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● *Original Contribution*

VIRTUAL TOUCH TISSUE QUANTIFICATION FOR ASSESSING RENAL PATHOLOGY IN IDIOPATHIC NEPHROTIC SYNDROME

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Abstract—The aim of this study was to evaluate Virtual Touch tissue quantification in assessing renal interstitial fibrosis in patients with idiopathic nephrotic syndrome. Ninety patients with idiopathic nephrotic syndrome were assigned to mild, moderate and severe groups depending on the degree of renal interstitial fibrosis on histopathologic examination of renal biopsy specimens. Thirty healthy patients were also selected as the control group. Virtual Touch tissue quantification was performed to measure the shear wave velocity of the renal parenchyma. There was no statistically significant difference in shear wave velocity between the mild and control groups ($p > 0.05$); however, the moderate and severe groups did significantly differ compared with the control ($p < 0.001$). The area under the receiver operating characteristic curve value for the shear wave velocity of renal interstitial fibrosis in the moderate group versus the control and mild groups together was 0.869 (95% confidence interval: 0.791–0.947) and that in the severe group versus the control, mild and moderate groups together was 0.954 (95% confidence interval: 0.917–0.998). The corresponding best cutoff points were 2.41 and 2.77 m/s, with sensitivities of 91.7% and 86.8%, specificities of 78.0% and 92.0%, negative predictive values 0.907 and 0.907, positive predictive values 0.800 and 0.971 and Youden index values of 0.697 and 0.788, respectively. Virtual Touch tissue quantification may non-invasively and quantitatively estimate the degree of renal interstitial fibrosis in patients with idiopathic nephrotic syndrome as a baseline for monitoring progression and treatment response. (E-mail: 17853297696@163.com)

Key Words: **Elastography, Ultrasound, Biopsy, Pathology, Nephrotic syndrome, Idiopathic.**

INTRODUCTION

Nephrotic syndrome (Luks et al. 2008), a critically important and common renal disease, affects both the pediatric and adult populations. Nephrotic syndrome (NS) is one of the most common diseases of the urinary system, with an incidence rate only secondary to that of acute nephritis and a long disease course of recurrence and persistency. Based on etiology, NS is classified into primary, secondary and congenital types (Hodson and Alexander 2008). Tubulointerstitial fibrosis occurs secondary to proteinuria and global glomerulosclerosis. Further, glomerulosclerosis, interstitial fibrosis and tubular atrophy play crucial roles in the pathogenesis of chronic kidney disease (CKD), as major determinants in CKD development and progression in patients with primary renal diseases characterized by persistent or recurrent proteinuria (Parolini et al. 2009).

Early detection of glomerulosclerosis and interstitial fibrosis may result in more favorable outcomes of CKD, if clinicians can initiate early protective treatment. Therefore, estimating the extent of glomerular and interstitial damage of the kidney is of crucial clinical significance. Pathologic types of idiopathic NS (INS) are diverse, and glucocorticoid sensitivity changes with the degree of glomerular and interstitial damage (Certikova-Chabova and Tesar 2013). In addition to glomerular damage, interstitial inflammatory cell infiltration, fibrosis and tubular atrophy also play an important role in determining treatment and prognosis. Therefore, it is of great clinical significance to assess the type of glomerular damage and degree of interstitial impairment. In patients with nephrotic syndrome, renal biopsy is the gold standard for diagnosis and also helps determine a suitable treatment plan (Mengel et al. 2007). However, it is harmful, with potential complications of hemorrhage and arteriovenous fistula, and yields limited

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amounts of kidney tissue (Maya and Allon 2009). Renal needle biopsy is inapplicable for adults with hemorrhagic tendency, solitary kidney, or obesity. The amount of kidney tissue obtained is limited, and so it is unable to reflect the systemic pathology of the kidney. Also, repeated performance of biopsy is unfeasible, not appreciated by patients (Maya and Allon 2009).

Elasticity varies under distinct pathophysiological conditions in the same or different tissue structures and constitutes an important feature of biological tissues. Renal interstitial fibrosis results in an alteration of resistance to kidney strain, the measurement of which can help estimate the extent of fibrosis (Li et al. 2013). Ultrasound elastography was first developed by Ophir et al. (1991), whereas Virtual Touch tissue quantification (VTQ) is a newer tool in this field. VTQ was used in this study and is different from conventional ultrasound elastography. It is a novel ultrasound elastography for harmless detection and evaluation of tissue stiffness. The primary mechanism of VTQ lies in transmission of an ultrasonic pulse, of short duration (<1 ms) and fixed frequency (2.67 MHz), on the target area, which causes strain in the target tissue and, thus, formation of a shear wave that travels perpendicular to the direction of the emission pulse. Elastic changes in the target tissue can be analyzed by calculation of shear wave velocity (SWV) in the tissue, followed by quantification of tissue stiffness (Yu et al. 2015). In tissues that with high elastic moduli and strong resistance to strain, SWV is low, but in tissues with reduced elastic moduli and poor resistance to strain because of fiber sclerification, SWV is high. Currently, ultrasound elastography is well established in the diagnosis of disorders of the mammary gland (Guo et al. 2016; Liu et al. 2016), vessel wall (Li et al. 2016), pancreatic masses (D'Onofrio et al. 2016) and thyroid gland (Lin et al. 2014). Among abdominal organs, most research on VTQ has focused on liver disease and indicates that SWV increases with liver fibrosis. Therefore, SWV is considered a reliable index for the degree of liver fibrosis (Gallotti et al. 2010).

We previously found that SWV significantly increases in early diabetic kidney disease (Yu et al. 2014), whereas serum bone morphogenetic protein-7 (BMP-7) decreases with increasing disease progression, with a significant negative correlation with SWV (Yu et al. 2015). However, renal biopsy remains the gold standard for diagnosing renal disease, especially fibrosis. Therefore, the primary objective of this study was to use VTQ for assessment of the SWV of renal parenchyma in patients with INS and compare the results with the histopathological diagnosis of renal interstitial fibrosis. Second, we explored the feasibility and prognostic value of VTQ in the quantitative estimation of renal interstitial fibrosis in patients with INS to guide treatment.

METHODS

Patients

This prospective study enrolled 90 consecutive patients clinically diagnosed with INS (63 males and 27 females; mean age of 49.9 ± 18.5 [range: 31.0–68.0] y), who were hospitalized between February 2012 and October 2015 in the Department of Nephrology, Affiliated Hospital of Qingdao University. All patients met the criteria for clinical diagnosis of nephrotic syndrome developed by the Chinese Medical Association (2001): (i) massive proteinuria (protein level >3.5 mol/L); (ii) low-albumin blood disease (plasma protein <30 mol/L); (iii) various degrees of edema; (iv) hyperlipidemia (plasma cholesterol >5.7 mol/ L).

Inclusion criteria were (i) age >18 y; (ii) fulfillment of the diagnostic criteria for nephrotic syndrome; (iii) provision of informed consent for renal biopsy; (iv) no history of liver or kidney disease; and (v) routine blood and urine tests, as well as renal function examinations, within the normal range.

Exclusion criteria comprised (i) inability to correctly cooperate with breath-holding activity or other exam requirements; (ii) secondary nephrotic syndrome; (iii) pathologic conditions that could affect measurements (*e.g.,* cystic renal disease), parenchymal echogenicity changes, and other non-renal intra-abdominal abnormalities; and (iv) advanced CKD and cortical thickness less than the VTQ-measured region of interest.

Thirty healthy patients (17 males and 13 females; mean age of 46.4 ± 19.7 [range: 26–66] y), recruited at their annual physical checkup, constituted the control group. Patients with normal renal function whose routine blood and urine were normal and who had no history of kidney diseases or other chronic diseases, such as hypertension and diabetes, were included as control patients.

The present study protocol was approved by the institutional review board of Qingdao University, Shan-Dong Province, People's Republic of China; all participants provided written informed consent before study participation. This research was conducted in adherence to the principles of the Declaration of Helsinki.

Patients were assigned to three groups based on the extent of tubulointerstitial damage indicated on histopathological findings from renal biopsy specimens (Solez et al. 1993): (i) mild (characterized by mild renal interstitial fibrosis, with few inflammatory cells in the stroma, no fibrous tissue hyperplasia and overall lesions constituting <20% of the renal tissue); (ii) moderate (characterized by moderate renal interstitial fibrosis, with atrophy and degeneration of renal tubular epithelial cells, slight necrosis distributed as plaques, mild inflammatory cell infiltration and fibrous tissue hyperplasia and lesions ranging between 20% and 50% of the renal tissue); (iii) severe (characterized by severe renal interstitial fibrosis, with