as an excretory organ. Whether the nephrocytes can also secrete back into the hemolymph (for example, after metabolism) remains to be investigated. Other obvious differences to podocytes are that nephrocytes are unipolar single cells that form intracellular and not intercellular slit diaphragms. Moreover, filtration is most likely facilitated by oscillating fluctuations caused by the contracting heart (for pericardial nephrocytes) and the peristaltic proventriculus (for garland nephrocytes) and not facilitated by a high-BP system, like in the glomerulus.

The demand is increasing for rapid functional validation of genes variants derived from the sequencing outputs for renal genetic diseases. Drosophila nephrocytes have proven to be an easy to use alternative for such efforts. As with any other existing model system, nephrocytes do not provide a complete solution. Yet, the effortless ex vivo analysis of nephrocytes and the structural and functional similarity to podocytes and proximal tubular cells as well as the plethora of powerful genetic tools from the Drosophila community can offer an intermediate platform that bridges the experimental gaps to other experimental models.

ACKNOWLEDGMENTS

Work in the Simons lab is supported by the ATIP-Avenir program as well as funding by the Agence Nationale de la Recherche (ANR) under the “Investissements d’avenir” program (ANR-10-IAHU-01) and the NEPHROFLY (ANR-14-ACHN-0013) grant.

DISCLOSURES

None.

REFERENCES


Mortality Risk in IgA Nephropathy

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doi: https://doi.org/10.1681/ASN.2018121255

IgA nephropathy (IgAN) is a common form of primary GN known to affect about 200,000–350,000 persons per year globally,1 most frequently in Asia and least frequently in Africa.2 Presently, the diagnosis of IgAN is established only by kidney biopsy and immunofluorescence microscopy; therefore, many individuals with this condition may go unrecognized for prolonged periods, and incidence estimates may underestimate the global burden of this disease. Like many forms of CKD, IgAN
is associated with an increased risk of ESRD and mortality. The rate of disease progression in IgAN tends to be slow, evolving over decades, with some exceptions. Spontaneous remissions are not common, at least in adults. Extrarenal involvement is very uncommon, except in the related disorder of IgA vasculitis. Factors that enhance the likelihood of progression and the risks of ESRD have been well studied, but the risks of mortality after long periods of follow-up are less well understood.2

The gaps in our understanding of the pattern of mortality associated with a diagnosis of IgAN have been lessened by several large observational cohort studies (single center or registry based) with long-term follow-up,3,4 including one published in this issue of the Journal of the American Society of Nephrology by Jarrick et al.5 Although each of these studies has varied somewhat in the design, they provide substantial support for the conclusion that a diagnosis of IgAN is associated with shortened life expectancy. Although in and of itself, this is not surprising, the details of these studies provide some interesting insights into the nature of this enhanced mortality risk in IgAN and raise several new questions—all hallmarks of excellent clinical research.

Jarrick et al.5 studied 3622 patients in Sweden with biopsy-proven IgAN (including 227 with IgA vasculitis) with a median follow-up of 13.6 years. The average age at diagnosis was 34.9 years old, and 70% were men. The data were secured from national registries. Comparisons were made with a matched age/sex cohort from the general population as well as with family members (spouses and siblings). The overall hazard ratio (HR) for mortality compared with controls was 1.53 (95% confidence interval [95% CI], 1.37 to 1.72), with no difference between men and women. The highest risk for mortality (and ESRD) was seen in the first year after diagnosis. These findings translated into a reduction of life expectancy of 6 years. The absolute death rate in patients with IgAN was 10.7/1000 person-years, with cardiovascular causes accounting for most of the deaths. Very interestingly, the mortality risk was not increased for the periods preceding the development of ESRD compared with population controls, spouses, or siblings, but it was increased in patients treated with steroids or immunosuppressive agents (higher for steroid treatment) and was not increased in renin-angiotensin inhibition or statin users. As expected, the HR for ESRD was greatly increased in patients with IgAN compared with controls (HR for ESRD, 100 [95% CI, 67.7 to 148]), with an absolute excess risk of ESRD of 18.6/1000 person-years. Very importantly, the risk of ESRD in a first-degree relative of a patient with IgAN was increased threefold in comparison with controls.

The strengths of this study are its size and nationwide scope, the duration of follow-up, and the comparison with population and intrafamilial cohorts. Unfortunately, no data were available on clinical features at diagnosis or follow-up or histologic scoring of biopsy findings (e.g., OXFORD-MEST-C). Smoking histories were also not obtained. These deficiencies may have a bearing on the observation that excess mortality was limited to individuals with IgAN and ESRD, a somewhat paradoxical finding considering that large epidemiologic studies have shown that mortality risk increases as stage of “generic” CKD (as defined by Kidney Disease Improving Global Outcomes [KDIGO] criteria) increases, well before ESRD has developed.6

A comparison with prior reports may provide some insight into some of the perplexing findings of the study by Jarrick et al.5 Knoop et al.4 conducted a nationwide, registry-based cohort study in Norway involving 663 subjects with biopsy-proven IgAN followed for a median of 11.3 years. The subjects were an average age 39 years old, and 74% were men. The comparisons were with the general population adjusted for age and sex, and therefore, a standardized mortality ratio (SMR) could be calculated. Unlike the study by Jarrick et al.,5 both clinical and histologic data were available to “risk stratify” patients at diagnosis. The overall SMR for patients with IgAN was 1.9, but the risk of mortality was strongly inversely related to eGFR at diagnosis. A composite risk score on the basis of a validated Japanese model7 also showed a significant mortality risk only in a high-risk group (21% of the entire cohort) with an eGFR at diagnosis of <60 ml/min per 1.73 m². Notably, the SMR was 4.9 (95% CI, 3.5 to 7.0) after development of ESRD but only 1.3 (95% CI, 1.0 to 1.7) in those patients with IgAN pre-ESRD, paralleling the findings of Jarrick et al.5 mentioned above. Treatment and follow-up clinical findings are not available in the study by Knoop et al.4 Patients with IgA vasculitis were also apparently not included in the cohort in the work of Knoop et al.4

Lee et al.3 conducted a single-center observational cohort study of mortality in 1364 Korean patients with biopsy-proven IgAN. The median follow-up was about 10.5 years. The average age at diagnosis was 33 years old, and 50% were men. Patients with IgA vasculitis were excluded. The comparisons were with the general population, and a calculated age and sex–adjusted SMR was used as done by Knoop et al.4 Treatment of IgAN consisted mainly of antiplatelet agents. Renin-angiotensin agents or immunosuppressive agents were used in only 31% and 13% of patients, respectively. The overall SMR was 1.43 (95% CI, 1.04 to 1.92), and it was not increased in men (1.22; 95% CI, 0.82 to 1.75) but was increased in women (2.17; 95% CI, 1.21 to 3.57). About 56% of the deaths occurred in the pre-ESRD period, and these patients were older (average age of 49 years old), had better preserved renal function, and had a higher frequency of cancer-related death (30%). On the basis of clinical and histologic factors, only high-risk subjects had an increased SMR, exclusively among women.

Collectively, the study of Jarrick et al.5 and the studies of Knoop et al.4 and Lee et al.3 weave a common theme: namely, that IgAN is accompanied by excess mortality and shortened life expectancy. The influence of treatment on these outcomes still remains uncertain, and bias by indication must be considered. Yet, the results from the prematurely terminated Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING) study should give pause for concern about the
adverse effect of treatment with high doses of steroids or immunosuppressive agents. Sex-related disparities in mortality risk in IgAN are inconsistent in these studies of IgAN. Studies of “generic” CKD seem to indicate a lower risk of CKD progression to ESRD and its attendant mortality risk in women compared with men. This is an area ripe for further investigation. The possibility that first-degree relatives of patients with IgAN face an enhanced risk of ESRD should raise a yellow flag of caution for using such subjects as live donors for kidney transplantation. What is most curious (at least to me) is the finding by Jarrick et al. confirming the findings of Knoop et al. that the great majority of the excess mortality risk in IgAN is experienced after ESRD has developed, not before. These findings in a single disease entity contradict the findings of large epidemiologic studies encompassing the broad category of “generic” CKD (defined by KDIGO criteria). These latter studies clearly show a graded enhanced mortality risk according to CKD “stages” even before ESRD is reached. This mortality risk-enhancing effect of CKD is greater in young persons than in the elderly. A precise explanation for this discrepancy between IgAN and “generic” CKD is lacking. Although all patients in the study by Jarrick et al. needed to survive to the time of renal biopsy diagnosis, I doubt that immortal time bias is a valid explanation for the findings. It does seem clear that patients with primary IgAN—patients who are generally young, lack involvement of extrarenal organ systems, and are relatively free from serious comorbidity at the time of diagnosis—are able to survive the burden of progressive CKD only to succumb during ESRD. These findings raise questions about generalization of mortality risk in progressive CKD from epidemiologic studies that conglomerate many specific kidney diseases under the heading of “generic” CKD. As has been pointed out before, in an era of “precision medicine,” the application of prognostic classification of “generic” CKD to specific diseases may not always be helpful. An important lesson from these studies is that they appropriately focus the interest on development (through multicenter randomized trials) of the means to safely and effectively prevent progression of IgAN to ESRD.

DISCLOSURES

Dr. Glassock is a consultant to Omeros (Chair of the Data Monitoring Committee), which has a trial of a new drug for treatment of IgA nephropathy. Dr. Glassock has also periodically consulted with other companies considering development of new agents for treatment of IgA nephropathy (Retrophin, Apellis, Ionis, and Chemocentryx) and received a stipend from Wolters-Kluwer for editorial services concerning UpToDate.

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See related article, “Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study,” on pages 866–876.

GNAS: A New Nephrogenic Cause of Inappropriate Antidiuresis

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doi: https://doi.org/10.1681/ASN.2019020143

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is the mirror image of nephrogenic diabetes insipidus (NDI): in NDI, the kidneys cannot concentrate the urine, whereas in

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Published online ahead of print. Publication date available at www.jasn.org.

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