EDITORIAL

How to diagnose and follow patients with glomerulonephritis without kidney biopsy?

Krzysztof Mucha[1,2], Bartosz Foroncewicz[1], Leszek Pączek[1,2]

1 Department of Immunology, Transplantology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland
2 Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland

The first kidney biopsy was performed by Alwall in 1944.[1] Although it is an imperfect and, to be honest, also unwanted diagnostic method, it still remains a gold standard in nephrology. However, the rapid progress in today's nephrology was possible mainly due to basic science research, especially "-omics" (FIGURE 1), which creates an opportunity to diagnose, follow up, and treat glomerulonephritis in the future, without the obligatory use of kidney biopsy.[2]

Firstly, since the last decade, we have observed a striking development regarding the search of the genetic background of most glomerulonephritides, as well as kidney disease in general.[3] It was possible thanks to the wide implementation of genomics into the nephrology world. The Genome Wide Association Studies (GWAS) facilitate to precisely identify genes, or their polymorphisms, that predispose to the development of the specific glomerulonephritis at certain point and, most importantly, in the particular individual. The good example are studies that have been led by Ali Gharavi and Krzysztof Kiryluk since the early 2000s in IgA nephropathy (IgAN), the most frequent primary glomerulopnephritis worldwide.[4,5] Actually, since 1968 when Berger and Hinglais[6] described IgAN, owing to above-mentioned genomic studies, the genetic background of this disease has been close to be defined. Consequently, we know much more about the etiopathogenesis, which results in our better understanding of IgAN and, finally, in a more individualized and effective treatment. Other genomic studies reveal multiple risk loci involved in, for example, renal function decline in individuals of European descent, the development of chronic kidney disease (CKD), congenital anomalies of the kidney and urinary tract, focal segmental glomerulonephritis, and others.[3,7]

Clearly, one of the main obstacles of GWAS is the number of the diseased patients and properly matched healthy control individuals that should be recruited. This in fact means a sufficient amount of money that is needed to organize such a study. On the one hand, this effectively limits the numbers of single nephrology centers to think about, but on the other hand, it promotes an international cooperation, which in the last years have yielded numerous breakthrough results.[3-5,7]

The next group consists of the transcriptomic-based studies that concentrate on the gene or genes either defined earlier by GWAS or simply proposed by authors as potential biomarkers that are believed to be involved in the disease. There are also many research projects focused on the role of microRNAs (miRNAs), a small noncoding RNA molecules that regulate gene expression. As we know, they play an important role during kidney development, homeostasis, and disease, especially during the progression of tubulointerstitial sclerosis and end-stage glomerular lesions that occur in different forms of CKD. Almost certainly they are involved in IgAN, diabetic nephropathy, lupus nephritis, polycystic kidney disease, as well as graft rejection. At the same time, there are diverse results and an expanding list of miRNAs indicated by various authors as unquestionable markers in the studied diseases, which dampens our enthusiasm. We have to bear in mind that the physiological role of each particular miRNA, as well as its variance and dependence on many factors, should influence the results and thereby bias our final conclusions.[8]

The expression of genes results in protein and cytokine production, which for the last 2 decades has been the main field of interest in nephrology research. There are numerous proposed biomarkers, discovered both in serum and urine, that are presumed to be responsible or directly held responsible for the pathogenesis of kidney diseases.[9,10] Some of them have been also correlated with biopsy findings in several studies.

Correspondence to:
Krzysztof Mucha, MD, PhD, Klinika Immunologii, Transplantologii i Chorób Wewnętrznych, Instytut Transplantologii, Warszawski Uniwersytet Medyczny, ul. Nowogrodzka 59, 02-006 Warszawa, Poland, phone: +48 22 502 16 41, e-mail: kjmucha@gmail.com
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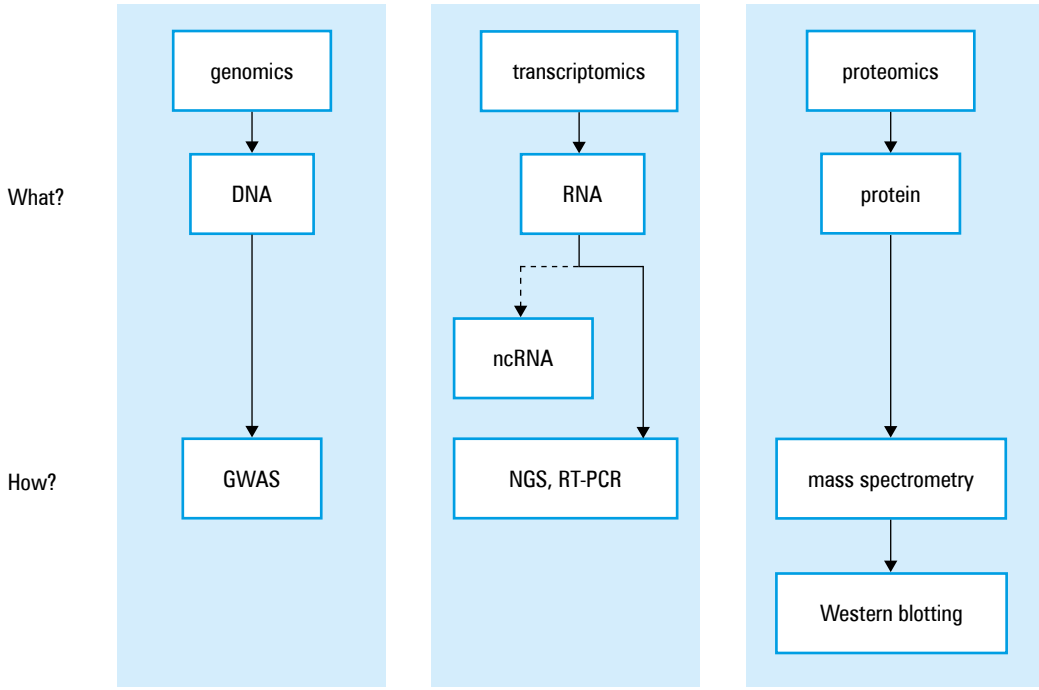

FIGURE 1 What do we measure with "-omics" methodology and how? Abbreviations: GWAS, Genome Wide Association Studies; ncRNA, noncoding RNA; NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction

A new era of protein research has begun along with "proteomics", which allows checking simultaneously millions of peptides in all types of studied fluids or tissues. There are multiple publications listing specific proteins in serum, urine, as well as kidney biopsy samples in glomerulonephritides.[11] Considering the challenges in methodology used in other studies, our group proposed a new protocol for urine collection and preparation. To date, we have published the results of proteomic studies in IgAN, autosomal dominant polycystic kidney disease, and healthy aging humans.[12-14] The next step is to perform complex assessment of selected candidate proteins and their molecular forms, to integrate these results with the "-omics" data in the ongoing cooperation and to identify their roles in renal pathophysiology.

Serwin et al,[15] in their article published in the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*), analyzed a number of factors that are used to measure kidney function.[15] Although the results indicate potential practical use of selected factors in disease prognosis, they should be interpreted with caution. The authors claim that renalase and monocyte chemoattractant protein 1 in nephrotic syndrome might regulate each others' levels. The study was designed to measure these proteins at certain time point, whereas regulation is a process that may change over time. Therefore, repeated measurements and long-term follow-up would be of great value, especially to confirm the role of neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, trefoil factor 3, interleukin 18, β_2-microglobulin, and calbindin as indicators of kidney function loss. We should remember that the described factors may be influenced by many individual parameters.

It is clear that kidney function differs between the diseases, but also depends on such factors as sex or age. Thus, if one measures factor X in glomerulonephritis A, one should precisely know how it behaves in glomerulonephritis B, C, D, or others, or how it behaves in men or women at different ages with or without concomitant diseases, such as diabetes, hypertension, vasculitis, or cancer. The level of any marker also depends on CKD stage, namely, it differs with different serum creatinine levels, for example, 1, 2, 3, or 5 mg%. We still do not know how most of the studied markers behave in the above conditions, let alone others. While acknowledging the results of studies published so far, including our own studies,[4,5,9,12-14] there is still a clear need for integration of these results.

Definitely, the last 10 years have brought a vast number of scientific data with new insights into kidney diseases, especially glomerulonephritis. What we know today is mainly thanks to the "-omics" methodology with the special emphasis on genetic information putting more light on the ethiopathogenesis of numerous glomerular diseases. Answering the question addressed in the title, any research methodology alone does not enable to either fully understand glomerular diseases or to replace a kidney biopsy in diagnosing and monitoring glomerulonephritides. Thus, integrating the results of genomics, transcriptomics, and proteomics with the clinical course of the disease in sufficiently large cohorts of patients with glomerulonephritis should provide insight into the pathogenesis of the particular disease. Like many others, we are also sure that this is the way we have to go on to develop new diagnostic, follow-up, and treatment tools for the awaiting 10% of the world population affected by CKD.[3]

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