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Validation of the interstitial fibrosis and tubular atrophy on the new pathological classification in patients with diabetic nephropathy: A single-center study in China

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ABSTRACT

Objectives: The association between interstitial fibrosis and tubular atrophy (IFTA) and the clinical outcomes in diabetic nephropathy (DN) remains unclear. This study is to evaluate the clinical predictors and renal prognosis of IFTA score in patients with DN.
Methods: 52 cases with DN with renal biopsy were divided into three groups according to IFTA score. The χ^2 test or Fisher's exact test, Mann–Whitney U-test, Kruskal–Wallis H-test and Spearman's correlation analysis were used in this subject. Ordinal regression mode was utilized to evaluate which clinical factors might be the predictors of IFTA score.
Results: Compared to IFTA score 1 group, the patients in score 3 were younger and have greatly lower level of eGFR and hemoglobin and higher serum creatinine ($p < 0.01$). A close relationship between the clinical findings and IFTA was observed, such as IFTA with eGFR($r = -0.58$, $P < 0.01$), triglyceride($r = -0.29$, $P = 0.04$), Hb ($r = -0.38$, $P < 0.01$), systolic blood pressure ($r = 0.29$, $P = 0.04$) and urinary protein level ($r = 0.46$, $P < 0.01$); in addition, eGFR (OR 0.31 (95%Cl −1.883 to −0.485) $p = 0.001$) showed statistical significance with IFTA. The 5-year renal survival rate was estimated as 100% in IFTA score 0, 88.9% in score 1, 76.9% in score 2, and 20.0% in score 3. Furthermore, greatly lower level of eGFR, and higher serum creatinine and BUN in the glomerular class IV were seen ($p < 0.01$ vs class II), with positive correlation with IFTA ($r = 0.51$, $P < 0.01$).
Conclusion: The renal pathologic diagnosis in IFTA score was a good predictor for renal prognosis in type II DM. eGFR might be a predictor of IFTA in patients with DN.

1. Introduction

A new classification for diabetic nephropathy (DN) was developed in 2010 supported by the Research Committee of the Renal Pathology Society, in order to develop a uniform classification system that discriminates lesions with various prognostic severities that would be easy to use internationally in clinical practice. This new classification divides DN into four glomerular lesions with a separate evaluation for degrees of interstitial and vascular involvement (Tervaert et al., 2010). The classification is mainly based on glomerular lesions, for glomerular lesions could best reflect the natural course of progressive DN. Research by Oh et al. (2012) has identified that the renal pathologic diagnosis with glomerular lesions was proved as a good predictor for renal prognosis in type II DM. Although glomerular classification is considered to be the gold standard for the evaluation of DN, interstitial fibrosis and tubular atrophy (IFTA) parameters are often under-recognized in pathological reports. In addition, the usefulness of new renal pathologic classification in DN remains debatable.

It was commonly recognized that the glomerulus damage is the main pathological change in DN which includes the thickening of the glomerular basement membrane, mesangial expansion, Kimmelstiel–Wilson, lesion and glomerulosclerosis (Espinel et al., 2015). However, in recent years, many researchers had found that glomerular and interstitial lesions may be independent factors in the progression of DN. Previous research in our laboratory suggests that tubular injury played a key role in the causation of kidney damage in DN. It has been reported that renal proximal tubule is uniquely susceptible to the high-glucose (HG) ambience; leading to apoptosis and further progression to tubulointerstitial lesions in DN (Sun et al., 2008; Xiao et al., 2014). In this new classification of pathological change by the Research Committee of the Renal Pathology Society in 2010, there was

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a separate evaluation for tubular–interstitial and vascular lesions in this classification by IFTA scores. Several researches evaluated the relationship between IFTA and the mortality, decline of renal function and proteinuria in patients with DN, such as Shimizu et al. (2013) who identified that IFTA is a predictor of all-cause mortality in DN, indicating the critical role of IFTA in the progression of DN. Tubulointerstitial lesions should be assessed to predict rapid eGFR decline in patients with DN who have overt proteinuria (Mise, Hoshino, Ueno et al., 2014; Mise, Hoshino, Ubara et al., 2014). Another study showed that tubulointerstitial lesions might be a significant indicator for anemia in DN through the multivariate mode (Mise, Hoshino, Ueno et al., 2014; Mise, Hoshino, Ubara et al., 2014). However, it remains unclear for the clinical evaluation of this new tubule-interstitial score in the new pathological classification of DN.

In this study, we investigate for the first time the clinical and pathological predictors of the IFTA scores and analyze its impact on renal death in patients with DN.

2. Methods

2.1. Patients and study design

Among 94 patients with diabetes conducting renal biopsy at our hospital from 2006 to 2010, 52 patients were confirmed to have the pathological and clinical change of DN. Exclusion criteria were renal transplantation, coexistence of other renal disease (except for nephrosclerosis) and renal tissue less than 5 glomeruli.

2.2. Assessment of laboratory data and definitions

The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation. Urinary protein excretion was measured from a 24-h urine sample. Hematuria was defined as the detection of more than five erythrocytes per high-power field in at least two or three consecutive urine tests. Acute onset of DN was defined as the main symptom of the DN had not lasted for 3 months.

2.3. Renal biopsy and pathological classification

All renal biopsies were conducted based on the indication of our primary doctors and at least two pathological doctors confirmed the pathological results. Basically, indications of the renal biopsy were proteinuria or coexistence of moderate lesions of the renal function without diabetic retinopathy. Classification of DN and histological scoring were calculated as previously described by the Renal Pathology Society (Tervaert et al., 2010).

2.4. End point

The primary end point was renal death, which was defined as commencement of dialysis due to ESRD. None of the patients received kidney transplantation during follow-up.

3. Statistical analysis

Data were summarized as percentage or the mean (± standard deviation, SD) as appropriate. χ^2 test or Fisher's exact test was used to analyze the categorical variables and continuous variables were compared by using t-test, Mann–Whitney U-test, or Kruskal–Wallis H-test. Spearman's correlation was used to evaluate the correlations among each histopathological and clinical finding. As for the Ordinal Regression, we used the median (quartile) to define the age: "1"referred to "<45"; "2 "referred to "45–54"; "3" referred to "55–64 ";"4" referred to ">65". According to the clinical definition, we defined the GFR as "1" "<30"; "2" "30–60"; "3" "61–90"; "4" ">90", and triglyceride was defined as "1" "<1.71" and "2" "≥1.71". Here we used the coefficient (B) and odds ratio (OR = EXP (B)) along with its 95% confidence interval (95% CI) to reflect the dependent variable to elevate one or more levels, in response to the independent variable changing for every one unit. Cumulative survival was estimated with Kaplan–Meier survival curves, and was compared by using the log-rank test. A P-value of <0.05 was regarded as statistical significance. But in the R _ C division χ^2 test, the P-value of <0.017 was statistically significant. SPSS 17.0 was used to store and analysis our data.

4. Results

4.1. Clinical characteristics of all patients

The characteristics of all patients are shown in Table 1. Of the 52 patients, 31 were men (72.1%). The mean (±SD) age at the renal biopsy was 47.1 ± 12.0 years (range: 25–70 years). The mean duration of DM was 3.77 ± 3.88 years and 26 patients had acute onset of DN (51%). The mean baseline serum creatinine level was 142.62 ± 80.17μmol/L; the mean baseline BUN level was 8.39 ± 2.84 mmol/l, and the mean eGFR was 59.44 ± 29.55 ml/min/1.73 m^2. Urinary protein excretion was 5.15 ± 5.18 g/day. 33 patients (63.5%) had hematuria (i.e. more than five erythrocytes per high-power field). The mean hemoglobin (Hb) was 115.75 ± 24.56 g/dl; mean serum albumin was 27.10 ± 5.95 g/dl; mean HbA1c was 7.79% ± 2.15% (Table 1).

4.2. Clinical findings among different IFTA scores

Clinical findings among different IFTA scores (0–3) are displayed in Table 1. Different scores of IFTA under light microscope were shown in Supplement Fig. 1. The patients whose IFTA score was 3 were younger than those whose IFTA score was 0 ($p < 0.05$). eGFR was greatly lower for patients in score 2 or score 3 than those in score 1 ($p < 0.05$). Serum creatinine was significantly higher for patients in score 2 or score 3 than those in score 1 ($p < 0.05$). Hb was significantly lower for patients in score 3 than those in score 0 ($p < 0.05$). The interstitial inflammation score was significantly higher for patients in score 1 or score 2 or score 3 than those in score 0 and higher for patients in score 2 or score 3 than those in score 1 ($p < 0.05$). The mean interstitial inflammation score was 1.54 ± 0.70. The mean arteriolar hyalinosis score was 1.25 ± 0.84 and the mean arteriosclerosis score was 0.85 ± 0.5.

4.3. Correlations among the clinical findings among different IFTA scores

Correlations among the clinical findings are displayed in Table 2. The IFTA showed positive correlation with urinary protein excretion ($r = 0.46$), strong negative correlation with eGFR ($r = -0.58$), as well as negative correlation with Hb ($r = -0.38$).

4.4. Multivariable logistical regression among different IFTA scores

Due to the small sample in score 0, we combined score 0 with score 1 in the multivariable logistical regression (Table 3). Multivariable logistical regression revealed that eGFR (OR 0.31 (95%CI −1.883 to −0.485) $p = 0.001$) was associated with IFTA. Moreover, it meant that when the IFTA score was raised, eGFR was decreased. There was no statistical significance between IFTA and Hb and bBP.

4.5. Kaplan–Meier survival curves in different IFTA scores

In Kaplan–Meier survival curves stratified according to the scores for IFTA, the presence of exudative lesions is shown in Fig. 1. There was a significant difference in renal survival among each IFTA score ($P < 0.05$). Log-rank test showed p value = 0.031.

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