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Original Article

Plasma endocan level and prognosis of immunoglobulin A nephropathy

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Abstract

Background: Endocan, previously called endothelial cell–specific molecule-1, is a soluble proteoglycan that is secreted from vascular endothelial cells. Elevated plasma endocan levels were shown to be associated with poor cardiovascular outcomes in patients with chronic kidney disease (CKD). We investigated the clinical relevance of plasma and urine endocan levels in patients with immunoglobulin A nephropathy (IgAN).

Methods: Sixty-four patients with IgAN and 20 healthy controls were enrolled in this study. Plasma and urine endocan levels were measured. Clinical parameters, pathologic grades, and renal outcomes were compared among subgroups with different plasma and urine endocan levels.

Results: Both plasma and urine endocan levels were significantly higher in patients with IgAN than in controls. Elevated serum phosphorus and C-reactive protein were independent determinants for plasma endocan, and elevated C-reactive protein was also an independent determinant for urine endocan levels in multivariate analysis. Plasma endocan level was not significantly different across CKD stages, but patients with higher plasma endocan levels showed adverse renal outcome. Urine endocan levels were also elevated in patients with poor renal function. Cox proportional hazard models showed that high plasma endocan was an independent risk factor for CKD progression after adjusting for the well-known predictors of outcome in patients with IgAN.

Conclusion: This study suggested that plasma endocan might be useful as a prognostic factor in patients with IgAN.

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis in Asian countries, including Korea [1]. The clinical course and renal prognosis of patients with IgAN are quite diverse; nevertheless, approximately 50% of patients eventually progress to end-stage renal disease, which requires renal replacement therapy within 20 years of the initial diagnosis [2]. The well-known risk factors for poor clinical outcome include elevated serum creatinine levels, at first presentation; sustained hypertension; persistent proteinuria; and specific pathologic features, including mesangial hypercellularity; segmental glomerulosclerosis; tubular atrophy; and interstitial fibrosis [3,4]. However, none of these

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markers are sensitive or specific; thus, predicting the risk of disease progression remains controversial. Several studies have described new kidney biomarkers that might predict renal outcome independently, such as kidney injury molecule-1, neutrophil gelatinase–associated lipocalin, and nestin, but these markers should be validated more thoroughly [5–7].

Endocan, also known as endothelial cell–specific molecule-1, is a 50-kDa proteoglycan that is composed of dermatan sulfate and mature polypeptide of 165 amino acids [8]. Unlike other ubiquitous proteoglycans, which are mainly located in the connective tissue, endocan is a soluble molecule, secreted from vascular endothelial cells of various organs, and it can freely circulate in the blood [9]. The exact role of endocan in humans remains to be elucidated. However, it has been reported that elevated plasma endocan levels could serve as an independent risk factor for poor survival in patients with malignancy, chronic kidney disease (CKD), preeclampsia, sepsis, and hypertension [10–14].

Several studies have documented endothelial injury in patients with IgAN by measuring plasma von Willebrand factor and soluble fms–like tyrosine kinase-1 [15,16]. Given that a key element in CKD progression is endothelial injury, we hypothesized that endocan could be linked to endothelial dysfunction, and thus, it may serve as a marker of CKD progression in patients with IgAN [17]. Currently, no study has investigated endocan levels in patients with IgAN. The aim of this study was to evaluate plasma and urine endocan levels in patients with IgAN to determine whether endocan could serve as a marker of clinicopathologic severity and prognosis.

Methods

Patient selection and study design

We retrospectively analyzed 64 patients diagnosed with IgAN based on a renal biopsy, in Kyung Hee University Hospital at Gangdong from June 2011 to October 2014. The diagnosis of IgAN was confirmed by an expert pathologist, based on the following criteria: IgA and/or C3 deposition in the mesangial area observed with immunofluorescence staining and electron-dense material deposited in mesangial and paramesangial regions observed with electron microscopy. Other glomerulopathies that mimicked IgAN, such as systemic lupus erythematosus and Henoch–Schonlein purpura as well as secondary IgAN, were excluded by identifying signs in a careful patient history and laboratory data. We also excluded patients who had superimposed acute kidney injury at the time of renal biopsy. We enrolled 20 additional healthy volunteers; serum creatinine and fasting glucose levels of those were within normal range, urinalysis revealed no proteinuria and hematuria, and blood pressure was normal on routine medical checkup. The Institutional Review Board of Kyung Hee University Hospital at Gangdong approved this study (KHNMC 2008-030). Informed consent was obtained from all patients and healthy controls.

Age, sex, height, weight, the presence of diabetes, and systolic and diastolic blood pressures were recorded at the time of admission. Blood samples were drawn for routine laboratory analyses in the fasted state, for measuring hemoglobin, total cholesterol, albumin, creatinine phosphorus, and C-reactive protein (CRP). The estimated glomerular filtration rate (eGFR) was calculated with the equation from the Modification of Diet in Renal Disease study. Patients were classified into different CKD stage groups, according to eGFR. Urine samples were collected on the morning of the day of renal biopsy. Urine was evaluated for the presence of hematuria and proteinuria. Proteinuria was expressed as the urinary protein-to-creatinine ratio (uPCR), calculated as urinary protein/urinary creatinine (g/gCr).

Collection of plasma and urine samples; measurement of endocan levels

Additional samples of plasma were collected on the day of biopsy and stored at −80°C. Urine samples were collected in 50-mL sterile conical tubes. After centrifugation of urine for 20 minutes at 2,000*g* at room temperature, the supernatant was collected in the tube and kept at a −80°C deep freezer. The enzyme-linked immunosorbent assay method was performed with a commercial kit (Boster Biological Technology, Pleasanton, CA, USA) to measure plasma and urine endocan levels. Urine creatinine was measured in the same urine specimens. The urine endocan level was expressed relative to the creatinine concentration: endocan/creatinine (pg/gCr).

Histologic grading of IgAN

The pathologic findings of IgAN were classified with both the Oxford classification and the modified H.S. Lee grading system [18,19]. The 4 pathologic variables of the Oxford classification were defined as the following: mesangial hypercellularity ≤ 0.5 (M0) or > 0.5 (M1); endocapillary hypercellularity absent (E0) or present (E1); segmental glomerulosclerosis absent (S0) or present (S1); and tubular atrophy and/or interstitial fibrosis $\leq 25\%$ (T0), 26–50% (T1), and $> 50\%$ (T2). The H.S. Lee system included 5 grades, defined by the percentage of glomeruli that exhibited crescent/segmental sclerosis (SS)/global sclerosis (GS). These grades were described as the following: grade I, normal or focal mesangial cell proliferation; grade II, diffuse mesangial cell proliferation or $< 25\%$ of glomeruli with crescent/SS/GS; grade III, 25–49% of glomeruli with crescent/SS/GS; grade IV, 50–75% of glomeruli with crescent/SS/GS; and grade V, $> 75\%$ of glomeruli with crescent/SS/GS.

Treatment of IgAN and follow-up

All patients included in this study visited our outpatient clinic regularly every 1–3 months. Patients were treated with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) unless proteinuria improved spontaneously to normal range. Patients who showed persistent proteinuria over 1 g/d despite optimal use of ACEi or ARB for 3 months received immunosuppressive agents. Routine laboratory parameters (described previously) were determined for each visit, and all patients were monitored for CKD progression and cardiovascular events, including myocardial infarction, stroke, and death from any cause. CKD progression was defined as more than 50% reduction in eGFR from the value observed at the time of biopsy [20,21].

Statistical analysis

Statistical analyses were performed with SPSS for Windows, version 20.0 (IBM Corp, Armonk, NY, USA), and P values < 0.05