Kidney Research and Clinical Practice

Editorial

Where do we stand on human diabetic nephropathy?

The prevalence of type 2 diabetes is rising rapidly in Asian populations due to lifestyle changes and increased life expectancy. With the rapidly increasing number of patients with diabetes worldwide, diabetic nephropathy (DN) is becoming one of the most common causes of renal disease. Indeed, approximately 20–40% of diabetic patients develop DN [1]. The diagnosis of DN is based primarily on clinical features such as lengthy duration of diabetes and presence of target organ damage, especially proteinuria usually preceding decreased renal function. Although validation of this clinical approach is well established in type 1 diabetes, it is much more difficult in patients with type 2 diabetes because of the unknown duration of the disease [2]. The characteristic pathological features of DN are diffuse or nodular mesangial sclerosis, glomerular basement membrane thickening accompanied by chronic interstitial fibrosis and tubular atrophy usually observed in advanced glomerulosclerosis, and hyaline changes in both afferent and efferent arterioles. However, nondiabetic renal disease (NDRD) occurs in patients with type 2 diabetes, and can be either isolated or superimposed on underlying diabetic glomerulosclerosis. Interestingly, NDRD is associated with a broad spectrum of symptoms [3–5]. The ability to clearly differentiate between renal lesions associated with DN and NDRD in diabetic patients is critical for making appropriate treatment decisions, and thus numerous research efforts are focused on how to identify DN in patients with diabetes. Recently, Liang et al [5] performed a meta-analysis of 26 relevant studies comprising 2,322 patients and suggested that the absence of diabetic retinopathy (DR), shorter duration of diabetes, lower HbA1$_C$, and lower BP may help to distinguish NDRD from DN in patients with diabetes [5]. In this issue of *Kidney Research and Clinical Practice*, Kim et al [6] retrospectively analyzed renal pathological findings including the incidence of NDRD in 75 diabetic patients who underwent renal biopsy for clinically suspected NDRD. They also analyzed the clinical characteristics and renal prognosis of patients with DN and NDRD. They found that 10 patients (13.3%) had only DN, 11 patients (14.7%) had DN with superimposed NDRD, and 54 patients (72%) had only NDRD. The most common pathological findings of NDRD were membranous nephropathy (23.1%), IgA nephropathy (21.5%), and acute tubulointerstitial nephritis (15.4%). Compared with DN and NDRD superimposed on DN, the clinical characteristics of NDRD consisted of a short duration of diabetes and less severe DR. Conversely, patients with combined DN and NDRD exhibited the lowest baseline estimated glomerular filtration rate (eGFR) with the greatest proportion of renal deterioration during follow-up. Based on these findings, Kim et al [6] concluded that renal biopsy should be recommended for type 2 diabetic patients with atypical nephropathy, because a considerable number of these patients may have NDRD. However, there were several limitations in their study. First, pathological determination of DN and NDRD was based only on histological findings by light microscopy rather than by electron microscopy. Because the early stages of DN may not be observed with light microscopy, electron microscopy findings may provide a clearer differentiation of renal lesions. Second, the follow-up duration for patients with NDRD was much shorter compared to that in patients with DN, and thus determination of renal prognosis was not appropriate between groups with different follow-up periods.

Recent updates in the field of human DN

The most conspicuous recent findings in the field of DN has been the identification of a number of biomarkers pertinent to the diagnosis of DN and a new pathology classification system launched in 2010 by the Research Committee of the Renal Pathology Society [7]. Highly heterogeneous renal lesions and a more unclear structure–function relationship in type 2 diabetes mellitus compared with type 1 diabetes mellitus has been reported, and thus combining the analysis of pathological grading and new biomarkers for DN will further increase our understanding of this complex disease manifestation. The pathogenesis of DN has a number of complex characteristics, with diverse renal pathological lesions observed in patients with type 2 diabetes. Although the number of patients with type 2 diabetes is rapidly increasing worldwide, DN is paradoxically the renal disease for which the fewest renal biopsies are performed. In many centers, DN is diagnosed on the basis of clinical parameters without renal biopsy. Specifically, renal biopsy is performed only for a small population of diabetic patients, typically cases with unusual clinical presentation such as sudden onset of nephrotic syndrome or sudden decrease in renal function, and then to exclude causes other than DN. As a result, there is insufficient clinical data regarding histopathological issues in DN.

New histopathological classification system for DN

The new classification system launched in 2010 distinguishes between four classes of DN, where essentially only

glomerular lesions are used to classify renal damage, characterized by the absence of histological lesions (Class I), mesangial changes (Class II), nodular lesions (Class III), or a predominance of global glomerulosclerosis (Class IV) [7]. However, this new classification system has not yet been fully validated, as it is unclear whether it can differentiate between DN in type 1 and type 2 diabetic patients. Specifically, the new classification system dictates that the only differences between DN in type 1 and type 2 diabetic patients are that the latter group has a more heterogeneous clinical course and more diverse renal lesions, as well as the difference in the relationship between DN and DR. It has generally been held that virtually all patients with type 1 diabetes and overt nephropathy have DR, whereas < 50% of patients with type 2 diabetes and DN have DR [8]. However, Pedro et al [9] looked at the prevalence and relationship between DN and DR in a population-based study in Spain, including 8,187 patients with type 2 diabetes and 488 patients with type 1 diabetes, and found that although the relationship between microalbuminuria and DR differs between type 1 and type 2 diabetics, the relationship between overt nephropathy and DR is similar in both types. Additionally, they found that overt nephropathy is a risk factor for DR in both types of diabetes. There are several other unresolved issues in the new classification system for DN, including whether the heterogeneity of histopathological lesions in DN represents only differences in time-points of the disease, whether different lesions have different pathophysiological mechanisms, and whether the new classification system can predict a more heterogeneous course of type 2 diabetes. Nevertheless, the revised paradigm represents a very important first step toward the development of a clinically useful classification system for DN.

Recent biomarker studies in human type 2 diabetic patients

A number of recent studies have reported new biomarkers for DN, especially in type 2 diabetics. Yan et al [10] reported an association between plasma concentrations of osteopontin and the presence and severity of DN in type 2 diabetics. In another study, plasma levels of methylglyoxal, a metabolic side-product, were found to be significantly higher in patients with type 2 DN than in those without DN, and correlated with urinary albumin excretion [11]. In addition, fibroblast growth factor 23 was found to be predictor of renal outcome in type 2 diabetics with macroalbuminuria [12]. Furthermore, baseline serum fibroblast growth factor 23 levels showed a significant association with serum creatinine and proteinuria. However, the most significant problem of such biomarker studies is the lack of validation in a study population by renal biopsy.

Accurate assessment of DN

A large number of clinical trials have been performed to identify DN in patients with diabetes without renal biopsy. Unfortunately, a major limitation in most of these biomarker studies is the absence of renal biopsy to determine the presence and severity of DN. Instead, virtually all such studies use albuminuria for the diagnosis of DN. However, chronic renal insufficiency and albuminuria may be derived from NDRD rather than classic DN, especially in type 2 diabetics. In a recent retrospective study of 69 patients with type 2 diabetes, 52% of patients with renal lesions confirmed by renal biopsy had NDRD rather than DN [13]. Nevertheless, care must be taken when interpreting the results of clinical studies using renal biopsies, because they are often performed if comorbidity is suspected, leading to selection bias. This important issue can also be applied to recent biomarker studies, where some patients were erroneously given a diagnosis of DN. Indeed, only one biomarker study used renal biopsy as well as urine proteome analysis, the results of which were used to propose a reliable classification model to differentiate between DN and NDRD, where ubiquitin and β2-microglobulin expression were among the best predictors of DN [14]. The major advantage and clinical relevance of this study was the considerable proportion of study patients who were at the beginning stages of DN without albuminuria. Araki et al [15] serially observed changes in urinary levels of type IV collagen in 254 patients with nonovert DN in type 2 diabetics. They observed that baseline urinary type IV collagen levels are higher in patients with microalbuminuria, and during a follow-up study with a median duration of 8 years, they found that levels of urinary type IV collagen inversely correlate with the annual decline in estimated GFR, whereas overt proteinuria does not manifest in the majority of patients. Inclusion of histopathological information from renal biopsy in these types of biomarker studies would certainly make a great contribution toward a better understanding of the mechanisms leading to DN.

Conclusion

DN exhibits significant pathological diversity, especially in patients with type 2 diabetes; however, there is little information regarding different mechanisms for various cases of NDRD. At present, the diagnosis of DN is based on typical clinical symptoms without renal biopsy. A new classification system launched in 2010 has the potential to be easy to use internationally in clinical practice, and aims to distinguish between different types of DN by identifying four hierarchical glomerular lesion types, with a separate evaluation for degrees of interstitial and vascular involvement. However, several unresolved issues remain in the new classification system, including whether the more heterogeneous course in type 2 diabetic patients can be predicted. Recent clinical efforts have focused on noninvasive identification of new biomarkers from plasma or urine for early detection of DN, differentiation from NDRD, and the clinical utility of these biomarkers for predicting renal outcome in patients with DN. Unfortunately, the majority of these recent biomarker studies have included neither renal biopsy nor histopathological diagnosis. Thus, combining histopathological grading and biomarkers for DN promises to provide a more reliable understanding of this complex disease manifestation.

Conflicts of interest

None to declare.

Acknowledgments

References

[1] Kikkawa R, Koya D, Haneda M: Progression of diabetic nephropathy. *Am J Kidney Dis* 42(3 Suppl 1):S19–S21, 2003

[2] Sachin SS, Gowrishankar S, Kishan AG, Anuradha R: Nondiabetic renal disease in type 2 diabetic mellitus. *Nephrology* 11:533–537, 2006

[3] Bi H, Chen N, Ling G, Yuan S, Huang Q, Liu R: Nondiabetic renal disease in type 2 diabetic patients: a review of our experience in 220 cases. *Ren Fail* 33:26–30, 2011

[4] Ghani AA, Waheeb SA, Sahow AA, Hussain N: Renal biopsy in patients with type 2 diabetes mellitus: indications and nature of the lesions. *Ann Saudi Med* 29:450–453, 2009

[5] Liang S, Zhang XG, Cai HY, Zhou JH, Chen P, Lin S, Qiu Q, Chen XM: Identifying parameters to distinguish non-diabetic renal diseases from diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. *PLOS One* 8:e64184, 2013. Doi: 10.1371/journal.pone.0064184

[6] Kim YJ, Kim YH, Kim KD, Moon KR, Park JH, Park BM, Ryu HW, Choi DE, Na KR, Suh KS, Lee KW, Shin YT: Nondiabetic kidney diseases in type 2 diabetic patients. *Kidney Res Clin Pract* 32:115–120, 2013.

[7] TWC Tervaert, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, Joh K, Noe LH, Radhakrishnan J, Seshan SV, Bajema IM, Bruijn JA: on behalf of the Renal Pathology Society pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 21:556–563, 2010

[8] Osterby R, Gall MA, Schmitz A, Nielsen FS, Nyberg G, Parving HH: Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36:1064–1070, 1993

[9] Pedro RA, Ramon SA, Marc BB, Juan FB, Isabel MM: Prevalence and relationship between diabetic retinopathy and nephropathy, and its risk factors in the North-East of Spain, a population-based study. *Ophthal Epidemiol* 17:251–265, 2010

[10] Yan X, Sano M, Lu L, Wang W, Zhang Q, Zhang R, Wang L, Chen Q, Fukuda K, Shen W: Plasma concentrations of osteopontin, but not thrombin-cleaved osteopontin, are associated with the presence and severity of nephropathy and coronary artery disease in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol* 9:70, 2010. Doi: 10.1186/1475-2840-9-70

[11] Lu J, Randell E, Han Y, Adeli K, Krahn J, Meng QH: Increased plasma methylglyoxal level, inflammation, and vascular endothelial dysfunction in diabetic nephropathy. *Clin Biochem* 44:307–311, 2011

[12] Alkhalaf A, Zurbig P, Bakker SJ, Bilo HJ, Cerna M, Fischer C, Fuchs S, Janssen B, Medek K, Mischak H, Roob JM, Rossing K, Rossing P, Rychlík I, Sourij H, Tiran B, Winklhofer-Roob BM, Navis GJ: PREDICTIONS Group: Multicentric validation of proteomic biomarkers in urine specific for diabetic nephropathy. *PLOS One* 5: e13421, 2010. Doi: 10.1371/journal.pone.0013421

[13] Mou S, Wang Q, Liu J, Che X, Zhang M, Cao L, Zhou W, Ni Z: Prevalence of nondiabetic renal disease in patients with type 2 diabetes. *Diabetes Res Clin Pract* 87:354–359, 2010

[14] Papale M, Di PS, Magistroni R, Lamacchia O, Di Palma AM, De Mattia A, Rocchetti MT, Furci L, Pasquali S, De Cosmo S, Cignarelli M, Gesualdo L: Urine proteome analysis may allow noninvasive differential diagnosis of diabetic nephropathy. *Diabetes Care* 33:2409–2415, 2010

[15] Araki S, Haneda M, Koya D, Isshiki K, Kume S, Sugimoto T, Kawai H, Nishio Y, Kashiwagi A, Uzu T, Maegawa H: Association between urinary type IV collagen level and deterioration of renal function in type 2 diabetic patients without overt proteinuria. *Diabetes Care* 33:1805–1810, 2010

Dae Ryong Cha
Department of Internal Medicine,
Korea University Ansan–Hospital,
Ansan City, Kyungki-do, Korea
E-mail address: cdragn@unitel.co.kr