Is Long-Term Prediction in Membranous Nephropathy (MGN) Better Than the Weatherman's Forecast Capacity?

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The natural history of membranous nephropathy (MGN) was first described in the late 1960s by Pollock *et al.* (1). This paper clearly identified that only 40%–50% of patients will progress over time and up to 30% will have a spontaneous remission. This natural history has both vexed and fascinated clinical nephrologists since that time.

All nephrologists can appreciate the value of early separation of progressors from nonprogressors given our current potent immunosuppressive drugs with their significant adverse effects. Conservative therapy alone has its own downsides, including an increased thromboembolic risk, premature atherosclerosis, and the potential for irreversible kidney injury (2,3). Recent data confirmed the significant spontaneous remission rate, regardless of initial proteinuria and, in some cases, regardless of the initial renal function (4,5).

Almost two decades ago, the Toronto group looked at whether the persistence of proteinuria above certain cutoff values would improve the overall accuracy of predicting chronic renal insufficiency. When we added initial renal function and rate of renal function decline over a time frame of observation to these proteinuria cutoffs, we improved baseline prediction from 25% to an accuracy of 80% (6). However, there are challenges with this prediction tool, including an observation period of up to 18 months and a somewhat complex calculation to determine the risk score.

Many advances in nephrology practice have been made since that time. Significant improvements in conservative management of the proteinuric patient include widespread use of renin-angiotensin system–blocking agents and lower target BP. In addition, there are now new options in immunosuppressive drugs. This is on a background of changing demographics with the average presenting MGN patient now older by two decades and many with additional comorbidities such as hypertension and obesity compared with the original cohort (7). All these changes bring into sharp focus the question of whether the old methods of prediction still apply.

This is a question addressed in an article by van den Brand *et al.* (8) on other urinary markers in this issue of *CJASN*. This different approach to prediction has been championed for over a decade by this group examining MGN outcome relative to the initial levels of low and high molecular urine protein biomarkers (9–12). The current article is the first to compare predictive accuracy of these two approaches in MGN.

The authors conclude that the area under the receiver operating characteristic curves (ROC-AUC) between the Toronto risk score and either of their urinary protein biomarkers, $\beta 2$ microglobulin or urinary $\alpha 1$ microglobulin are very similar despite exposure to the newer conservative treatment agents including angiotensin-converting enzyme and/or angiotensin II receptor blocker therapies (ROC-AUC 0.78 versus 0.795; 95% CI, 0.69–0.88). This conclusion must be tempered in light of the limited details about renin angiotensin system blockade exposure because neither dose nor duration of treatment is known, and the relationship between treatment and BP was not discussed. Additional informative data from the paper suggest that the use of the Modification of Diet in Renal Disease 6 (MDRD6) formula to estimate renal function had a similar utility in prediction as the more complex and cumbersome 24-hour creatinine clearance estimate used in the Toronto formula. They take this analysis one step further and suggest that, based on the logistic regression coefficients integrative discrimination index (IDI) and relative IDI (rIDI) from the original model and estimated GFR, MDRD6-based risk scores calculated at the start of follow-up remain as strong a predictor of progression as the original Toronto risk score and do not require including any measures of persistent proteinuria. They do not compare this method of prediction to their urinary biomarkers, although presumably they also would not be required using this method. This is in direct contrast to a considerable body of work relating proteinuria reduction to slowing progression in many types of kidney disease including MGN (13), and therefore the statistical methodology underpinning their conclusions warrants a closer look.

The IDI is a difference in means of predicted probabilities for events and nonevents (13). However, it cannot be specified what the magnitude of the difference implies nor does it calculate the predicted probabilities of progression. The authors therefore introduced the rIDI, which is the ratio in discriminating slopes for a model with and without a specific marker of interest.

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Application of this technique suggested that persistent proteinuria did not substantially contribute to the prediction of progression and that the change in creatinine clearance was more important than the baseline creatinine clearance (although in the estimated GFR-MDRD6–based models, the opposite effect was observed; *i.e.*, baseline GFR contributed the most to the prediction). Although impressive, one needs to look at the GFR-MDRD6–based risk score calculated using the first 6 months of follow-up related to their Kaplan-Meier survival curve. It shows a significant difference between the lowest tertile of risk and the highest (although the differences between the other curves were not significant).The common starting point on this curve is generated by looking at change in renal function over the first 6 months of observation. If patients are ranked from 1 to 100 in terms of rate of decline in renal function over the first 6 months, those with the most rapid deterioration would very likely turn out to be the ones in the highest tertile of risk (the worst outcome). However, without the context of what this means from a clinical perspective such as what is the average rate of decline in the whole cohort, what is the range, and how many of these patients actually would have significant progression, this approach is speculative and much larger cohorts need to be examined before implementation. Most studies find very little changes in GFR in the first 6 months of observation in patients with MGN. Certainly, there have been additional advances in the way prediction models are evaluated, as well as how survival end points with competing events are handled, and these need to be assessed in this type of modeling (14).

The other feature that seems dramatically different from earlier risk scores (although the authors suggest changing end points do not affect the comparison, these data are not presented) is the frequency of their end point. Overall, 47% of their cohort, followed on average for only 4 years, had progression versus only 26% of the original Toronto cohort, only 13% in the Finish group, and only 25% in the Italian group in the Toronto validation paper (15). This is likely related to the different definitions of their end points of progression. One is clear: a 50% increase in baseline serum creatinine, which is an end point acceptable to all clinical nephrologists. If patients with this outcome could be identified early in their disease with a high degree of accuracy, this would be a major advance. The other major end point definition was less definitive and may represent a different cohort, *i.e.*, a rise in serum creatinine of only 25% and to >135 μmol/L. Although the breakdown by definition of the end points was not identified within this paper, in the same population studied in their earlier paper (12), only 50% of the progressive cohort belongs in the first category. The possibility of a false-positive end point seem substantially higher in the second category (25% increase in creatinine) and, given the concerns about overtreatment and its prevention by using these urinary biomarkers, this seems an important area for further examination and assessment before its adoption.

The authors suggest that there is little evidence that underlying pathology will help to discriminate progressors from nonprogressors. We agree, and previous studies have indicated that the majority of the chronic damage at presentation can be attributed to preexisting disease (16). However, this does bring into focus why they found that the initial GFR could or should explain those most likely to progress. Certainly, rate of decline following presentation has not been associated with initial pathology nor with initial GFR in the past, regardless of how it was measured (17,18).

Regardless of these variations in comparison to the literature, the utilization of these urinary biomarkers, if validated, would be an important additional parameter that clinicians should consider to help define those MGN patients at high risk of progression. In an earlier paper using a similar patient cohort, the authors were able to demonstrate using repeated measures of these biomarkers over time further increased the prognostic accuracy, although they warned that something as simple as lowering BP can affect their excretion rate, and in addition, these authors have previously published that significant treatment improvements in proteinuria and kidney function are not associated with the absolute or percentage reduction in these biomarkers measurements at baseline or between baseline and 12 months (10,11,19).

It must be emphasized that our capacity to predict outcome in MGN should not be considered a competition. One wonders whether the combination of these approaches, *i.e.*, changes in proteinuria over a shorter time frame plus estimates of these urinary biomarkers, might allow even better discrimination between those likely to truly progress and those that will not. This remains an important question because it is this group (between 4 and 8 g/d of proteinuria) that represents the largest population of MGN patients at risk and those we are still concerned about introducing immunosuppressive treatment too early. The bottom line of all of these urinary protein biomarkers is that they represent phenotypes that result from immune complex deposition and subsequent injury rather than reflecting immunologic disease activity. This is the promise of the recently discovered autoantibody to the phospholipase A2 receptor antigen present in idiopathic MGN (20). This exciting discovery and the finding that certain mutations in the phospholipase A receptor are associated with a susceptibility to develop MGN underlines this antibody's relevance as a marker of disease activity (21). Clinical studies now available support this hypothesis (22,23). If confirmed, substantial clarity would be brought not only to the the field of prediction but to therapy. Specifically the knowledge of who to treat, what drugs to use, when to use them, and for how long would be dramatically improved. Progress is being made in predicting progression in MGN. The utilization of these multiple biomarkers including measures of immunologic activity and the application of state-of-the-art class statistical methodology to measure outcome in MGN will continue to keep us ahead of the nightly weatherman capacity to do long-term forecasts.

Disclosures

None.

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