Original Research Article

IgA nephropathy clinicopathologic study following the Oxford classification: Progression peculiarities and gender-related differences

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ABSTRACT

Background and aim: Immunoglobulin A nephropathy (IgAN) is the most frequent glomerular disease worldwide and one of the main causes of chronic kidney disease. We aimed to investigate clinicopathological correlations in IgAN patients by gender.

Materials and methods: The study was based on a retrospective analysis of renal biopsy data and clinical manifestations of the disease. Consecutive 73 biopsy-proven IgAN cases of male (62%) and female (38%) patients were investigated. Renal biopsies were reviewed using the new Oxford classification assessing the MEST (mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis/adhesion, tubular atrophy/interstitial fibrosis) score. The most powerful IgAN prognostic risk factors, morphological (segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis) as well as clinical (proteinuria and hypertension) were taken into account in the correlation analysis. The mean rate of renal function decline was expressed as a slope of eGFR during the follow-up (FU) dividing delta GFR with the FU years.

Results: The mean age of the patients was 33.7 years (range, 16–76). Follow-up data were available for 64 patients with the mean follow-up of 4.1 years. The mean proteinuria at biopsy was 0.79 g/24 h. The mean arterial pressure (MAP) was 94.5 ± 16.7 mmHg and 7% of the patients were hypertensive. The initial mean estimated glomerular filtration rate (eGFR) was 94.9 ± 30.7 mL/min, at the end of the follow-up it was 86.2 ± 27.1 mL/min. The mean rate of renal function decline was -3.4 ± 11.9 mL/min/1.73 m^2 per year in males ($P < 0.05$)

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and -0.7 ± 5.3 mL/min/1.73 m^2 per year in females. The Spearman correlation analysis confirmed a higher MEST score in the whole cohort and in males correlated with disease progression. In patients with proteinuria below 1.0 g/24 h, disease progression was faster in males.

Conclusions: According to the correlation analysis of the main prognostic risk factors, affecting the progression of IgAN, we can conclude that IgA nephropathy in males progresses more rapidly compared to females.

1. Introduction

IgA nephropathy (IgAN), or Berger's disease, is recognized as the most widespread type of glomerulonephritis worldwide and as one of the main causes of chronic kidney disease (CKD) [1–5]. Morphologically, the disease is defined by the predominance of diffuse, mainly mesangial deposition of IgA, identified by immunofluorescence or immunohistochemistry and by a variable degree of glomerular damage by light microscopy; whereas the pathogenesis of the disease still remains largely unknown [2,5]. Mesangial IgA deposition might be present in about 5%–15% of healthy individuals, but only about 1 in 50 people with IgA deposits present with clinical disease [1]. IgAN is potentially progressive to end-stage kidney disease (ESKD); however, its clinical presentation and progression in individual patients is variable and its course is generally benign in cases without proteinuria, hypertension or the reduced glomerular filtration rate (GFR). Also, in IgAN, overweight/obesity, present at diagnosis, is associated with an increase in the major risk factors (hypertension, proteinuria and severe renal lesions) which translate into a worse final outcome [6].

The Oxford classification of IgAN, published in 2009 [3], aimed to define reproducible and useful renal biopsy-based prognostic indicators. The study was based on a retrospective analysis of 265 IgAN patients of different age groups from four continents where renal biopsies were reviewed by expert pathologists focusing on prognostic information provided by renal biopsy [3]. As a result, the Oxford classification of IgAN based on the MEST score (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) was proposed to predict renal outcome independently from all clinical indicators at the time of biopsy and during the follow-up [3]. According to these guidelines, several papers of investigations involving large cohorts of IgAN patients have been published [7–10] and comparisons of different IgAN validation studies have been presented [11–14].

We present a retrospective analysis of biopsy-proven IgAN during an 11-year period with a follow-up of the disease progression in Estonian population. The IgAN cases were classified according the Oxford classification, clinical-morphological correlations and performance of the prognostic scoring system was evaluated, with special attention to potential gender-related differences. The aim of this study was to investigate clinicopathological correlations in IgAN patients by gender.

2. Materials and methods

2.1. Demographic data and setting

All native kidney biopsies ($n = 578$) performed between 2001 and 2010 at the Department of Pathology of Tartu University Hospital were retrospectively reviewed and the data of all patients with biopsy-proven IgAN from this period and also from the year 2011 were collected. IgAN formed the main part of primary glomerulopathies (35.5%) [15]. A total of 88 cases of IgAN during the 11 years were registered. To compose the patients' cohort, we followed the recommendations of the International Consensus of IgAN study – the Oxford's classification of IgAN [3,4] – and, thus, 73 IgAN cases were selected for the study. By design, our study included the whole spectrum of IgAN cases represented in clinical practice. Demographic data included data on gender and age at the time of biopsy. Children were defined as ≤18, adults as 19–65, and elderly patients as >65 years of age.

Only biopsy-proven IgAN cases (standard light microscopy and immunofluorescence in all cases were performed), defined by a predominant diffuse deposition of IgA in the glomerular mesangium (both children and adults, with any level of eGFR and any level of proteinuria or without it) were included in the study. Antihypertensive or immunosuppressive treatment was not considered as an exclusion criterion. Patients with renal biopsies including less than 8 glomeruli, secondary IgAN such as Henoch–Schönlein purpura, IgAN with the combination of advanced diabetes mellitus, and cases with less than 1 year of follow-up were excluded.

2.2. Pathology data

A simplified score sheet of the Oxford classification of IgA nephropathy study was used [3]. Each biopsy was scored by two independent pathologists according to the Oxford classification [3]: total number of glomeruli, mesangial hypercellularity, M0/M1 (< or equivalent to >50% of glomeruli showing >4 mesangial cells in one area); endocapillary proliferation, E0/E1 (present/absent), segmental glomerulosclerosis/adhesion, S0/S1 (present/absent); glomerular membrane duplication, necrosis, cellular/fibrocellular crescent were categorized as present or absent; tubular atrophy/interstitial fibrosis, T0/T1/T2 as arteriosclerosis as well, A0/A1/A2 were categorized as absent/mild (0%–25%), moderate (26%–50%) or severe (>50%); arteriolar hyalinosis was categorized as absent or present. A0–A2 and

arteriolar hyalinosis are not parts of the Oxford classification and the items were included in investigation as an important morphological features associated with hypertension. Interstitial fibrosis and tubular atrophy were taken as one item. According to the Oxford classification, tubular atrophy/interstitial fibrosis is measured as percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater.

For immunofluorescence (IF) investigation, tissue samples were snap-frozen with freezing spray in tissue freezing liquid and were subsequently cut by cryostat. IF was based on the use of antisera conjugated with fluorescein directed against human antigens such as IgA, IgG, IgM, complement fractions (C3, C1q), and kappa and lambda light chains of immunoglobulins (DAKO products). IgAN in the native kidney was defined as dominant or codominant staining with IgA in glomeruli by IF. The intensity of IgA staining was more than trace (moderate (++) or marked (+++/++++)). Not all glomeruli showed this positivity. SLE-nephritis was excluded having an intense positivity for all immunoglobulin antigens and complement fragments, especially C1q, IgG and IgM, which causes the so-called "full house" pattern.

2.3. Clinical data

Baseline clinical data were collected within 3 months of the biopsy and at the end of a follow-up (FU): weight, height, body mass index (BMI), smoking history, presenting clinical syndrome at the time of biopsy, systolic and diastolic blood pressure (mmHg), serum creatinine (μmol/L), serum albumin (g/L), serum cholesterol (mmol/L) and serum triglycerides levels (mmol/L). Proteinuria was expressed in grams (g) per 24 h/1.73 m^2 in children and in g per 24 h in adults; microhematuria was ranked at the intervals of <75, 76–150, >150 erythrocytes/μL. eGFR (mL/min/1.73 m^2) was calculated using the modified MDRD formula for adults and the Schwartz formula for children [16]. ESKD was defined as eGFR <15 mL/min/1.73 m^2 and as transition to dialysis or transplantation. A 50% reduction of the renal function from baseline eGFR was defined as an endpoint. The mean rate of renal function decline was expressed as a slope of eGFR during the FU (delta GFR divided with the FU years). Mean arterial pressure (MAP) was defined as diastolic pressure plus a third of the pulse pressure.

The treatment information included antihypertensive, immunosuppressive, fish oil and statins medications as well as tonsillectomy. The data on antihypertensive treatment and immunosuppression were detailed, showing the number of medications and the classes of antihypertensives: treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and treatment with calcium channel blockers (CCB).

2.4. Statistical analysis

All data were collected in a standard Excel spreadsheet and stored on a standard Excel database. Statistical analysis was performed using the Statistics 12.0 statistical program. Descriptive statistics were used to characterize the cohort. Spearman rank order correlations were used to assess bivariate relationships. Qualitative data are presented as absolute and relative (percentage) frequencies. Quantitative data are expressed as means ± standard deviation (SD). A P value of <0.05 was considered to be statistically significant in all analyses. The rate of renal function decline, expressed as slope of eGFR at the end of the FU, and which was shown as clinical outcome, was analyzed.

2.5. Ethics

The Research Ethics Committee of the University of Tartu approved this study (protocol no. 212/T-13, 2012).

3. Results

3.1. Patients' characteristics and outcome data

A total of 73 biopsy-proven IgAN cases were analyzed: 62% of them were male and 38% were female cases. Patients' mean age at presentation was 33.7 years (16–76 years): 32.0 for males and 36.4 for females. Five percent of the patients were children, among whom slight female predominance was noted. The mean time between the first clinical presentation and kidney biopsy in the cohort was 2.6 years, the mean BMI was 26.4 ± 5.2, and 29% of all patients were smokers, male predominance occurred (23%). Asymptomatic microhematuria and asymptomatic microhematuria with proteinuria were the main presenting clinical syndromes, comprising 48% and 39% of all cases, respectively. Nephrotic syndrome (NS) at presentation was rare (7%). MAP was 94.5 ± 16.7 mmHg and 7% of the patients were hypertensive and/or were having antihypertensive treatment. The mean proteinuria at the time of biopsy was similar in both male and female patients, 0.91 g/24 h and 0.95 g/24 h, respectively, whereas 81% of the patients had mild proteinuria <1 g/24 h. The mean eGFR for all cases was 94.9 ± 30.7 mL/min/1.73 m^2, which was 100.5 ± 32.7 and 85.8 ± 25.3 for male and female groups, respectively. The distribution of patients to CKD G1, G2 and G3 stages at presentation was 55%, 34% and 10%, respectively (men 66%, 23%, 10% and women 37%, 52%, 11%), while only 1% of the patients in the male group was within the G5 stage, and no cases within the G4 stage were registered. Previous immunosuppressive therapy was documented in 3% of the patients.

Nine patients were lost to follow-up. For the rest of the 64 patients (59% of males and 41% of females), the mean FU was 4.1 years. Initial and follow-up clinical data are presented in Table 1. The final comparison of initial and follow-up data was performed only in cases where both periods were available for analysis (64 patients in total).

The decline of eGFR in males was faster compared to females within a shorter follow-up time than in females (Fig. 1). The mean rate of renal function decline in the cohort was −2.6 ± 9.6 mL/min/1.73 m^2 per year (−3.4 ± 11.9 in males, P < 0.05, and −0.7 ± 5.3 in females, not significant). The endpoint was reached in 3% of the cases (CKD G4 in two males and in one female) and no ESKD cases were registered. Other clinical data, such as BMI, smoking and tonsillectomy, showed little differences in presentation between males and females: the mean BMI was higher than normal in both

Table 1 – Clinical features at the time of kidney biopsy of 73 patients with IgA nephropathy and during the follow-up.

Items	At the time of biopsy			During the follow-up		
	All cases	Male	Female	All cases	Male	Female
Gender, n (%)	73 (100)	45 (62)	28 (38)	64	38 (59)	26 (41)
Age, years, mean (range)	33.7 (16–76)	32.0 (17–61)	36.4 (16–76)			
Children (<18 years), %	5	1	4			
Time between onset and first clinical presentation, years, mean (range)	2.6 (0.1–21.2)	2.9 (0.1–14.3)	2.4 (0.1–21.2)			
Duration of follow-up, months, mean (range)				48.9 (12–144)	45.1 (12–135)	55 (12–144)
BMI, kg/m^2	26.4 ± 5.2	26.1 ± 4.8	27.1 ± 5.8	27.1 ± 4.8	26.5 ± 4.2	28.1 ± 5.5
Smokers, %	29	23	6	20	16	5
Presenting clinical syndrome						
Macroscopic hematuria, %	4	5	4			
Asymptomatic microhematuria, %	48	53	39			
Asymptomatic microhematuria and proteinuria, %	39	31	50			
NS, %	7	7	7			
Acute renal failure, %	1	2	–			
Chronic renal failure	1	2	–			
eGFR <60 mL/min/1.73 m^2, %						
SAP, mmHg	129.6 ± 16.7	127.7 ± 16.3	132.6 ± 17.2	127.8 ± 13.9	129.1 ± 15.1	126.6 ± 12.6
DAP, mmHg	79.6 ± 11.4	78.4 ± 10.7	81.6 ± 12.4	78.6 ± 7.7	79.2 ± 8.0	78.1 ± 7.4
MAP, mmHg	94.5 ± 16.7	94.6 ± 12.0	95.2 ± 22.5	95.4 ± 9.1	95.9 ± 9.6	94.6 ± 8.5
S-creatinine, μmol/L	93.4 ± 70.7	102.8 ± 87.5	78.2 ± 20.7	94.3 ± 38.9	102.3 ± 38.3	83.2 ± 37.7
eGFR, mL/min/1.73 m^2	94.9 ± 30.7	100.5 ± 32.7	85.8 ± 25.3	86.2 ± 27.1	88.0 ± 28.7	83.6 ± 25.2
S-albumin, mmol/L	42.0 ± 7.2	43.3 ± 8.2	39.7 ± 4.1	43.1 ± 6.9	45.2 ± 7.5	40.1 ± 5.0
S-cholesterol, mmol/L	5.3 ± 1.3	5.2 ± 1.3	5.5 ± 1.4	5.5 ± 1.2	5.5 ± 1.3	5.5 ± 0.9
S-triglycerides, mmol/L	1.9 ± 1.2	2.0 ± 1.2	1.2 ± 0.6	1.9 ± 1.0	1.8 ± 1.1	2.2 ± 0.9
Proteinuria, g/day, mean (range)	0.91 (0–10.2)	0.95 (0–10.2)	0.86 (0–4.06)	0.79 (0–8.5)	0.73 (0–8.5)	0.9 (0–5)
Proteinuria, %						
<1 g/day	81	84	75	79	84	72
1–3.49 g/day	11	7	18	15	8	24
>3.5 g/day	8	9	7	6	8	4
Microhematuria, %						
<75 erythrocytes/μL	20	11	36			
76–150 erythrocytes/μL	11	16	3			
>150 erythrocytes/μL	66	69	61			
No data	3	4	0			
Antihypertensive treatment, %	Previous, 7%	Previous, 9%	Previous, 4%	54	55	54
Treating with ACE inhibitors or ARBs				43	39	50
Treating with calcium channel blockers				11	16	4
Immunosuppression, %	Previous, 3%	Previous, 0%	Previous, 7%	10	9	11
Fish oil, %				11	7	18
Tonsillectomy, %	Previous, 13%	Previous, 9%	Previous, 18%	8	11	4
CKD G1, %	55	66	37	52	50	54
CKD G2, %	34	23	52	29	33	23
CKD G3A, %	6	5	7	10	8	11
CKD G3B, %	4	5	4	6	6	8
CKD G4, %	0	0	0	3	3	4
CKD G5, %	1	1	0	0	0	0
Lost to follow-up, n				9	7	2

BMI, body mass index; NS, nephrotic syndrome; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease.

Values are expressed as mean ± standard deviation unless otherwise stated. Values of creatinine and eGFR at the time of biopsy were missing in 2 cases.

genders and overweight/obese patients in the male and female groups composed 58% and 65%, respectively.

3.2. Correlations between renal pathology and clinical findings at the time of biopsy and at the end of the follow-up

Pathology findings of renal biopsies are presented in Fig. 2. The frequency of MEST findings was similar in males and females, except arteriosclerosis that was more frequent in male patients (P = 0.004). No correlation between the MEST score or arteriolosclerosis as well as the levels of MAP in the whole cohort and in both genders was found (Table 2). However, M1, E1, S1, T1 and A2 scores were correlated with the levels of eGFR and proteinuria. We found a positive correlation between the levels of proteinuria and M score (rs = 0.44, P < 0.001), E score (rs = 0.35, P < 0.01), S score (rs = 0.46,
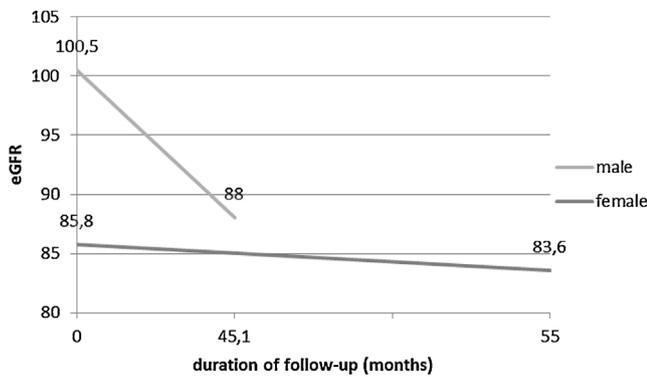
Fig. 1 – IgA nephropathy male and female patients' outcome showing eGFR decline during the follow-up. The mean rate of renal function decline was -3.4 ± 11.9 mL/min/1.73 m^2 per year in the male group (P < 0.05) and -0.7 ± 5.3 mL/min/1.73 m^2 per year in the female group (NS). y-axis, mean values of eGFR; x-axis, mean duration of follow-up (months).

P < 0.001), and arteriolosclerosis score ($rs = 0.28$, $P = 0.02$). Negative correlation with the levels of eGFR and M score ($rs = -0.26$, $P < 0.03$), S score ($rs = -0.28$, $P < 0.02$), arteriolosclerosis score ($rs = -0.29$, $P = 0.02$) and between T score and eGFR ($rs = -0.38$, $P = 0.001$) was found. Pathology scoring of the same categories revealed differences in males and females as follows: statistically significant correlation in males observed between the MEST score and the eGFR (M $rs = -0.46$, $P < 0.001$; E $rs = -0.33$, $P = 0.03$; S $rs = -0.36$, $P = 0.02$; T $rs = -0.45$, $P = 0.002$; arteriosclerosis $rs = -0.38$, $P = 0.02$), and proteinuria as well (M $rs = 0.62$, $P < 0.001$; S $rs = 0.51$, $P < 0.0001$; T $rs = 0.35$, $P = 0.002$; arteriosclerosis $rs = 0.44$, $P = 0.004$). E score did not reveal significant correlation with proteinuria. In females no significant statistical correlation between the MEST score and the eGFR was found, except correlation between proteinuria and E score ($rs = 0.56$, $P = 0.002$) and S score ($rs = 0.38$, $P < 0.05$). The mesangial score did not reveal correlation with eGFR, also arteriosclerosis score correlation with proteinuria in females was statistically insignificant.

3.3. Treatment effect for outcome in different patients' groups

IgAN patients' therapies correlations with MAP, eGFR and proteinuria after the biopsy and FU are presented in Tables 3 and 4. Less than half (43%) of all patients belonged to ACE or ARBs treatment-receiving patients' group. At the end of the follow-up, ACE and/or ARBs treatment was required in 50% of the patients. The rate of renal function decline in this group was -4.1 ± 9.6 mL/min/1.73 m^2 per year. One patient reached the end point; cases with ESKD were not registered.

One-tenth (11%) of all patients received antihypertensive treatment with CCBs. At the end of the FU, 13% of the patients had CCBs used as antihypertensive treatment. The rate of renal function decline in this group was -0.04 ± 12.2 mL/min/1.73 m^2 per year. One patient reached the end point; cases with ESKD were not registered.

More than one-tenth (13%) of the patients belonged to immunosuppression-receiving patients' group. The majority of patients received corticosteroids and only one patient received a combined therapy with cyclophosphamide and mycophenolate mofetil. At the end of the follow-up, 8% of the patients needed immunosuppression. The rate of renal function decline in this group was -1.5 ± 14.5 mL/min/1.73 m^2 per year. Cases with 50% of renal function decline and cases with ESRD were not registered.

More than half (51%) of the patients did not receive any antihypertensive and immunosuppressive treatment. The rate of renal function decline in this group was -2.7 ± 11.3 mL/min/1.73 m^2 per year. One patient reached the end point, and cases with ESKD were not registered. Statistically, insignificant renal function decline for the treated patients was found: -4.4 ± 12.7 mL/min/1.73 m^2 per year in males, and -2.3 ± 5.3 mL/min/1.73 m^2 per year in females. In patients without any hypertensive and/or immunosuppressive treatment also a statistically insignificant renal function decline was found: -3.2 ± 10.7 mL/min/1.73 m^2 per year in males, and -0.8 ± 3.9 mL/min/1.73 m^2 per year in females.
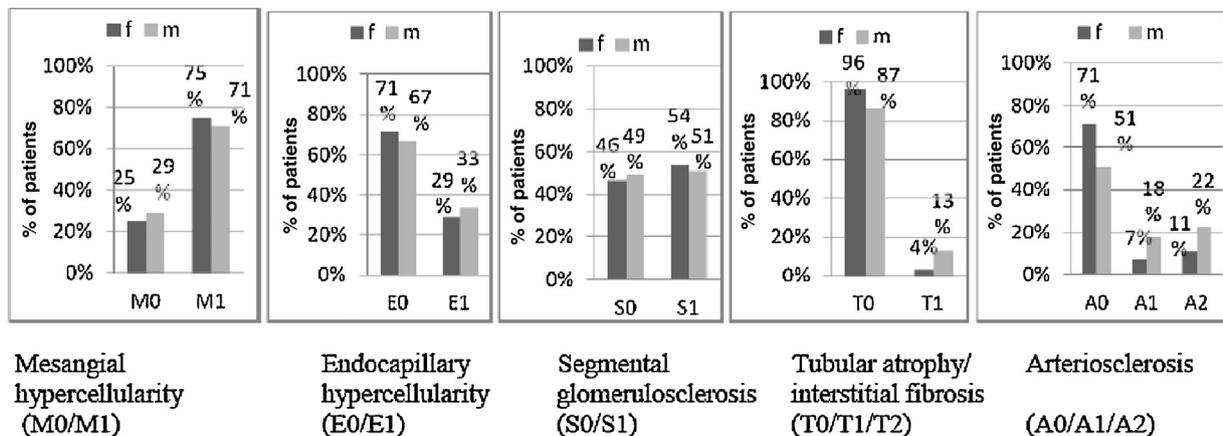

Fig. 2 – Frequency of pathological findings in 73 kidney biopsies.

Table 2 – Correlations between pathological and clinical features at the time of renal biopsy for the whole cohort and by gender.

Items	MAP, mmHg			eGFR, mL/min/1.73 m^2					Proteinuria, g/24 h					
	All[*]	Men[*]	Women[*]	All	P-value	Men	P-value	Women[*]	All	P-value	Men	P-value	Women	P-value
Mesangial hypercellularity					0.03		0.002			0.001		0.0001		
M0 ≤50%	92.8 ± 9.6	91.2 ± 10.2	95.8 ± 8.4	107.5 ± 23.5		120.4 ± 15.8		83.5 ± 15.0	0.3 (0–2.2)		0.1 (0–0.3)		0.5 (0–2.2)	
M1 >50%	97.5 ± 13.2	96.1 ± 12.6	99.8 ± 14.2	89.9 ± 31.9		92.1 ± 34.4		86.6 ± 28.1	1.2 (0–10.2)		1.2 (0.01–10.2)		1.0 (0–4)	
Endocapillary hypercellularity							0.03			0.003				0.002
E0 (absent)	94.7 ± 11.2	94.1 ± 10.8	95.8 ± 12.1	100.0 ± 29.8		108.5 ± 30.0		86.9 ± 24.8	0.5 (0–5)		0.6 (0–5)		0.5 (0–2.2)	
E1 (present)	99.2 ± 14.4	95.8 ± 14.4	105.6 ± 12.9	84.2 ± 30.4		84.8 ± 32.9		83.0 ± 27.2	1.8 (0–10.2)		1.7 (0–10.2)		1.8 (0.3–4.1)	
Segmental glom. sclerosis					0.02		0.02			0.001		0.0004		0.04
S0 (absent)	94.0 ± 12.7	92.4 ± 10.8	96.7 ± 15.4	103.8 ± 28.2		112.5 ± 27.1		89.1 ± 24.7	0.3 (0–2.2)		0.2 (0–0.9)		0.5 (0–2.2)	
S1 (present)	98.2 ± 12.0	96.8 ± 12.9	100.6 ± 10.3	86.2 ± 30.7		88.4 ± 33.8		82.7 ± 26.0	1.5 (0–10.2)		1.6 (0.1–10.2)		1.2 (0–4.1)	
Tubular atrophy and interstitial fibrosis					0.001		0.002					0.02		
T0 (0–25%)	95.3 ± 11.6	93.0 ± 10.0	98.7 ± 12.9	99.2 ± 27.8		107.1 ± 28.0		87.7 ± 23.4	0.8 (0–10.2)		0.7 (0–10.2)		0.9 (0–4)	
T1 (26–50%)	105.6 ± 18.4	105.6 ± 18.4	–	54.9 ± 28.5		58.3 ± 29.7		–	2.1 (0–6.7)		2.4 (0.1–6.7)		–	
T2 (>50%)	–	–	–	–		–		–	–		–		–	
Arteriosclerosis					0.02		0.02			0.02		0.004		
A0 (0–25%)	96.0 ± 13.9	94.0 ± 14.1	98.4 ± 13.8	99.7 ± 29.9		108.3 ± 29.7		89.2 ± 27.2	0.7 (0–4.3)		0.4 (0–4.3)		1.0 (0–4.1)	
A1 (26–50%)	91.7 ± 8.6	93.8 ± 7.6	83.3 ± 9.4	89.1 ± 31.4		90.2 ± 33.0		81.7 ± 33.5	1.4 (0.1–10.2)		1.7 (0.1–10.2)		0.2 (0.16–0.2)	
A2 (>50%)	100.8 ± 8.8	99.7 ± 9.6	104.4 ± 3.8	81.1 ± 35.6		84.3 ± 40.6		71.6 ± 14.4	1.6 (0.2–6.7)		1.8 (0.2–6.7)		1.0 (0.2–6.7)	

MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; segmental glom. sclerosis, segmental glomerular sclerosis/adhesion.
[*] P value, not significant.
Mesangial hypercellularity: M0 ≤50% of glomeruli; M1 >50% of glomeruli.

Table 3 – Correlations between prescribed therapy and clinical features at the time of biopsy.

Treatment	At the time of biopsy						
	%	MAP, mmHg	P value	eGFR, mL/min/1.73 m^2	P value	Proteinuria, g/24 h	P value
ACE inhibitors or ARBs	43	102.8 ± 14.2	0.0001	82.1 ± 32.2	0.008	1.2 (0–10.2)	0.005
M	39	100.5 ± 14.3	0.02	87.4 ± 38.8	0.02	1.4 (0–10.2)	0.02
F	50	110.5 ± 16.4	0.001	75.6 ± 21.5	0.03	1.0 (0–3.9)	NS
Calcium channel blockers	11	110.5 ± 16.4	0.007	49.5 ± 20.4	0.0001	3.4 (0.1–10.2)	0.002
M	16	108.6 ± 16.8	0.005	46.8 ± 20.5	0.0001	3.6 (0.1–10.2)	0.003
F	7	–	NS	–	NS	–	NS
Immunosuppression	13	109.8 ± 15.5	0.002	71.1 ± 43.5	<0.01	3.5 (0–10.2)	0.01
M	9	112.1 ± 19.3	0.03	48.8 ± 36.8	0.01	5.5 (0.9–10.2)	0.001
F	18	107.6 ± 13.2	NS	89.0 ± 43.3	NS	1.9 (0–4.1)	NS
Patients without any antihypertensive and immunosuppressive treatment	51	90.5 ± 7.9	0.0001	106.1 ± 22.9	0.0008	0.3 (0–2.2)	0.0005
M	57	90.1 ± 8.8	0.002	113.2 ± 20.6	0.002	0.2 (0–0.7)	0.001
F	43	91.3 ± 7.5	0.001	90.1 ± 20.3	NS	0.5 (0–2.2)	NS

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; M, male; F, female; NS, not significant.

Table 4 – Correlations between received therapy and outcome clinical data at the end of the follow-up.

Treatment	At the end of the follow-up						
	%	MAP, mmHg	P value	eGFR, mL/min/1.73 m^2	P value	Proteinuria, g/24 h	P value
ACE inhibitors or ARBs	50	98.2 ± 9.6	0.004	72.1 ± 26.1	0.0001	1.1 (0–8.5)	NS
M	45	99.1 ± 10.9	NS	73.1 ± 27.2	0.002	1.1 (0–8.5)	NS
F	58	97.2 ± 8.0	NS	71.0 ± 25.6	0.001	1.0 (0–5)	NS
Calcium channel blockers	13	104.6 ± 12.8	0.001	49.7 ± 27.8	0.0001	1.7 (0–8.5)	NS
M	16	105.6 ± 14.7	0.04	54.9 ± 29.6	0.005	2.2 (0–8.5)	NS
F	8	101.7 ± 7.1	NS	34.1 ± 20.0	0.03	0.1 (0–0.3)	NS
Immunosuppression	8	93.1 ± 13.4	NS	68.6 ± 27.9	NS	2.4 (0.2–3.7)	NS
M	8	96.3 ± 17.2	NS	76.4 ± 32.3	NS	1.5 (0.1–3.7)	NS
F	8	88.3 ± 7.1	NS	57.0 ± 24.0	NS	3.8 (2.5–5)	0.03
Patients without any antihypertensive and immunosuppressive treatment	50	92.6 ± 7.8	0.004	101.1 ± 19.3	0.0001	0.5 (0–4.1)	NS
M	55	93.3 ± 7.8	NS	101.4 ± 23.2	0.002	0.4 (0–4.1)	NS
F	42	91.1 ± 8.2	NS	100.7 ± 10.5	0.001	0.7 (0–3.5)	NS

ACE inhibitors, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; M, male; F, female; NS, not significant.

4. Discussion

We presented long-term follow-up data on IgAN patients with kidney biopsy diagnosis performed at the Tartu University Hospital. We applied the Oxford classification of IgAN to re-classify all cases. Main demographic, clinical and pathology data and treatment in 64 Estonian IgAN patients were evaluated. Patients were followed up for an average of 4.1 years similar to other IgAN studies [4,7,8,10], representing the whole spectrum of cases appearing in the local clinical practice. Probably, the most interesting characteristics of the cohort were that almost half of the patients had only microscopic hematuria presenting very early or mild disease. In some European centers including ours and also in Japan, patients with persistent microscopic hematuria are included in the kidney biopsy procedure which gives a diagnosis and a chronicity level as well to clinicians for further management of patients with early and mild disease. And, this is also a

meaning of the Oxford classification – to find out a MEST score which may help to manage patients better during a long-lasting disease course.

Our main findings were as follows: first, as in the Oxford classification study [3,4], the Estonian cohort's pattern of mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis/adhesion and tubular atrophy/interstitial fibrosis (MEST) confirmed having a correlation with clinical data as their higher score was linked to eGFR decline; second, we found a statistically significant correlation between the M score and the eGFR decline in males, but not in females. This finding shows gender-related differences having a prognostic value of M score in males. Although gender-related differences someway have been observed or even reported in other papers [4,7,8,10,17], this investigation, in our opinion, is the first direct looking at just for these differences and finding such a considerable result. According to our study, higher mesangial score (M1) did not correlate with eGFR decline in female patients, furthermore, it did not have an impact on an

unfavorable IgAN outcome, showing little eGFR changes during the follow-up and highlighting a difference of the disease progression in males and females.

In the pathology baseline data, we noticed a relatively better starting position in the male patients' group compared to females. According to the Oxford classification, M0E0S0T0 in male and female groups was 21% and 15%, respectively. However, among higher scores, female patients had more cases of higher mesangial scores (M1E0S0T0, 27% and 16% in female and male groups, respectively) and more cases of complex higher scores (M1E1S1T0 was 31% and 26%, respectively). Segmental sclerosis/adhesion cases in both groups were registered to a similar extent; however, the complex score M1S1 in males occurred more frequently (M1E0S1T0 score was observed in 37% males and 27% females) as well as cases with tubular atrophy/interstitial fibrosis (T1) (13% and 4% in males and females, respectively). On the other hand, baseline clinical data in males showed a correlation to the M1 score, whereas in females M1 score did not show any correlations with eGFR decline (eGFR at M0 was 83.5 ± 15.0 and at M1 was 86.6 ± 28.1 mL/min/1.73 m^2). On the contrary, M1 was correlated with eGFR decline in the whole cohort and in males. Other, E1, S1 and T1 lesions were correlated with proteinuria level and eGFR decline at the time of renal biopsy in both genders, complex M1S1T1 lesions in 2 male patients were correlated with 50% of renal function decline.

Some chronic glomerulonephritis studies have reported that females have a more favorable outcome in chronic glomerular disease, including IgAN, compared with males [18,19] but other investigators have found either no gender-related differences or have observed women to be at a greater risk of a progressive loss of renal function [20,21]. By Cattran et al., IgAN outcome for female patients was reported as contrary results pointing to worse disease outcome [22]. Cattran et al. in their chronic glomerulonephritis study found that a better outcome of IgAN disease was mostly mediated through both lower proteinuria and blood pressure at presentation and throughout the follow-up, although the study reported that females did have an independent advantage at higher levels of proteinuria [22]. Our study confirms that proteinuria above 1.0 g/24 h, which was correlated with E1 and S1 pathology scores, has a direct impact on disease progression and on an unfavorable disease outcome in females. However, for patients with proteinuria levels lower than 1.0 g/24 h, disease progression was faster in males. It is possible that the M1 score correlation with eGFR decline plays an important role here, greatly affecting the progression of the disease in males.

Similar to others [4,7,8,10], our results confirm the higher MEST score (in the whole cohort and in the male group) being correlated with disease progression. However, this was not a rule for female patients, where the M1 score did not show any correlations with eGFR decline. There is previously published evidence that the male gender is associated with a more rapid rate of progression of non-diabetic chronic kidney disease [18,19,23], either independently or through the modulation of other known risk factors. Our study confirms this in IgAN patients, where in males we found more rapid disease progression compared with females. However, proteinuria >1.0 g/24 h and S1 pathology score bring women to an equal level with men or even place them in a less favorable position.

Finally, we explored possible impact of the treatment modalities applied on the clinical course and outcome of the disease. All patients were divided into 4 subgroups: patients receiving ACE or ARBs, CCBs, having immunosuppression therapy, and patients without any antihypertensive or/and immunosuppressive treatment. In receiving any treatment, the male group (57% of all male patients) saw a statistically significant decline in all three clinical parameters (MAP, eGFR and proteinuria). However, in the female group (43% of all female patients), MAP and eGFR did not change, only proteinuria increased slightly. In both, different antihypertensive treatment receiving patient subgroups (ACE or/ARBs and CCBs), the treatment positively influenced clinical parameters. The impact of immunosuppression in male and female groups was different: in males, immunosuppressive treatment showed a clear positive effect as MAP, eGFR and proteinuria data improved, whereas in females, only MAP and eGFR improved, while proteinuria worsened. There is a lack of high-quality evidence that advocates the use of corticosteroids for IgAN with minimal lesions but, according to a recent study by Wang et al., corticosteroid therapy is likely to be effective and safe [24]. Others also confirm this approach and stress the potential long-lasting "legacy effects" of immunosuppressive treatments which are more likely to be achieved in the early stages of IgAN [25]. A tendency for a slower decline of renal function in patients without any hypertensive and/or immunosuppressive treatment group was found (-3.2 ± 10.7 mL/min/1.73 m^2 per year in males, and -0.8 ± 3.9 mL/min/1.73 m^2 per year in females). Among those patients, a third had MEST 0 score, two thirds had M1 or combined MEST scores.

The limitation of our study is related to a small patients' cohort and retrospective data collection on the follow-up and treatment modalities. Therefore, the findings remain to be verified by appropriate controlled studies.

5. Conclusions

According to the correlation analysis of main prognostic risk factors, morphological and clinical, affecting the progression of IgAN, we can conclude that more rapid IgAN progression occurs in males compared with females through faster eGFR decline that makes the prognosis worse. Our findings imply a necessity to pursue gender-specific approach to the management of IgAN patients, following the different male and female peculiarities of the progression of IgAN: screening, monitoring and optimal treatment.

Conflict of interest

The authors declare no conflict of interest.

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