ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20230239

Sclerostin and TNF-related weak inducer of apoptosis: can they be important in the patients with glomerulonephritis?

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SUMMARY

OBJECTIVE: Sclerostin is a protein produced by osteocytes, kidneys, and vascular cells and has many effects on kidney and vascular structures. Soluble TNF-related weak inducer of apoptosis is a proinflammatory cytokine that may cause glomerular and tubular injury and increase sclerostin expression. This study aimed to investigate serum sclerostin and soluble TNF-related weak inducer of apoptosis levels in patients with glomerulonephritis and the effects they may be associated with.

METHODS: This cross-sectional study included 93 patients, 63 of whom were glomerulonephritis and 30 were healthy controls. Serum sclerostin, soluble TNF-related weak inducer of apoptosis, and 24-h urinary protein excretion were measured, and pulse wave velocity was calculated for arterial stiffness.

RESULTS: Serum sclerostin and soluble TNF-related weak inducer of apoptosis were higher in glomerulonephritis patients than in the control group, and serum sclerostin and soluble TNF-related weak inducer of apoptosis levels were correlated with both proteinuria and pulse wave velocity. In addition, in the regression analysis, serum sclerostin and soluble TNF-related weak inducer of apoptosis levels were found to be independent predictors of proteinuria in patients with glomerulonephritis.

CONCLUSION: This is the first study to show that serum sclerostin and soluble TNF-related weak inducer of apoptosis are elevated in glomerulonephritis patients, and these two markers correlate with arterial stiffness and proteinuria in these patients. Considering the effects of sclerostin and soluble TNF-related weak inducer of apoptosis in patients with glomerulonephritis, we think these mechanisms will be the target of both diagnosis and new therapies.

KEYWORDS: Glomerulonephritis. Pulse wave velocity. Proteinuria. Vascular stiffness.

INTRODUCTION

Glomerulonephritis (GN) is glomerular inflammation caused by immune- or non-immune-mediated injury. In GN patients, cardiovascular disease (CVD) risk increases due to systemic inflammation[1]. There are many pathogenetic mechanisms in GN, and many new mechanisms have been discovered recently.

Sclerostin is a protein produced by osteocytes, kidneys, and vascular cells. As kidney functions decrease, serum sclerostin levels increase[2]. One of the critical mechanisms by which sclerostin affects bone regulation is the modulation of the Wnt/β-catenin pathway. Sclerostin is a Wnt signaling pathway antagonist that causes suppression of osteoblast differentiation and proliferation[3]. Wnt pathway, inhibited by sclerostin, plays a central role in bone turnover and remodeling. Sclerostin is also involved in the pathophysiological process of atherosclerosis, due to its roles in the regulation of endothelial inflammation, vascular calcification (VC), and mesenchymal stem cell differentiation[4]. These pathways have roles in various pathological processes such as renal fibrosis, podocyte injury, proteinuria, and chronic kidney disease (CKD)-related vascular injury. While inhibition of the Wnt/β-catenin pathway by sclerostin inhibits osteoblast differentiation and proliferation, the effects of this inhibition on VC development and its renal effects are still complex[3,4].

Soluble TNF-related weak inducer of apoptosis (sTWEAK) is a proinflammatory cytokine belonging to the TNF ligand superfamily that may cause glomerular and tubular injury[5]. It regulates pathways with potential pathophysiological implications for kidney injury, such as the induction of inflammatory cytokines[5]. sTWEAK also increases the expression of sclerostin[6]. Fibroblast growth factor inducible-14 (Fn14) is a TWEAK receptor, and its expression is induced secondary to inflammatory events. Activating the Fn14 receptor by TWEAK contributes to glomerular and tubulointerstitial injury[7].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 07, 2023. Accepted on April 28, 2023.

Pulse wave velocity (PWV) is the gold standard for measuring arterial stiffness. Recently, the relationship between sclerostin and PWV has been investigated in different patient groups, but this relationship has not been revealed in GN patients[8,9]. This relationship becomes more intriguing as new information emerges regarding the roles of TWEAK and sclerostin in the VC process.

TWEAK and its associated receptors are involved in pathogenetic processes that affect overall and renal survival in GN patients through inflammatory and non-inflammatory pathways. Both the renal and vascular effects of sclerostin become evident day by day. Anti-sclerostin treatments have become popular in recent years. Based on these ideas, we aimed to detect serum TWEAK and sclerostin levels in GN patients and their relationship with outcomes that may affect the prognosis of the disease.

METHODS

This cross-sectional study includes 63 GN patients and 30 healthy matched controls. The study protocol was approved by our institution. Informed consent was obtained from all subjects. A review of medical records (including information on age, sex, weight, medications, and duration of the disease) was recorded from hospital system.

Inclusion criteria were as follows: (1) patients diagnosed with GN confirmed by kidney biopsy; (2) patients who aged 18–70 years; and (3) patients who gave written informed consent. Exclusion criteria were as follows: (1) patients who have other diseases, including diabetes mellitus, osteoporosis, malignities, and active infectious diseases; (2) patients with estimated glomerular filtration rate (e-GFR) below 60 mL/min; (3) patients who do not feel willing to participate in the study; (4) patients who have parathyroidectomy; (5) patients with a history of CVD in the past 3 months; (6) post-menopausal women; (7) patients who have received immunosuppressive therapy for any disease; and (8) presence of emergency medical (such as respiratory failure due to interstitial disease) status.

Diagnosis of glomerulonephritis

Patients who were previously diagnosed with GN by kidney biopsy and had no history of GN treatment were included in the study. The distribution of GN patients included in the study was as follows: membranous nephropathy (n=23, 37%), IgA nephritis (n=17, 27%), lupus nephritis (n=16, 25%), and pauci-immune GN (n=7, 11%).

24-h urine proteinuria measurements

Samples for 24-h urinary protein excretion were collected before renal biopsy. Total protein concentration levels were measured by a turbidometric assay using benzethonium chloride. The results were expressed as mg/day.

Serum TNF-related weak inducer of apoptosis measurements

Serum sTWEAK levels were measured by a commercially available kit based on an enzyme-linked immunosorbent assay (eBiosience, Human sTWEAK Instant Elisa, Cat No.: BMS2006INST). The results were expressed as pg/mL. The calculated overall intra-assay coefficient of variation was 7.8%.

Serum sclerostin measurements

Concentrations of human sclerostin were measured with enzyme-linked immunosorbent assay (ELISA) kits (Biomedical Medizinprodukte GmbH & Co. KG, Vienna, Austria) according to the manufacturer's instructions. Intra- and inter-assay coefficients of variation were 5 and 4%, respectively, for sclerostin. The results were expressed as pg/mL.

Pulse wave velocity measurements

The Arterio Vision device (OSACHI Co. Ltd.) simultaneously measured brachial-ankle pulse wave velocity (baPWV; units: m/s) on each side of the body, arterial stiffness index (units: arbitrary) in each limb, and blood pressure and heart rate in each limb. Measurements were made in duplicate, separated by 1 min. If the second blood pressure value was >5 mmHg to the first measurement, a third measure was collected, and the closest two measures were averaged. The baPWV was calculated by dividing the arterial path length by the pulse transit time between the brachial and ankle arterial segments.

Statistical analyses

Clinical data were analyzed using Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics for each variable were determined. Data were expressed as mean±standard deviation. Results for continuous variables without normal distribution were presented as median [interquartile range (IQR)]. A statistically significant difference between the groups was determined by the χ^2 test for categorical variables. Nonparametric statistics (Mann-Whitney U test) and parametric statistics (independent sample t-test) were all used for continuous variables. Associations between the variables were explored using Spearman's rho test. A linear regression analysis was also performed to define variables associated with proteinuria. A statistically significant difference was considered when $p \leq 0.05$.

RESULTS

Demographic, clinical characteristics, and biochemical parameters of 63 patients with GN and 30 healthy subjects are depicted in Table 1. The control group had significantly lower serum urea and uric acid levels, while serum albumin levels were significantly higher in this group. When 24-h proteinuria levels were compared, the median proteinuria level was higher in the GN group as expected (GN: 752 (1401) mg/day; control group: 72 (73) mg/day (p=0.008)) (Table 1).

Serum sclerostin and soluble TNF-related weak inducer of apoptosis levels

The median sTWEAK level of the GN group was 77.95 (7.3) pg/mL, and the control group was 57.02 (1.94) pg/mL, and the difference was statistically significant (p=0.001). Serum sclerostin was higher in the GN group [2322.92 (1857.11) pg/mL vs. 470.21 (685.65) pg/mL (p=0.003), respectively].

Factors associated with proteinuria in patients with glomerulonephritis

Factors associated with proteinuria were evaluated in patients with GN. There was a positive correlation between proteinuria and sTWEAK (r_s=0.409; p=0.021), sclerostin (r_s=0.426; p=0.013), and PWV (r_s=0.342; p=0.007) (Table 2).

Evaluation of arterial stiffness in patients with glomerulonephritis

The effect of inflammatory markers on arterial stiffness in GN patients was investigated. Brachial PWV was used for arterial stiffness measurement. PWV was significantly higher in GN patients compared to healthy controls (7.71±1.45 vs. 8.57±1.75; p=0.043). Both sTWEAK and serum sclerostin levels were correlated with PWV. The correlation with both sTWEAK (r_s=0.260, p=0.043) and sclerostin was statistically significant (r_s=0.310, p=0.015, respectively).

Table 1. Demographic, clinical characteristics, and biochemical parameters of patients with glomerulonephritis and healthy subjects.

Parameters	Healthy subjects (n=30) Mean±SD or Median (IQR)	Patients with glomerulonephritis (n=63) Mean±SD or Median (IQR)	p-value
Age (years)	38.8±9.22	43.59±13.92	0.231
Female/male	15/15	29/34	0.828
Glucose (mg/dL)	94.5±13.15	94.79±17.53	0.996
Urea (mg/dL)	28 (10.3)	38 (44.3)	**0.048**
Serum creatinine (mg/dL)	0.83 (0.17)	0.92 (0.11)	0.235
e-GFR (mL/min)	97.88 (22.21)	89.63 (17.92)	0.352
White blood count	7.87±1.47	8.26±2.65	0.651
Hemoglobin (g/dL)	13.87±1.92	12.94±2.24	0.223
Platelet count (10^3/μL)	266.9±56.68	290.46±115.12	0.317
Uric acid (mg/dL)	4.82±1.28	6.39±1.68	**0.009**
Albumin (g/L)	4.5±0.49	4.09±0.56	**0.037**
ALT (U/L)	18 (10.3)	14.5 (9.3)	0.507
Calcium (mg/dL)	9.45 (0.63)	9.25 (0.82)	0.481
Phosphorus (mg/dL)	3.65±05	3.79±0.94	0.641
24-h proteinuria (mg/day)	72 (73)	752 (1401)	**0.008**
CRP (mg/L)	2.4 (5.15)	2.1 (6.03)	0.284
PWV (m/s)	7.71±1.45	8.57±1.75	**0.043**
sTWEAK (pg/mL)	57.02 (1.94)	77.95 (7.3)	**0.001**
Sclerostin (pg/mL)	470.21 (685.65)	2322.92 (1857.11)	**0.003**

E-GFR: estimated glomerular filtration rate; CRP: C-reactive protein; ALT: alanine aminotransferase; PWV: pulse wave velocity. Bold values indicate statistical significance at the p<0.05 level.

Predictors of proteinuria in patients with glomurlonephritis

In patients with GN, traditional and correlated factors were included in the regression model to determine independent predictors of proteinuria. sTWEAK and sclerostin were identified as independent predictors of proteinuria (Table 3).

DISCUSSION

In this study, we found three essential conclusions in GN patients. First, serum sclerostin and sTWEAK were higher in GN patients than in the healthy group. Second, proteinuria was correlated with serum sclerostin, sTWEAK, and arterial stiffness. Another significant result was that serum sclerostin and sTWEAK were independent predictors of proteinuria. This is the first study that shows the correlation of serum sclerostin and sTWEAK with the PWV in GN patients.

Especially below GFR 60 mL/min, as kidney function declines, serum sclerostin increases[10]. As GFR decreases, urinary sclerostin excretion increases. This indicates increased serum sclerostin in CKD is due to increased osteocyte-mediated production rather than reduced urinary excretion[11]. In our study, although e-GFR was similar between the two groups, the serum sclerostin levels were higher in GN group. Apart from decreased GFR and increased uremia in patients with GN, additional factors arising from the primary disease may increase sclerostin or cause insufficient suppression of sclerostin levels. sTWEAK contributes to kidney inflammation by promoting the production of cytokines in kidney cells, and as a result, kidney injury is increased[7]. TWEAK is also an essential inducer of sclerostin[6]. Studies investigating serum sclerostin and sTWEAK levels in patients with GN are insufficient. A few studies have shown that sclerostin and sTWEAK levels increase in GN patients[12-14]. These markers have been shown to correlate with the severity of renal involvement in patients with lupus and IgA nephritis. TWEAK induces a local inflammatory environment and plays a crucial pathogenic role in developing GN[5]. Therefore, high serum sclerostin and sTWEAK in our GN patient group are expected depending on the underlying inflammatory response. But, the overexpression of Fn14, which is a TWEAK receptor, has also been shown in immune and non-immune glomerulopathies. This suggests that the role of TWEAK in the mechanism of kidney injury is not through immune effects alone[7]. Our study is valuable because it is the first to show that both sclerostin and TWEAK increase together in GN patients.

We found that, in GN patients, serum sclerostin and sTWEAK were correlated with proteinuria, and these markers were independent predictors of proteinuria. Increased Wnt expression causes proteinuria secondary to podocyte injury[15]. WNT activity increases rapidly in the early stages of proteinuria and tubular injury and decreases as the injury progresses. In addition, the development of apoptosis in renal cells following decreased WNT activity suggests that the WNT pathway has protective effects on renal cells[16,17]. However, if the activity in this pathway persists, it causes cellular injury[17]. The Wnt-β-catenin pathway can be considered both a cause and a result of increased proteinuria. It is a pathway that should be considered as a treatment target

Table 2. Bivariate correlations between 24-h proteinuria and other parameters in glomerulonephritis patients.

Parameters	r_s	p-value
sTWEAK (pg/mL)	0.409	**0.021**
Sclerostin (pg/mL)	0.426	**0.013**
PWV (m/s)	0.342	**0.007**

PWV: pulse wave velocity. Bold values indicate statistical significance at the p<0.05 level.

Table 3. Independent variable of proteinuria in glomerulonephritis patients.

Parameters	Standardized beta	t	p-value	95%CI
Step 1				
BMI (kg/m²)	0.057	0.420	0.677	-48.09 to 73.35
Creatinine (mg/dL)	-0.027	-0.209	0.835	-183.03 to 148.64
CRP (mg/L)	-0.082	-0.568	0.573	-10.24 to 5.74
PWV (m/s)	0.026	0.184	0.855	-163.56 to 196.41
sTWEAK (pg/mL)	0.429	3.185	0.003	5.341–23.84
Sclerostin (pg/mL)	0.3	2.266	0.029	0.048–0.82
Step 5				
sTWEAK (pg/mL)	0.424	3.435	**0.001**	5.97–22.9
Sclerostin (pg/mL)	0.307	2.483	**0.017**	0.085–0.811

BMI: body mass index; CRP: C-reactive protein; PWV: pulse wave velocity; CI: confidence interval. Bold values indicate statistical significance at the p<0.05 level.

in patients with proteinuria in the future since its long-term activation facilitates the progression to renal fibrosis[18]. In GN patients, increased TWEAK levels may cause an increase in sclerostin and proteinuria. Urinary sclerostin excretion was increased due to increased serum sclerostin, and proteinuria was correlated with urinary sclerostin excretion[11,19]. Although increased urinary sclerostin excretion contributes little to total proteinuria, this is one of the mechanisms that can explain the correlation between serum sclerostin levels and proteinuria in GN patients. Our study found that both serum sclerostin and sTWEAK levels were correlated with proteinuria in GN patients.

This is the first study to show the correlation of serum sclerostin and sTWEAK levels with PWV in GN patients. Recently, it has been shown that sclerostin is associated with arterial stiffness in different patient groups[8,9,20-22], but it is still unclear whether the role of sclerostin in VC development is to increase or inhibit VC[20,21]. Due to the similarities between osteogenesis and VC, the Wnt-β-catenin pathway may also play an important role at this point[23]. Moreover, increased Wnt signaling activity and sclerostin expression during calcification of vascular smooth muscle cells draw attention to the role of this pathway in increased VC. However, some studies still claim that sclerostin preserves vascular smooth muscle integrity. Also, TWEAK promotes angiogenesis by increasing the proliferation and migration of endothelial cells[24]. As can be seen, the relationship between sclerostin TWEAK and VC is still a subject with many unknowns. In our study, both TWEAK and sclerostin are related to PWV in GN patients and draw attention to the possible roles of these molecules in the increased CVD risk in GN patients.

Our study has some limitations. First, our patient group was insufficient to perform subgroup analysis for each GN subtype. This limitation prevents us from direct propositions about a specific GN type. Second, the fact that the entire patient is Turkish makes our results not be applicable to all patients due to the differences between nationalities.

CONCLUSION

This is the first study showing that serum sclerostin and sTWEAK levels are increased together in GN patients, and it also demonstrated for the first time that these two markers were correlated with arterial stiffness and proteinuria in GN patients. Considering the effects of sclerostin and TWEAK in patients with GN, we think our study will guide the development of new treatment strategies.

AUTHORS' CONTRIBUTIONS

HO: Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **İB:** Conceptualization, Data curation, Formal Analysis, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **TA:** Conceptualization, Data curation, Investigation, Resources, Visualization. **MAD:** Data curation, Investigation, Resources, Visualization. **FHYA:** Formal Analysis, Methodology, Validation. **KT:** Formal Analysis, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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