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## Plasma sTWEAK levels in chronic kidney disease stages

*Niveles plasmáticos de sTWEAK en estadios de enfermedad renal crónica*

Mahmut Gok<sup>1</sup>, Hakkı Cetinkaya<sup>1</sup>, Yusuf Oguz<sup>2</sup>

### ABSTRACT

**Objective:** Soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) is a cytokine of the TNF superfamily that has a role in injury of different organs including kidney. We hypothesized that in patients with chronic kidney disease (CKD), sTWEAK levels may be related to endothelial dysfunction that usually accompanies the decline of estimated glomerular filtration rate (eGFR). **Methods:** In 199 patients with different stages of CKD we examined the relationship between sTWEAK plasma levels and CKD stages and the relationship between high sensitivity C reactive protein (hs-CRP), homeostatic model assessment of insulin resistance (HOMA-IR) and sTWEAK concentrations. **Results:** A gradual decrease in sTWEAK was observed as eGFR decreased. sTWEAK plasma levels were diminished in all stages of CKD and strongly correlated with eGFR. A negative correlation was found between sTWEAK and hs-CRP ( $p < 0.001$ ) and while a positive correlation was found between sTWEAK and eGFR ( $p < 0.001$ ). No significant correlation was found between sTWEAK and HOMA-IR. In multivariate regression eGFR, diabetes mellitus and hs-CRP parameters were found to be significant independent variables in decreasing plasma sTWEAK levels. **Conclusion:** Diminishing of eGFR is accompanied by gradual decreases in sTWEAK plasma

levels. Since sTWEAK is strongly and independently correlated with CRP, our study reveals new connections between sTWEAK and endothelial dysfunction in patients with CKD.

**KEYWORDS:** chronic kidney disease; sTWEAK; endothelium; C reactive protein

### RESUMEN

**Introducción:** El inductor débil de apoptosis (sTWEAK) de necrosis tumoral soluble es una citoquina de la superfamilia TNF que tiene un papel en la lesión de diferentes órganos, incluido el riñón. Se planteó la hipótesis de que en pacientes con enfermedad renal crónica (ERC), los niveles de sTWEAK pueden estar relacionados con la disfunción endotelial que generalmente acompaña a la disminución de la tasa de filtración glomerular estimada (TFGe). **Material y métodos:** En 199 pacientes con diferentes estadios de ERC, se examinó la relación entre los niveles plasmáticos de sTWEAK y los estadios de ERC y la relación entre la proteína reactiva C de alta sensibilidad (hs-CRP), la evaluación del modelo homeostático de resistencia a la insulina (HOMA-IR) y las concentraciones de sTWEAK. **Resultados:** Se observó una disminución gradual en sTWEAK a medida que disminuyó la TFGe. Los niveles plasmáticos de sTWEAK disminuyeron en todas las etapas de la ERC y se correlacionaron

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fuertemente con la TFG<sub>e</sub>. Se encontró una correlación negativa entre sTWEAK y hs-CRP ( $p < 0,001$ ) y mientras que se encontró una correlación positiva entre sTWEAK y eGFR ( $p < 0,001$ ). No se encontró correlación significativa entre sTWEAK y HOMA-IR. En la TFG<sub>e</sub> de regresión multivariada, se encontró que los parámetros de diabetes mellitus y PCR-hs eran variables independientes significativas en la disminución de los niveles plasmáticos de sTWEAK. **Conclusión:** La disminución de la TFG<sub>e</sub> se acompaña de disminuciones graduales en los niveles plasmáticos sTWEAK. Dado que sTWEAK se correlaciona fuerte e independientemente con la PCR, nuestro estudio revela nuevas conexiones entre sTWEAK y la disfunción endotelial en pacientes con ERC.

**PALABRAS CLAVE:** enfermedad renal crónica; sTWEAK; endotelio; proteína C-reactiva

## INTRODUCTION

Cardiovascular diseases (CVD) are the most common cause of morbidity and mortality in all stages of chronic kidney disease (CKD).<sup>(1)</sup> Although CVD risk factors are excluded, CVD-related mortality is 10-20 times higher in people with CKD.<sup>(2)</sup> Endothelial dysfunction (ED) due to uremia has an important role in the development of CVD in the process of CKD.

ED has a high prevalence in moderate to severe CKD and is associated with an increased cardiovascular risk.<sup>(3-4)</sup> ED etiopathogenesis involves dysregulation of many complex pathways. Soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) is a molecule that is thought to be effective in atherosclerosis, endothelial dysfunction and mortality.<sup>(5)</sup> Also, low sTWEAK levels have been found associated with the presence of carotid atherosclerotic plaques in patients with CKD and a higher risk of cardiovascular morbidity and mortality.<sup>(6)</sup> Therefore, it was suggested that sTWEAK would be a good target for therapeutic intervention in renal and vascular injury.<sup>(7)</sup> In recent years, confirming studies have been done consecutively.

High sensitivity C reactive protein (hs-

CRP) is the most used marker to evaluate inflammation. As the close relationship between CRP levels and morbidity and mortality in CKD has been shown in numerous studies, it is accepted as an important cardiovascular risk factor.<sup>(8-9)</sup>

The aim of this study is to investigate the factors affecting ED in patients with CKD in various steps according to the glomerular filtration rate. It is aimed to determine the level of sTWEAK, which is thought to play a role in the pathogenesis of endothelial dysfunction in patients with CKD, according to CKD stages and to determine its interaction with previously known CVD risk factors.

## MATERIAL and METHODS

### Patients

This study was conducted cross-sectionally in CKD patients who applied to our Nephrology clinic. Patients diagnosed with CKD according to the NKF Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)<sup>™</sup> were included in the study.<sup>(10)</sup> Patients diagnosed with active glomerulonephritis, tubulointerstitial nephritis, heart failure, hepatic disease and patients who received immunosuppressive or cytotoxic drug therapy and renin-angiotensin blocker were excluded from the study. Patients included in the study were subdivided according to glomerular filtration rate (GFR) which is calculated according to the MDRD formula. When determining groups, those with similar body mass index (BMI), age, gender, lipid parameters and blood pressures were included. Subgroups were determined as the following: stage 1 with normal or high GFR (GFR  $>90$  mL/min/1.73m<sup>2</sup>); stage 2 Mild CKD (GFR =60-89 mL/min/1.73m<sup>2</sup>), stage 3 Moderate CKD (GFR =30-59 mL/min/1.73m<sup>2</sup>); stage 4 Severe CKD (GFR =15-29 mL/min/1.73m<sup>2</sup>); stage 5 End Stage CKD (GFR  $<15$  mL/min/1.73m<sup>2</sup>)

The connections between the CKD stages and the following parameters were examined: proteinuria (mg/day), SBP (mmHg), DBP (mmHg), plasma insulin (IU/mL), plasma glucose (mg/dL), HOMA-IR, total cholesterol (mg/dL), serum triglyceride (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), hemoglobin (g/dL), hematocrit (%), serum

albumin (g/dL), uric acid (mg/dL), calcium (mg/dL), phosphorus (mg/dl), parathormone (pg/mL), hs-CRP (mg/L), sTWEAK (pg/mL).

### Laboratory evaluations

Insulin resistance score was calculated with HOMA-IR.

All blood samples were collected after 12 hours of fasting and all samples were stored at - 80 °C. After the completion of the samples, the levels of plasma TWEAK (sTWEAK) were determined in duplicate with commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN), following the manufacturer's protocol. TWEAK assays were performed blindly, without knowledge of the patients' disease status or activity.

### Statistical analysis

The 'one sample Kolmogorow Smirnow' test was used to determine the distribution properties of the variables. Differences in determining the significance between groups of chronic kidney

disease stages were appropriately tested with One Way Analysis of Variance (ANOVA). The correlation of variables with each other was investigated with the 'Pearson' test. The 'stepwise linear regression' method was used for multivariate analyzes,  $p < 0.05$  was considered statistically significant.

### RESULTS

There was no significant difference between patient groups according to age, gender, body mass index, diabetes mellitus (DM), smoking and hypertension parameters.

According to the stages of CKD, GFR ( $p < 0.001$ ), proteinuria ( $p = 0.007$ ), hemoglobin ( $p = 0.018$ ), hematocrit ( $p = 0.005$ ), albumin ( $p < 0.001$ ), uric acid ( $p < 0.001$ ), calcium ( $p < 0.001$ ), phosphorus ( $p < 0.001$ ), parathormone ( $p < 0.001$ ), hs-CRP ( $p < 0.001$ ) and sTWEAK ( $p < 0.001$ ) levels were significantly different. There was no significant difference in systolic and diastolic blood pressure, lipid parameters, HOMA-IR, glucose, and insulin parameters. (Table 1)

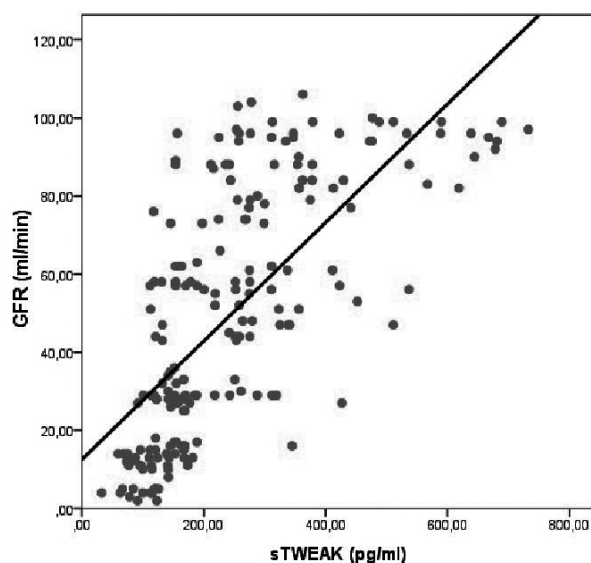
**Table 1** Laboratory and clinical parameters according to CKD stages

Parameters	Stage I (n=33)	Stage II (n=42)	Stage III (n=46)	Stage IV (n=39)	Stage V (n=39)	P
GFR (ml/min/1.73 m <sup>2</sup> )	96.5 ± 3.5	77.5 ± 9.4	48 ± 9.1	24 ± 5.8	8.9 ± 4.2	<0.001
Proteinuria (mg/day)	1393.9 ± 489.7	1749.2 ± 771.5	1946.6 ± 933.7	1889.8 ± 1034	2215.6 ± 1265.9	0.007
SBP (mmHg)	133.5 ± 7.6	138.1 ± 11.1	133.9 ± 8.8	133.9 ± 12.1	137.1 ± 12.2	0.171
DBP (mmHg)	82.6 ± 4.4	84 ± 3.7	85.3 ± 4.2	84.9 ± 5.5	84.2 ± 4.3	0.102
Plasma Insulin (IU/ml)	6.9 ± 1.4	6.7 ± 1.3	7.4 ± 1.6	7 ± 1.6	7.6 ± 1.7	0.092
Plasma glucose (mg/dl)	96.7 ± 27.7	104.1 ± 35.8	102.7 ± 40	108.7 ± 42.9	93.9 ± 17.5	0.344
HOMA-IR	1.7 ± 0.7	1.7 ± 0.7	1.9 ± 1.1	1.9 ± 0.8	1.8 ± 0.6	0.724
Total cholesterol (mg/dl)	204.2 ± 16.4	207.3 ± 16.9	206.7 ± 20	203.2 ± 20	197.1 ± 18.4	0.107
Serum triglyceride (mg/dl)	148.2 ± 14.3	151.1 ± 11.3	151.1 ± 15.2	150.8 ± 13.7	143.4 ± 21.4	0.123
LDL cholesterol (mg/dl)	127.8 ± 16.7	130 ± 14.1	127.5 ± 14.8	130.7 ± 14.2	124.5 ± 22.8	0.494
HDL cholesterol (mg/dl)	43.3 ± 4.6	43.1 ± 5.3	41.2 ± 5.6	42 ± 7	43.5 ± 7.1	0.328
Hemoglobin (g/dl)	12 ± 2.1	11.9 ± 2.3	11.5 ± 1.9	11.1 ± 2.2	10.5 ± 2.1	0.018
Hematocrit (%)	36.3 ± 5.9	36.5 ± 6.3	34.6 ± 5.7	33.8 ± 5.5	32.1 ± 5.4	0.005
Serum albumin (g/dl)	4 ± 0.3	3.9 ± 0.4	4.2 ± 0.4	4 ± 0.3	3.8 ± 0.3	<0.001
Uric acid (mg/dl)	4.4 ± 0.9	4.7 ± 1.3	6.9 ± 1	7.4 ± 1.1	7.8 ± 1.1	<0.001
Calcium (mg/dl)	8.9 ± 0.4	8.7 ± 0.6	8.3 ± 0.5	8.1 ± 0.4	8 ± 0.3	<0.001
Phosphorus (mg/dl)	4.2 ± 0.5	4.4 ± 0.8	4.6 ± 0.7	5.9 ± 1.4	6.9 ± 1.6	<0.001
Parathormone (pg/ml)	50.9 ± 12.8	70.6 ± 31.2	154.3 ± 46.1	172.5 ± 35.7	256.2 ± 38.9	<0.001
HsCRP (mg/l)	9.2 ± 2.4	12.2 ± 2.1	17.3 ± 4.7	19.1 ± 8.4	31.2 ± 11.9	<0.001
sTWEAK (pg/ml)	438.6 ± 163.4	297.1 ± 115.6	237.9 ± 103.9	176.1 ± 72.4	110.3 ± 34.9	<0.001

**GFR:** glomerular filtration rate; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **HOMA-IR:** homeostasis model assessment - insulin resistance; **hs-CRP:** high sensitivity C reactive protein; **sTWEAK:** soluble tumor necrosis factor-like weak inducer of apoptosis

Correlation analysis was made between the parameters obtained from the patients and plasma sTWEAK levels. sTWEAK levels were found to have a negative correlation with proteinuria ( $p=0.003$ ), uric acid ( $p<0.001$ ), phosphorus ( $p<0.001$ ) and parathormone ( $p<0.001$ ). Albumin ( $p=0.038$ ) and calcium ( $p<0.001$ ) levels and sTWEAK levels showed positive correlation. Correlation analysis with sTWEAK showed no significant correlation between age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin, hematocrit, lipid parameters, glucose, insulin, and HOMA-IR. A positive correlation was found between the decrease in GFR level and plasma sTWEAK level, ( $p<0.001$ ). (**Figure 1**)

**Figure 1.** Correlation between GFR and plasma sTWEAK level



**GFR:** glomerular filtration rate; **sTWEAK:** soluble tumor necrosis factor-like weak inducer of apoptosis

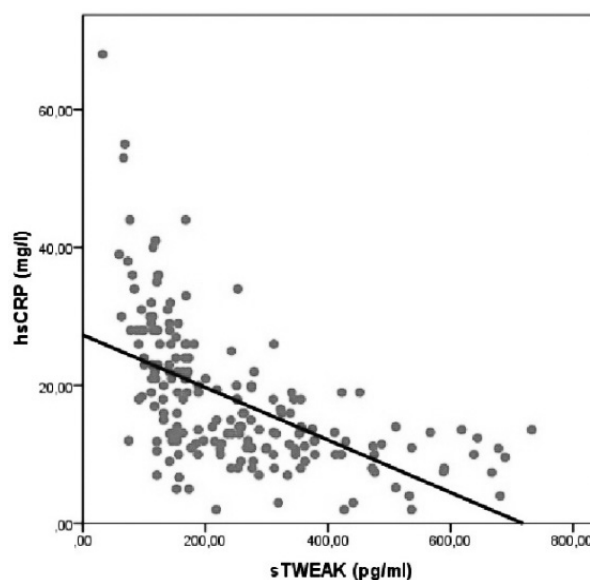
The level of hs-CRP, which is a marker of inflammation, has been shown to increase statistically with the progression of kidney disease since the early stages of CKD. A negative correlation was found between GFR and hs-CRP. ( $p<0.001$ )

A negative correlation was found between hs-CRP level and plasma sTWEAK level, ( $p<0.001$ ). (**Figure 2**)

As a result of the multivariate regression

analysis, plasma sTWEAK level decreased; significant results were found in GFR ( $p<0.001$ ), DM ( $p=0.004$ ), male gender ( $p=0.02$ ) and hs-CRP ( $p=0.003$ ). Parameters of age, SBP, DBP, LDL cholesterol, serum calcium, serum phosphorus, serum parathormone, serum albumin, and proteinuria did not make a significant change on plasma sTWEAK level.

**Figure 2.** HsCRP correlation with plasma sTWEAK levels



**hs-CRP:** high sensitivity C reactive protein; **sTWEAK:** soluble tumor necrosis factor-like weak inducer of apoptosis

## DISCUSSION

In this cross-sectional study we conducted, we evaluated the relationship between sTWEAK levels and factors involved in the etiology of CKD and various parameters of patients in all CKD stages. We found a decrease in sTWEAK levels with GFR reduction compared to CKD stages.

In the study of Kralisch *et al.* in diabetic and end-stage renal failure patients, sTWEAK levels were found to be significantly decreased compared to the control group, and it was stated that this molecule may be a marker of atherosclerosis.<sup>(11)</sup> In the 24-month follow-up of patients with CKD in terms of atheromatous progression, it was found that sTWEAK levels decreased more in patients with progression.<sup>(12)</sup> Similarly, in the study of Yilmaz *et al.*, 295 non-diabetic patients with chronic renal

failure at different stages were examined and the relationship between TWEAK level and endothelial dysfunction was investigated. As a result; it was found that as the CKD stage increases, TWEAK levels decrease and endothelial dysfunction increases which is claiming TWEAK as an independent predictor of endothelial dysfunction.<sup>(5)</sup> Although the mechanism is not clear, it has been suggested that the expression of TWEAK receptor Fn14 increases in pathological processes, and thus the levels of serum TWEAK may decrease.<sup>(13)</sup>

In our study, a negative correlation was found between sTWEAK, which is thought to be a proinflammatory cytokine and hs-CRP. As GFR decreased, hs-CRP levels increased. On the contrary, in the study of Carrero *et al.*, it was observed that increased TWEAK levels and inflammatory markers (CRP, IL-6) in 208 hemodialysis patients contributed to mortality. In this study sTWEAK levels were lower in hemodialysis patients as compared to healthy controls confirming other studies, however, within the hemodialysis patients' range, higher sTWEAK was associated with a shorter time to death and high sTWEAK were associated with increased mortality.<sup>(14)</sup>

sTWEAK is known to stimulate the release of MKP-1 in human smooth muscle cell culture. It is also known that TWEAK is released from macrophages in the atherosclerotic plaque in humans. Blanco-Colio *et al.* compared thirty consecutive patients with carotid stenosis >70%, with 28 healthy volunteers, and found that plasma TWEAK levels showed a reduced concentration in subjects with carotid stenosis compared with healthy subjects. Furthermore, in a test population of 106 asymptomatic subjects, they showed that sTWEAK concentrations negatively correlated with the carotid intima-media thickness which is an index of subclinical atherosclerosis.<sup>(15)</sup> In this study, surprisingly, no relationship was found between other inflammatory markers (CRP, Fibrinogen) and sTWEAK levels. In the study of Xiaosong *et al.*, the relationship between the healthy group and peritoneal and hemodialysis patients with carotid intima-media thickness and TWEAK was evaluated. There was no significant difference in TWEAK levels between peritoneal dialysis patients and hemodialysis

patients, and it was found to be lower in both than the control group. The carotid intima-media thickness and acute inflammation parameters were negatively correlated with TWEAK levels.<sup>(16)</sup> It is well known that TWEAK increases proinflammatory activity. However, it is recently argued that TWEAK can play a protective role against excessive inflammation. In inflammatory conditions, TWEAK levels have been claimed to decrease protectively, and it has been suggested that expression and release may decrease in atherosclerotic conditions.

In our study, correlation with chronic kidney disease progression and sTWEAK level was found to be positively correlated with serum calcium, while it was negatively correlated with serum phosphorus and parathormone levels. These findings suggest that TWEAK levels correlate with secondary hyperparathyroidism, which is known to occur in further CKD stages. Secondary hyperparathyroidism is known to cause the development of vascular calcification. Henaut *et al.* demonstrated its pro-calcific activity and showed that it may cause cardiovascular mortality by causing an increase in calcification in atheroma plaques.<sup>(17)</sup> It can be thought that the increase in cardiovascular mortality caused by secondary hyperparathyroidism may have caused TWEAK with this efficacy.

As another result of our study, uric acid and sTWEAK levels were found to be negative correlated. It is well known that uric acid metabolism is impaired by chronic kidney disease progression. Lowering serum uric acid levels slows CKD progression by reducing endothelial dysfunction and inflammation. The negative correlation with uric acid level also suggests that sTWEAK levels can be used as a marker to reflect endothelial dysfunction.

Since our study was performed cross-sectionally in patients with CKD, sTWEAK levels could not be evaluated on CVD development and mortality, and no other method to detect endothelial dysfunction has been studied. This is the most obvious limitation of our study.

As a result, we found that plasma sTWEAK levels decreased with GFR decrease. In multiple regression analyzes, GFR, DM and

hs-CRP were the parameters affecting plasma sTWEAK levels in CKD. So, prospective studies are needed to evaluate sTWEAK on progression and mortality in CKD.

## CONCLUSION

We show that plasma TWEAK levels are associated with inflammation and CKD progression, so this relationship might be thought associated with endothelial dysfunction. Therefore, larger prospective studies are needed to properly evaluate CKD progression, endothelial dysfunction, and values of plasma TWEAK in this population.

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