangial deposits were scored from zero to 3+ intensity for immunofluorescence assessment. The diagnosis of IgAN requires significant granular IgA deposits (≥2+ in the mesangial or mesangiocapillary area) along with insignificant deposits of C1q (3, 4).

To conduct this study, we extracted the archived biopsy blocks and restudied the glass slides stained with periodic acid–Schiff (PAS), Jones stain, Masson's Trichrome, and H&E (hematoxylin and eosin), according to the revised Oxford classification (3,12). Other information, such as age, gender, serum creatinine, and the amount of proteinuria, was obtained through biopsy request forms. Exclusion criteria were; lack of demographic or laboratory information, pregnancy, diabetes, cancer, presence of renal transplantation, or single kidney. In addition, renal biopsies with less than eight glomeruli were excluded from the study.

The morphological variables included mesangial hypercellularity (M) (M0 for mesangial cellularity in <50% of glomeruli; M1 for >50%), endocapillary hypercellularity (E) (E0 for the absence of proliferation; E1 for the presence of endocapillary hypercellularity in the glomeruli), presence of segmental glomerulosclerosis (S) (S0 when no segmental sclerosis present and S1 in the presence of segmental glomerulosclerosis in even one glomerulus), interstitial fibrosis/tubular atrophy (T) variable (T0 for 0-25%; T1 for 25-50%; T2 for >50% involvement), and finally the presence of extra-capillary proliferation(crescents) or C-score (where C0 for no crescents, C1for crescents in less than one-fourth of glomeruli, and C2 for crescents in over one-fourth of glomeruli) (3,4,12).

### *Statistical analysis*

The data were entered and analyzed in SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean and standard deviation (SD) or median and ranges (minimum and maximum) for quantitative variables and as frequency and percentage for qualitative variables. Comparative analyses were conducted using chi-square and unpaired student's t-test for male and female genders. A *P* value less than 0.05 was considered statistically significant.

## Results

This investigation included 246 biopsy-proven cases of primary IgAN patients with a mean age of 38.23 ± 13.71 years. Among all, 67.1 % (n=161) were males. The mean ± SD serum creatinine and proteinuria were 1.47±1.06 mg/dL and 1753.63 ± 1049.418 mg/d, respectively. Table 1 presents the primary demographic and laboratory data of all patients.

In our study, 171 (69.5%) biopsies had mesangial

**Table 1.** The primary demographic and laboratory data of all patients (n = 246)

| Variables | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|
| Age (y) | 38.23 | 13.71 | 35 | 15 | 85 |
| Serum creatinine (mg/dL) | 1.47 | 1.06 | 1.2 | 0.5 | 13 |
| Proteinuria (mg/d) | 1753.63 | 1049.418 | 1800 | 50 | 7230 |

proliferation (M1), 158 (64.2%) had segmental sclerosis (S1) and 87 (35.4%) had endocapillary hypercellularity (E1). In addition, 106 (43.1%) biopsies showed T0, 92 (37.4%) biopsies had T1, and 48 (19.5%) renal biopsies had T2. Table 2 shows the MEST-C scores and the intensity scores of the deposited immunoglobulins and C3.

Comparison of various parameters, such as age, serum creatinine, amount of 24-hour proteinuria, number of sclerotic glomeruli, and percent of interstitial fibrosis, showed only serum creatinine to be significantly higher in males as compared to females ($P=0.017$). Furthermore, the degree of proteinuria was higher in males than in females ($P=0.047$; Table 3).

Our study also showed that, among MEST variables, either separately or in total, MEST scores were not significantly different among males and females except for the S variable, which was significantly higher in male patients ($P=0.023$). Crescent score was not significantly different across genders ($P=0.486$; Table 4).

However, we found that males had significantly higher IgM intensity scores versus females ($P=0.003$; Table 5). Additionally, this table shows that mean scores of deposited immunoglobulins of IgA, IgG, and C3 were not significantly different between males and females ($P>0.05$).

**Table 2.** Frequencies of different morphological variables on renal biopsies according to revised Oxford classification and intensity scores of deposited immunoglobulins and C3 (n = 246)

| Variables | | No. | % |
|---|---|---|---|
| M | M0 | 75 | 30.5 |
| | M1 | 171 | 69.5 |
| E | E0 | 159 | 64.6 |
| | E1 | 87 | 35.4 |
| S | S0 | 88 | 35.8 |
| | S1 | 158 | 64.2 |
| T | T0 | 106 | 43.1 |
| | T1 | 92 | 37.4 |
| | T2 | 48 | 19.5 |
| C3 complement deposit | 0 | 43 | 17.5 |
| | 1+ | 92 | 37.4 |
| | 2+ | 84 | 34.1 |
| | 3+ | 27 | 11.0 |
| IgG complement deposit | 0 | 167 | 67.9 |
| | 1+ | 61 | 24.8 |
| | 2+ | 17 | 6.9 |
| | 3+ | 1 | 0.4 |
| IgM complement deposit | 0 | 169 | 68.7 |
| | 1+ | 60 | 24.4 |
| | 2+ | 17 | 6.9 |
| IgA complement deposit | 1+ | 7 | 2.8 |
| | 2+ | 78 | 31.7 |
| | 3+ | 161 | 65.4 |

M (Mesangial hypercellularity), E (endocapillary hypercellularity), S (segmental sclerosis), T (tubular atrophy/interstitial fibrosis).

## Discussion

IgA nephropathy was detected in 22% of all glomerular disorders in Europe and up to 39% in Asia, according to the International Kidney Biopsy Survey on glomerular disease frequencies investigated over 42 000 renal biopsies from four continents (15). According to the ERA-EDTA registry, IgAN is the primary illness in 35% of transplanted patients aged 20 to 44 in Europe. In recent years, the diagnosis of IgAN among older persons in Spain has steadily grown (16). Due to the importance of this disease worldwide, we analyzed 246 cases of renal biopsy-proven IgAN to find the possible gender-related differences regarding demographic, biochemical, and morphological findings. Based on our research, we found that being a man is a significant risk factor. Higher serum creatinine, more proteinuria, greater IgM intensity scores, and the S variable among MEST variables were more common in male patients than females.

In the study by Wen et al, 1096 adult IgAN (475 males and 621 females) patients have compared with

**Table 3.** The demographic and laboratory variables were compared across male (n=165) and female (n=81) patients

| Variables | Gender | Mean | SD | *P* value |
|---|---|---|---|---|
| Age (y) | Male | 39.35 | 14.06 | 0.068 |
| | Female | 35.95 | 12.76 | |
| Serum creatinine (mg/dL) | Male | 1.5870 | 1.20 | 0.017 |
| | Female | 1.2421 | 0.67 | |
| Proteinuria (mg/d) | Male | 1846.84 | 1085.52 | 0.047 |
| | Female | 1563.74 | 950.05 | |
| Interstitial fibrosis (%) | Male | 15.18 | 13.83 | 0.874 |
| | Female | 14.86 | 15.79 | |

**Table 4.** Comparison of MEST scores among male and female patients

| Variable | | Gender | | *P* value |
|---|---|---|---|---|
| | | Male | Female | |
| M | 0 | 52 | 23 | 0.617 |
| | 1 | 113 | 58 | |
| E | 0 | 108 | 51 | 0.701 |
| | 1 | 57 | 30 | |
| S | 0 | 51 | 37 | 0.023 |
| | 1 | 114 | 44 | |
| T | 0 | 64 | 42 | 0.147 |
| | 1 | 67 | 25 | |
| | 2 | 34 | 14 | |
| MEST | Mean | 2.53 | 2.27 | 0.192 |
| | SD | 1.45 | 1.52 | |
| Crescent | Mean | 0.55 | 1.06 | 0.486 |
| | SD | 0.46 | 0.97 | |
| Total MEST | Mean ± SD: 2.45±1.47 | | | |

**Table 5**. Comparison of C3, IgG, IgM, and IgA among male and female patients.

| Variable | | Gender | | *P* value |
|---|---|---|---|---|
| | | Male | Female | |
| C3 | 0 | 23 | 20 | 0.099 |
| | 1 | 62 | 30 | |
| | 2 | 58 | 26 | |
| | 3 | 22 | 5 | |
| IgG | 0+ | 111 | 56 | 0.628 |
| | 1+ | 41 | 20 | |
| | 2+ | 12 | 5 | |
| | 3+ | 1 | 0 | |
| IgM | 0+ | 119 | 50 | 0.003 |
| | 1+ | 41 | 19 | |
| | 2+ | 5 | 12 | |
| IgA | 1+ | 3 | 4 | 0.330 |
| | 2+ | 51 | 27 | |
| | 3+ | 111 | 50 | |

clinicopathological features and risk factors among the genders. They found that male patients had higher serum creatinine, proteinuria, serum uric acid, lower levels of estimated glomerular filtration rate, and higher blood pressure. Analysis of morphological features showed tubular atrophy/interstitial fibrosis (T) lesions were more frequent in male cases. During their follow-up, renal survival rates of male IgAN patients were significantly lower than female patients (17). Consistently, other studies found that being male was associated with greater levels of serum creatinine and a worse outcome (17,18). An analysis by Riispere et al on 73 biopsy-proven IgAN cases (62% males and 38% females) held the same view that IgAN progresses more rapidly in male than in female patients through faster glomerular filtration rate declines. They also found a higher MEST score in males related to disease progression (19). In contrast, the study by Deng et al showed that male IgAN patients presented with worse clinicopathological changes than female patients, however when controlled for the confounding effect of renal function by glomerular filtration rate and serum creatinine, no significant differences in the long-term renal survival were observed between male and female patients (20). According to some studies, estrogen can protect the kidneys in both humans and animals (21). In our results, the amount of 24-hour proteinuria was significantly higher in males than in females. In previous studies, the kidney outcomes of IgAN have conclusively been shown to be impacted by proteinuria too (22). Lv et al demonstrated, proteinuria of more than 1 g/d connected to poor prognosis in patients with an average of 6.1 years (23). Contrary to these results, Sevillano et al in a cohort of 151 patients ≥65 years old, and Tan et al on 126 patients with a mean age of 57.12 ± 6.24 years, reported proteinuria was not significantly associated with poor outcomes(16,18).

We suggest that the disparity between these studies can be due to several variables, including the patient population, the duration of follow-up, age, behavioral patterns such as individual physical activity or eating habits, race, biopsy practice, and various outcome definitions. Additionally, O'Shaughnessy et al hypothesized that inconsistent results might be partially due to variations in genetic and environmental exposures (15).

## Conclusion

In conclusion, serum creatinine and 24-hour proteinuria were significantly higher in males. Among morphological features, segmental sclerosis, and IgM intensity scores were more prevalent in males and required more attention.

## Limitations of the study

This study was conducted on a limited number of patients, and the data is limited to two neighbor provinces. It is a cross-sectional study with no follow-up data on the outcome of patients. Thus, further large-scale, multiple, longitudinal studies on this feature of IgAN are necessary to corroborate these findings.

## Authors' contribution

Conceptualization: AB.
Data curation: AB.
Formal analysis: RV.
Funding acquisition: AB.
Investigation: AB and RM.
Methodology: RV.
Project administration: AB.
Resources: AB.
Supervision: AB.
Validation: RV and RM.
Visualization: AB and RV.
Writing–original draft: RM.
Writing–review & editing: MM.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical issues

This investigation was conducted in accordance with the Declaration of Helsinki. This study was performed on paraffin-embedded blocks of renal biopsies. Informed consent was obtained routinely at the time of renal biopsies. The ethical board committee of the National Institute for Medical Research Development approved this study (Ethical code #IR.NIMAD.REC.1399.222). The authors have also observed ethical issues, including plagiarism, data fabrication, and double publication.

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