THE HISTOPATHOLOGIC SIGNIFICANCE OF THE RENAL RESISTIVE INDEX

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INTRODUCTION AND AIMS: Renal resistive index (RRI) measured by Doppler sonography is increasingly used in nephrology for the evaluation of renovascular disease, chronic nephropathies and allograft dysfunction. This study aimed to evaluate the relationship between RRI and histopathologic parameters of renal damage.

METHODS: This cross-sectional, single-center study prospectively enrolled 44 consecutive CKD patients (57% male gender, 54.1 (95%CI: 49.7–58.6) years, median eGFR

RESULTS:

- Underlying causes: 50% hypertension, 30% diabetes, 24% glomerulonephritis, 24% chronic interstitial nephropathy, 24% chronic pyelonephritis, 11% polycystic kidney disease, 8% transplant nephropathy, 2% obstructive nephropathy.
- RRI: mean 0.72 (range 0.50–0.86).
- Histology: 21% MP, 28% MP and SMC, 35% SMC alone, 16% non-proliferative glomerulonephritis, 4% proliferative glomerulonephritis.

- RRI was significantly higher in patients with MP (p = 0.0003, HR 3.68 (1.05, 12.89); p = 0.04).
- Only independent predictors of decreased renal survival were higher age (HR 1.05 (1.00, 1.11); p = 0.04), systolic blood pressure (p = 0.04), proteinuria (p = 0.01), and renal survival (p = 0.04).

- Thirty percent of the patients had GS, advanced age and lower eGFR (41.9 (35.0, 48.9) vs. 56.7 (49.8, 66.6) mL/min; p = 0.03). IINF was found in 41%, they were older, had lower hemoglobin, lower eGFR (41.5 (32.1, 50.3) vs. 56.7 (48.8, 66.6) mL/min; p = 0.03). MCP-1 mRNA expression was significantly higher in patients with GS (p = 0.001), and fibrinoid necrosis (p = 0.04).

- Only 7 (9%) patients died, mainly because cardiovascular (24%). 32% of the patients had MP, they reached the renal survival endpoint (54% vs. 27%; p = 0.001). TM had a potent effect in reducing ICAM-1 expression in kidneys of rats with nephrotoxic serum nephritis compared to vehicle (saline) control, but this reduction did not persist until the end of the protocol.

- In the protocol 1, TM-treated rats had less proteinuria (p < 0.05), MCP-1 (p < 0.001), IL-6 (p < 0.001), IL-1β (p < 0.001), and higher serum HMGB1 levels (p < 0.001) compared to controls. In the protocol 2, ICAM-1 expression was significantly reduced (p < 0.001) and urine (p < 0.001), MCP-1 (p < 0.001), TNF-α (p < 0.01), serum creatinine, patient and kidney survival.

- In the protocol 3, TM significantly reduced proteinuria from Day 14 (p < 0.05) and from Day 4 to Day 10 in the protocol 3. Rats were sacrificed 7 days, 6 hrs, and 56 hrs after the injection. The rats with NTS-N were given either TM or vehicle (saline), from Day 0 to -1 hr prior to NTS injection in the protocol 2, 0 to 7 days, and from Day 0 to 56 days in the protocol 3. Rats were sacrificed 7 days, 6 hrs, and 56 hrs after the injection.

- The protective effects of TM were examined in nephrotoxic serum nephritis (NTS-N) in Wistar Kyoto rats by showing that TM significantly reduced proteinuria from Day 14 (p < 0.05) and from Day 4 to Day 10 in the protocol 3. Rats were sacrificed 7 days, 6 hrs, and 56 hrs after the injection.

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28.1 (15.0-47.7) mL/min) diagnosed by renal biopsy during 6 months in a large tertiary hospital. Data regarding the clinical presentation, comorbidities and treatment were retrieved from the patients' files. RRI was measured in the interlobar arteries (3 recordings were performed at upper, middle, and lower parts of the kidney) in both kidneys during the 48 hours preceding kidney biopsy. A mean RRI value was obtained for each patient by averaging the two kidneys’ mean RRIs (Pearson’s r correlation coefficient r > 0.90).

All biopsies were evaluated using a standardized protocol according to the Mayo consensus. Arteriosclerosis, arteriolosclerosis, interstitial fibrosis/tubular atrophy, glomerulosclerosis, extracapillary proliferation, endocapillary hypercellularity and fibro-necrosis were quantitatively assessed. Also, electronic microscopy parameters were assessed: glomerular basement membrane (GBM) thickness, podocyte effacement and endothelial swelling. The patients were grouped and compared according to the RRI: high (r > 0.7; n = 17; 39%) versus normal (≤0.7; n = 27; 61%). Spearman test was used to assess correlations and multiple regression analysis to investigate the relationship between RRI and the studied parameters.

RESULTS: Primary glomerulonephritis (75%), diabetic nephropathy (14%), vascular nephropathies (7%), and tubulointerstitial nephropathies (4%) were the main causes of CKD. Patients with high RRI were older (62.1 vs. 49.1 years; p < 0.001), had higher mean arterial pressure (172.9 (156.2-189.7) vs. 154.9 (143.0-165.0) mmHg; p = 0.04), had diabetes mellitus more often (35% vs. 11%; p = 0.05) and higher abdominal aortic calcification score (Kappa score 3 (0-6) vs. 0 (0-1); p = 0.02). Patients with abnormal RRI had higher percentage of global glomerulosclerosis (25.2 (14.3-36.1) vs. 15.1 (7.1-23.2); p = 0.05), more often arteriolosclerosis (88 vs. 52%; p = 0.01), higher interstitial fibrosis/tubular atrophy score (2 (1-3) vs. 1 (0.5-3); p = 0.03) and thicker GBM (475 (350-713) vs. 400 (370-470) mm; p = 0.05). RRI was directly correlated with age (r = 0.55; p < 0.001), Kappa score (r = 0.50; p = 0.002), global glomerulosclerosis percentage (r = 0.31; p = 0.03), interstitial fibrosis/tubular atrophy score (r = 0.35; p = 0.02), GBM thickness (r = 0.22; p = 0.08), and inversely correlated with eGFR (r = -0.34; p = 0.02). In a binary logistic regression model in which the dependent variable was RRI and the independent variables were those resulted from the univariate analysis, only older age (HR 1.07 (1.00-1.14)), arteriolosclerosis (HR 11.3 (1.0-124.9)) and diabetes mellitus (HR 2.5 (1.9-129.3)) were significantly and independently related to RRI > 0.7.

CONCLUSIONS: To the best of our knowledge this is the first study to evaluate the relationship between RRI and detailed renal histological parameters. RRI seems to correlate well with some renal histopathologic characteristics, particularly with arteriolar sclerosis. Moreover, RRI appears to have a multifaceted significance because it is related both with systemic atherosclerosis and renal arteriolosclerosis.