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See related article, "Measurable Urinary Albumin Predicts Cardiovascular Risk among Normoalbuminuric Patients with Type 2 Diabetes," on pages 1717–1724.

# How Benign Is IgA Nephropathy with Minimal Proteinuria?

Benjamin J. Freda and Gregory L. Braden
Division of Nephrology, Baystate Medical Center, Springfield, Massachusetts; and Tufts University School of Medicine, Boston, Massachusetts

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IgA nephropathy (IgAN) is the most common primary GN in the world.[1] Although IgAN is characterized by dominant mesangial IgA deposits, the overall histologic features and clinical course are highly variable, resulting in controversy regarding optimal approaches to guide assessment of prognosis and treatment.[2,3] The natural history of IgAN can range from clinically silent urinary abnormalities and preserved renal function over many decades to ESRD. Progression to ESRD occurs in 10%–50% of patients, usually developing slowly over 20 years.[4,5] Ten-year renal survival rates (62%–98%) are also highly variable.[6,7]

In regions where renal biopsies are routinely performed for isolated urinary abnormalities (microscopic hematuria, minimal proteinuria $<0.5$ g/d), the incidence of IgAN is higher, and the estimates of renal survival are affected by lead-time bias. A more fully informed understanding of the natural history of IgAN across its entire clinical and histologic spectrum could assist clinicians in assessing prognosis and implementing treatment.

Much has been learned over the last 20–30 years regarding risk stratification of IgAN.[3] Clinical parameters that correlate with increased risk of progression of disease include proteinuria $>1$ g/d, hypertension, and reduced GFR. The impact of these variables on prognosis is strengthened when they are followed over time. In contrast to other glomerular diseases, proteinuria in IgAN at an excretion rate of even 0.5–1.0 g/d is associated with risk of ESRD.[3]

Histologically, two of the strongest pathologic predictors of progression of IgAN have been the degree of tubulointerstitial fibrosis/tubular atrophy and glomerulosclerosis.[3] Previous histologic scoring systems focused on glomerular lesions and have not been conclusively shown to offer prognostic information independent of clinical factors.[8] Recently, the Oxford Classification of IgAN was published describing reproducible histologic parameters in 265 patients from 17 centers in Asia, Europe, North America, and South America with IgAN and proteinuria $>0.5$ g/d.[9] Mesangial hypercellularity, endocapillary

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**Correspondence:** Dr. Gregory Braden, Baystate Medical Center/Tufts University School of Medicine, 100 Wason Avenue, Suite 200, Springfield, MA 01108. Email: Benjamin.freda@bhs.org

hypercellularity, segmental glomerulosclerosis, and the percentage of cortical area with either tubular atrophy or interstitial fibrosis were each shown to independently predict outcomes beyond clinical parameters, including GFR and proteinuria. The Oxford classification has been validated in both North American and Asian populations.[10,11]

Many of the studies reviewing long-term prognosis of IgAN have not included patients with microscopic hematuria and minimal proteinuria (0.5–1.0 g/d) at time of diagnosis. This represents a significant percentage of patients with IgAN, especially in countries with aggressive biopsy practices. Highlighting the importance of studying these patients is the recent finding of an independent association between isolated microscopic hematuria and risk of ESRD in a cohort of >1,000,000 young persons being screened for military service.[12]

In this issue of *JASN*, Gutiérrez *et al.*[13] report their study of 141 Caucasian patients with IgAN who had a renal biopsy performed for microscopic hematuria, normal renal function, and proteinuria <0.5 g/d. Patients were recruited from eight Spanish hospitals between 1975 and 2008, when an active policy of renal biopsy was in place for patients with minimal urinary abnormalities. Patients with liver or systemic disease, diabetes, Henoch-Schönlein purpura, or secondary IgAN were excluded. Data were retrieved over a median follow-up of 9 years. Additionally, a blinded nephropathologist at each center reviewed the renal biopsy according to the Oxford Classification of IgAN.[9]

All patients were Caucasian, and ~64% were male, with a mean age of 23.7 years. At baseline, none of the patients had renal insufficiency. All patients had microhematuria, ~18% did not have detectable proteinuria, and only 16% were hypertensive. None of the patients were treated with immunosuppressive therapy, and ~42% received either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) during follow-up. The primary outcome of >50% increase in serum creatinine (SCr) occurred in only 3.5%, and only one patient had a doubling in SCr and none developed ESRD. Interestingly, almost 38% of patients developed clinical remission despite only 23% receiving an ACEI or ARB. About 15% of patients developed worsening proteinuria (>0.5 g/d) over time. Almost all were then treated with an ACEI or ARB, with a total of ~4% of the entire cohort developing further worsening of proteinuria to >1g/d. There was a slight increase in the percentage of patients with hypertension from 16.3% at baseline to 21.3% at end of follow-up. Using the Oxford classification, 95% of patients had no significant tubulointerstitial abnormalities, and only 8.5% and 15.6% had endocapillary proliferation and focal segmental glomerulosclerosis, respectively. The latter was the only variable independently associated with an increasing SCr in multivariate analysis. This is the first study published to apply the Oxford classification system to patients with IgAN and minimal proteinuria. The authors conclude that the long-term prognosis of IgAN in patients with microhematuria, minimal proteinuria, and normal BP and normal renal function was excellent.

Prior to the study of Gutiérrez *et al.*, there was only a handful of studies describing the prognosis of IgAN with minimal proteinuria. These studies have not shared the same favorable outcome. Lai *et al.*[14] studied 45 Chinese patients from Hong Kong with IgAN with a SCr <1.3 mg/dl, proteinuria <0.4 g/d, and no hypertension. In patients with a mean sclerosis per glomerulus of 10%–15%, 25% developed a decreased GFR of <60 ml/min per 1.73 $m^2$, and 44% developed proteinuria >1 g/d over a median follow-up of 10 years. The subgroup with 25%–50% mean sclerosis per glomerulus developed a decreased GFR in 40% and increased proteinuria in 60%.[14] Even in the group with no glomerulosclerosis or <10% mean sclerosis per glomerulus, 21% of patients developed proteinuria >1 g/d. These investigators extended their observations in a larger study of 72 normotensive Chinese patients with IgAN, normal renal function, and proteinuria <0.4 g/d.[15] Over a median follow-up of 7 years, 33% developed proteinuria >1 g/d, 26% developed hypertension, and 7% developed impaired renal function (creatinine clearance <70 ml/min per 1.73 $m^2$).

These observations are supported by an additional study of 177 normotensive Chinese patients with proteinuria <0.4 g/d and normal renal function. Shen and Huang[16] showed that after a median of 9 years of follow-up, 46% of patients developed increased proteinuria >1 g/d, 38% developed hypertension, and 24% developed a GFR <60 ml/min per 1.73 $m^2$. Clinical remission occurred in 9% of patients, but their clinical characteristics and treatment were not specified. Pathologic correlates that predicted disease progression included the degree of interstitial cell infiltrate and fibrosis and tubular atrophy, but not the degree of glomerulosclerosis. Taken together, these studies suggest that the outcome of IgAN presenting with minimal proteinuria, at least in Asian patients, is often associated with some degree of progressive renal disease during long-term follow-up. However, some patients with IgAN and minimal proteinuria may undergo remission, usually occurring in patients with minimal interstitial or glomerular histologic changes.

The prevalence of IgAN is highest in Asian countries compared with European countries and the United States and is rare in African countries. It is possible that variances in genetic susceptibility to IgAN may explain differences in prognosis among different races or populations. Most studies evaluating the relationship of genetic polymorphisms to IgAN have occurred in patients of Asian ancestry. Only in Asian patients have polymorphisms in the 3′ untranslated region of the *megsin* gene, particularly 2093C and 2180T, been associated with both susceptibility to and prognosis of IgAN.[17,18] Megsin is a serine protease inhibitor that is upregulated in mesangial cells in IgAN. In Asian patients, the 2093-2180T haplotype was more often present in patients whose disease progressed and correlated with hypertension, proteinuria, worsened histologic changes, and more rapid loss of renal function.[17,18] A third polymorphism of megsin, A23167G, has also been associated with susceptibility to and prognosis of IgAN in Asian patients.[19]

Several genomewide association studies have identified loci within the MHC that are associated with susceptibility to IgAN in patients of either Asian or European ancestry.[20–22] However, Gharavi *et al.*,[20] studying both European and Chinese populations, identified a common deletion of *CFHR1* and *CFHR3* at chromosome 1q32 that was associated with IgAN in only Chinese patients. How these complement regulatory genes, which regulate the alternate complement cascade, are involved in the pathogenesis of IgAN awaits further study. Finally, Yu *et al.*[22] performed a genomewide association study in Han Chinese patients with IgAN using two methods to minimize the effects of population stratification on their analyses. The authors confirmed the previous association of HLA and MHC loci and now correlated the MHC region, rs 660895, to clinical subtypes of IgAN, IgA levels, and the severity of proteinuria. Two new loci associated with IgAN were identified at chromosome 17p13 rs3803800, implicating genes that code for TNF and chromosome 8p23 versus 2738048 implicating genes for $\alpha$-defensin. These genes are involved in innate immunity and inflammation. Although further study is needed, these studies suggest that genetic differences in European and Chinese populations may be associated with variation in susceptibility and prognosis of IgAN.

The important study by Gutiérrez *et al.* is unlikely to be repeated in the United States or in European countries, because the practice of liberal renal biopsy for isolated microhematuria has been abandoned, including at the authors' hospitals. This study makes it difficult to decide how to evaluate and follow patients with microhematuria. Persistent microhematuria is common in medical practice, and in most centers, a urological evaluation is first performed to rule out infection, renal cystic disease, nephrolithiasis, and genitourinary malignancy. Without proteinuria, the majority of the patients have early IgAN, with the remainder having thin basement membrane disease, Alport's syndrome, interstitial diseases, papillary necrosis, hypercalciuria, hyperuricosuria, or sickle cell trait/disease.[23–25] However, in most centers, a renal biopsy is not warranted unless the result would be useful for screening potential living related kidney donors for genetically determined diseases such as Alport's syndrome, for life insurance and employment purposes, or for providing reassurance to the patient. Although the study by Gutiérrez *et al.* gives clinical reassurance that the long-term prognosis of IgAN with minimal proteinuria is favorable, the true prognosis of patients with isolated microhematuria is not completely elucidated, and the findings that isolated microhematuria is an independent risk factor for ESRD is concerning.[12,26]

Although some studies have found a high frequency of glomerular disease in patients with isolated microhematuria, the renal biopsy added little to the therapy and clinical management of these patients.[23–25] Because some of these patients may later develop hypertension, proteinuria, and/or renal insufficiency, especially those with Asian ancestry, we recommend at least yearly follow-up in any patient with isolated microhematuria to monitor BP, renal function, and the level of proteinuria. We do not recommend a renal biopsy at the time of diagnosis of isolated microhematuria because the studies to date do not show that identifying glomerular disease affects clinical management or therapy. We look forward to the possibility that the prediction of disease progression and response to therapy in glomerular disease will be further clarified by the development of urinary biomarkers, but further studies are needed.[27] Until then, the results of the study by Gutiérrez *et al.* add important information that further characterize the natural history and prognosis of IgAN.

## DISCLOSURES

None.

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