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THE RELATIONSHIP BETWEEN SOLUBLE TUMOR NECROSIS FACTOR-LIKE WEAK INDUCER OF APOPTOSIS LEVELS AND CARDIAC FUNCTIONS IN PERITONEAL DIALYSIS PATIENTS

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Tumor necrosis factor (TNF)-like weak inducer of apoptosis (sTWEAK) levels has been reported to be decreased in patients on hemodialysis (HD) and patients with heart failure. We aimed to study the relationship between sTWEAK levels and cardiac functions in peritoneal dialysis (PD) patients. This cross-sectional study was carried out on patients on chronic PD programs for more than three months. Patients aged under 18 or over 80 years, patients with overt cardiac disease, overt hypervolemia, active systemic infection, malignancy, peritonitis within the last month were excluded. The patient group was compared with the control group including healthy adults aged 24-61 years. Fifty-two PD patients were included in the study (mean age: 52.7±15.4 years; female/male ratio: 30/22). The corresponding data of the control group were 41.3±10.7 years and 17/14. There was no statistically significant difference between demographic parameters of the groups except age. The mean sTWEAK level of the patient and the control groups were similar (564±17 pcg/ml *vs* 535±126 pcg/ml, p=0.419). No correlation was detected between any of the demographic variables and sTWEAK levels. Among the echocardiographic parameters, only ejection fraction was found to be correlated negatively with sTWEAK levels. Patients with ischemic heart disease (IHD) and heart failure had significantly higher sTWEAK levels compared with the patients without these diseases. With linear regression analysis, only age and the presence of heart failure were found to be the independent determinants of sTWEAK levels. Level of sTWEAK is significantly high in PD patients with heart failure and IHD. sTWEAK may be a marker of cardiac functions in PD patients.

Cardiovascular disease (CVD) is the major cause of mortality in patients with chronic kidney disease (CKD) (1, 2). Uremia aggravates chronic inflammation (3) and causes a propensity for both traditional and non-traditional risk factors for CVD leading to accelerated atherosclerosis (1, 2, 4). Early detection of patients at risk has prime importance for proper management of them.

Tumor necrosis factor (TNF)-like weak inducer of apoptosis (sTWEAK), a member of the TNF

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superfamily, is structurally similar to a cytokine and causes programmed cell death (5). The binding of sTWEAK to Fn14 (6) causes many biological effects, such as cellular growth and proliferation (7, 8), osteoclastogenesis (9), angiogenesis (10), inflammatory microenvironment and programmed cell death (11). Nuclear factor kappa B (NF-κB) activates the signal pathway and promotes activation of various proinflammatory cytokines and cellular adhesion molecules (12). sTWEAK levels have been reported to be decreased in patients on hemodialysis (HD) or those with carotid atherosclerosis (13). Studies have shown that sTWEAK and Fn14 are expressed in human carotid atherosclerotic plaques, and that sTWEAK has important roles in the inflammatory process associated with kidney injury (14), therefore sTWEAK has been claimed to be a new biomarker for CVD. A recently published study showed that peritoneal fluid sTWEAK level is elevated in case of peritonitis, and is correlated with inflammation and fibrosis in the peritoneal membrane (15).

Different effects of sTWEAK on CVD have been proposed (16). Patients with heart failure were detected to have lower sTWEAK levels than the control subjects. Moreover, the level decreased in concordance with the increasing level of heart failure graded according to the New York Heart Association (NYHA) classification system (17).

The relationship between sTWEAK and cardiovascular parameters has not been studied in patients on HD or peritoneal dialysis (PD). We aimed to study the relation between sTWEAK levels and cardiac functions in PD patients.

MATERIALS AND METHODS

This is a cross-sectional study carried out on patients on chronic PD programs. Patients aged under 18 or over 80 years, those with dialysis duration less than three months, patients with overt cardiac disease (New York Heart Association-NYHA- class 3 and 4 heart failure, valvular disease, dysrhythmias like atrial fibrillation), active systemic infection, malignancy, history of peritonitis within the last month, and those with overt hypervolemia were excluded from the study. The patient group was compared with the control group including healthy adults aged 24-61 years. All of the participants provided informed consent. The study was approved by the local ethics committee.

The demographic parameters [age, gender, weight, height, body mass index (BMI)], primary kidney diseases, comorbidities, the duration of CKD and PD treatment, and the medications used by the patients were recorded. Patients were recorded to have ischemic heart disease (IHD) if they had strong evidence by exercise electrocardiography and scintigraphic methods or had vascular lesions documented angiographically. Heart failure was recorded to be present if there were consistent symptoms, physical and echocardiographic finding, and was graded according to the NYHA classification.

Systolic and diastolic blood pressures (BP) measured at optimal conditions and on both arms were recorded. Mean BP was calculated with the following formula: Mean BP: [(Diastolic BPx2) + Systolic BP]/3.

Laboratory analysis: serum and plasma samples obtained after 12 h of fasting were kept at -80°C until the time of analysis. Serum glucose, urea, creatinin, uric acid, sodium, potassium, calcium, phosphorus, parathyroid hormone, total protein, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, alanine transaminase, aspartate transaminase, hemoglobin, hematocrit, leukocyte, platelet, ferritin and high sensitive C-reactive protein (hsCRP) levels were measured as well as sTWEAK levels. Parathyroid hormone and ferritin levels were measured by immunoassay method using Siemens Advia Centaur® XP machine. Other biochemical and hematological parameters were measured by appropriate methods using Siemens Advia 2400 autoanalyzer and ABX Pentra DX120 machine, respectively. sTWEAK measurements were performed by competitive enzyme linked immunoassay method (ELISA) with Bender MedSystem (Vienna, Austria) sTWEAK ELISA kit. Peritoneal equilibration test results were also recorded.

Echocardiographic examination of all the patients was performed by the same physician using General Electric VIVID 7 machine. Cardiac chamber diameters and wall thicknesses were measured by M-mode. Modified Simpson method and Deveroux formula were used for calculation of ejection fraction (EF) and left ventricular mass (LVM). Left ventricular mass index was gained by dividing LVM by body surface area. Left ventricular hypertrophy was defined as LVMI above 110gr/m^2 and 134gr/m^2 for females and males, respectively.

Statistical analysis

Statistical analysis was conducted by using SPSS (Statistical Package for Social Sciences) for Windows 14.0 program. Numerical parameters were expressed as mean±standard deviation (SD). Student's t-test and Mann Whitney U test were used for comparison of the two groups. Yates corrected chi-squared test and Fisher's

exact test were used for 2x2 contingency tables of nonnumerical variables when necessary. For correlation analysis of numerical and non-numerical parameters were carried out by Pearson and Spearman's rho correlation tests, respectively. The variables found to be correlated with sTWEAK were analyzed further by linear regression analysis (stepwise method). Confidence interval of 95% and p value less than 0.05 were regarded as statistically significant.

RESULTS

Fifty-two PD patients were included in the study. The mean age and the female/male ratio were 52.7±15.4 years and 30/22. The PD modality was continuous ambulatory peritoneal dialysis in 32 (61.5%), automated PD in 17 (32.7%) and hybrid regimes in three (5.8%) patients. The demographic and clinical data of the patients are presented in Table I. The most common reason of end stage renal disease (ESRD) was diabetic nephropathy. The most frequent comorbidity was hypertension which was recorded in 40 patients (77%). Laboratory analysis results of the patients are presented in TableII, and the demographic and physical examination findings of the control group compared with the patients are presented in Table III.

The mean sTWEAK levels of the patients and the control groups were 564±17 (min-max: 168-1049) pcg/ml; and 535±126 (min-max: 306-831) pcg/ml, respectively (Fig. 1). The two groups were similar regarding sTWEAK levels (p=0.419). There was no statistically significant difference between demographic parameters of the groups except age which was lower in the control group (52.7±15.4 years *vs* 41.3±10.7 years; p<0.001) (Table III). No correlation was detected between any of the

Table I. *The demographic and clinical data of the patients.*

		Mean±SD	Minimum	Maximum
Age (years)		52.7±15.4	24	75
Gender (Female/Male)		30/22		
Height (cm)		161±11.5	142	190
Weight (kg)		70.9±16.4	42	108
BSA (kg/m²)		1.74±0.22	1.28	2.24
BMI (m²)		27.5±6.5	15.9	43.6
Duration of CKD (years)		7.2±4.7	1	26
Systolic BP (mmHg)		128±21	90	180
Diastolic BP (mmHg)		80±11	60	100
Mean BP (mmHg)		96±14	70	126
PD duration (months)		41.7±25.1	4	96
Primary kidney disease [n (%)]	**DM**	14 (27)		
	Unknown	14 (27)		
	Postrenal causes	8 (16)		
	Hypertension	7 (13)		
	Glomerulonephritis	6 (11)		
	ADPKD	3 (6)		
Comorbidities [n (%)]	**Hypertension**	40 (77)		
	Hyperlipidemia	21 (40)		
	DM	15 (29)		
	IHD	9 (17)		
	Heart failure	4 (8)		

BSA: Body surface area; BMI: Body mass index; CKD: Chronic kidney disease; BP: Blood pressure; PD: Peritoneal dialysis; DM: Diabetes mellitus; ADPKD: Autosomal dominant polycyctic kidney disease; IHD: Ischemic heart disease.

Table II. *Laboratory data of the patients.*

	Mean±SD	Minimum	Maximum
Glucose (mg/dl)	137±82	72	479
Urea (mg/dl)	102±33	58	211
Creatinin (mg/dl)	8±2.9	4.0	16.3
Uric acid (mg/dl)	5.9±1.1	4.0	8.80
Sodium (mmol/L)	138±3.8	128	148
Potassium (mmol/L)	4.1±0.7	3	6
Parathyroid hormone (pg/ml)	563±433	80	1900
Calcium (mg/dl)	9.1±0.6	7.9	10.3
Phosphorus (mg/dl)	5.1±1.2	2.9	8.6
Calcium x phosphorus (mg^2/dl^2)	46.2±12	24	77
Albumin (g/dl)	3.8±0.4	2.7	4.5
Total cholesterol (mg/dl)	189±45	113	338
HDL-cholesterol (mg/dl)	42±17	20	90
LDL-cholesterol (mg/dl)	113±35	58.00	235.00
Triglyceride (mg/dl)	173±95	35	475
AST (U/L)	17±7	6	45
ALT (U/L)	17±11	5	68
ALP (U/L)	135±193	45	1423
Hemoglobin (g/dl)	10.9±1.3	7.5	14.3
Hematocrite (%)	32.8±4.1	21.4	42.7
Leukocyte ($/mm^3$)	8176±2408	3500	14000
Platelet ($x10^3$)	273±98	40	567
MCV (fl)	92±5	82.1	107
Ferritin (ng/ml)	387±322	25	1650
hsCRP (mg/dl)	2.07±4.28	0.01	26.01

AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphtase; MCV: Mean corpuscular volume.

demographic variables and sTWEAK levels.

The echocardiographic data are presented in Table IV. Among them, only EF was found to be correlated negatively with sTWEAK levels (r=-0.354, p=0.010).

There was no correlation of sTWEAK levels with biochemical variables and PET results which are presented in Table V. Residual renal function (RRF) and residual urine volume were not correlated with sTWEAK levels. When patients with and without significant RRF were considered as separate groups, there were no differences regarding sTWEAK levels (543±197 pcg/ml *vs* 597±137 pcg/ml; p=0.119).

Patients with IHD (n=9) had significantly higher sTWEAK levels compared with the patients without IHD (n=43) (726±222 pcg/ml *vs* 531±146 pcg/ml; p=0.002). Likewise, patients with heart failure were detected to have higher levels of sTWEAK (853±216 pcg/ml *vs* 541±151 pcg/ml; p<0.001). But other comorbidities (diabetes mellitus, hypertension, hyperlipidemia and left ventricular hypertrophy) did not have any effect on sTWEAK levels.

When we compared patients with and without ischemic heart disease, the only parameter differing

Table III. *Comparison of the groups regarding demographic and clinical parameters.*

	Patient group	Control group	P
Age (years)	52.7±15.4	41.3±10.7	<0.001
Gender (Female/Male)	30/22	17/14	0.872
Weight (kg)	70.9±16.4	75±13.5	0.285
Height (cm)	161±11.5	168±9.5	0.007
BMI (m^2)	27.5±6.5	26.7±4.6	0.454
BSA (kg/m^2)	1.74±0.22	1.84±0.19	0.04

BMI: Body mass index; BSA: Body surface area.

Table IV. *Echocardiographic findings of the patient group.*

	Mean±SD	Minimum	Maximum
Left atrial diameter (cm)	3.57±0.56	2.10	4.90
Left ventricular end-diastolic diameter (cm)	4.63±0.59	3.30	5.80
Left ventricular end-systolic diameter (cm)	3.01±0.58	2.10	4.80
Left ventricle posterior wall thickness (cm)	1.14±0.18	0.80	1.60
Ejection fraction (%)	62±9	32.00	75.00
Interventricular septum thickness (cm)	1.24±0.22	0.90	2.00
Right ventricular diameter (cm)	2.52±0.27	2.00	3.40
Aortic diameter (cm)	3.21±0.33	2.40	3.90
Pulmonary artery diameter (cm)	2.1±0.25	1.70	3.00
Left ventricular mass (gr)	248±83	87	470
Left ventricular mass index (gr/m^2)	142±43	58	270

Table V. *Peritoneal equilibration test results of the patients.*

	Mean±SD	Minimum	Maximum
Peritoneal membrane permeability	0.67±0.10	0.47	0.87
Total Kt/V	2.51±0.67	1.42	4.00
Dialysate Kt/V	1.80±0.47	0.71	3.38
Renal Kt/V	0.71±0.72	0.00	2.59
Total urea clearance	88±23.9	53.8	159.1
Dialysate urea clearance	61.4±13.6	35.3	99.7
Residual renal urea clearance	25.6±26.4	0.00	97.7
Total creatinin clearance	78±28.3	34.4	173.1
Dialysate creatinin clearance	45±11.8	21.5	83.9
Residual renal creatinin clearance	33.8±32.2	0.00	131.4

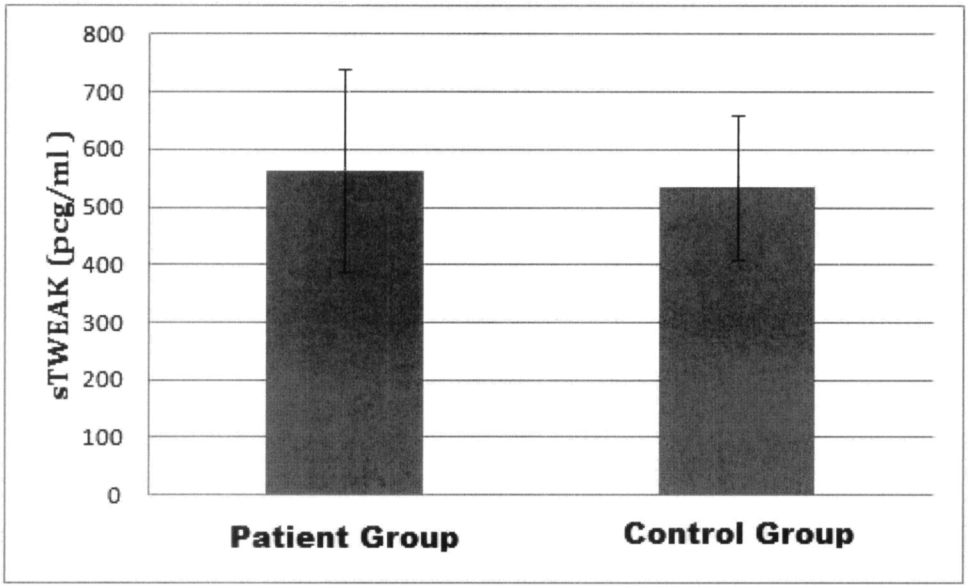


Fig. 1. *Comparison of sTWEAK levels in the patient and the control groups. Mean sTWEAK levels of the patient and the control groups. sTWEAK levels of the groups were not significantly different (p=0.419).*

between the groups was age which was higher in patients with ischemic heart disease (62.11±7.18 years *vs* 50.67±15.96 years, p=0.041). But age was not found to be effective on sTWEAK levels in multivariate analysis. The demographic, clinical and laboratory parameters, apart from sTWEAK levels, were similar in patients with and without heart failure.

Patients using angiotensin converting enzyme inhibitors (n=7) (544±230 pcg/ml *vs* 568±168 pcg/ml; p=0.746), angiotensin receptor blockers (n=6) (670±144 pcg/ml *vs* 551±176 pcg/ml, p=0.117), statins (n=13) (603±139 pcg/ml *vs* 552±186 pcg/ml, p=0.367) and acetyl salicylic acid (n=11) (637±243 pcg/ml *vs* 545±150 pcg/ml, p=0.112) had similar sTWEAK levels compared with their counterparts who did not use the mentioned drugs.

With linear regression analysis; only age (B=-3.099, beta=-0.272, p=0.029) and the presence of heart failure (B=312,4, beta=0.479, p<0.0001) were found to be the independent determinants of sTWEAK levels (constant=701, standard error: 74).

DISCUSSION

Cardiovascular risk is increased in patients with CKD especially in those with ESRD, and is the major cause of mortality (18). The risk of CVD is increased 3.5-50 times in CKD according to registry reports of USRDS (United States Renal data System) and ERA-EDTA (European Renal Association-European Dialysis Transplantation Association) (19). Hence, full understanding of the pathologies that increase risk of CVD in uremic patients may provide opportunity for proper diagnosis and treatment of these diseases and may also decrease mortality.

We detected no differences between the patient and the control groups regarding sTWEAK levels. No data was found in the current literature on sTWEAK levels in PD patients. Carrero et al. and Kralisch et al. studied with HD patients who had lower sTWEAK levels than the control group (20, 21). Yilmaz et al. found sTWEAK levels low in all stages of CKD and detected a strong correlation with glomerular filtration rate (22). The similar values detected in our study may be related with the difference in the patient groups and dialysis modality, but there is no data in the literature about whether sTWEAK is dialyzable or not through HD membranes or peritoneal membrane.

Endothelial dysfunction in uremia is known to be associated with inflammation, albuminuria

and oxidative stress (18). TNF and TNF receptor superfamily play important roles in the atherogenesis. TNF-CD40 ligand and the receptors of this family are accepted as proatherogenic (23). sTWEAK and Fn14 were detected in human atherosclerotic plaques (14). sTWEAK induces vascular smooth muscle cell proliferation (8) and metalloproteinase activity (12), so impairs the stability of the atherosclerotic plaque. In another study by Blanco-Colio et al., sTWEAK level was found to be negatively correlated with carotid intima media thickness (24). The higher sTWEAK levels found in patients with IHD in our study may be regarded as a clue for the relationship between sTWEAK and atherosclerosis, but as the metabolism of sTWEAK is not fully elucidated, it is not known

sTWEAK levels were significantly higher in patients with IHD in the present study (p=0.002). Carrero et al. found lower sTWEAK levels in HD patients with CVD (13). Kralisch et al. detected sTWEAK levels lower in patients with ESRD and diabetes mellitus, and claimed that sTWEAK would be a new atherosclerotic marker (21). Hassan et al. reported that the lowest levels of sTWEAK were in patients with CKD stage 4 and 5, and sTWEAK is negatively correlated with interleukin-6 and carotid intima media thickness. Patients with ischemic cardiovascular or cerebrovascular disease were found to have higher sTWEAK levels at the end of the two-year follow-up compared with the basal evaluation. Finally, they claimed that sTWEAK would be a new biomarker for atherosclerosis, ED and cardiovascular morbidity and mortality (25).

There were only four patients with heart failure in our study, all due to IHD. In spite of the small number of cases, they had higher sTWEAK levels than those without IHD. Moreover, there was a strong relationship between heart failure and sTWEAK levels in linear regression analysis. There are conflicting data in the literature about the relationship between sTWEAK and cardiac functions. It was shown that increased sTWEAK levels caused dilated cardiomyopathy, cardiac dysfunction though an Fn14 cell receptor-dependent pathway and early death in mice (26). Jain et al. reported that sTWEAK levels were higher in patients with idiopathic dilated cardiomyopathy compared with patients with ischemic cardiomyopathy and control subjects; and no correlation was detected between sTWEAK levels and the degree of heart failure (26). On the contrary, another study showed lower sTWEAK levels in patients with systolic heart failure than in the control group; and they detected a negative correlation between sTWEAK levels and the degree of heart failure. They claimed that sTWEAK level below 227pg/ml is a mortality predictor (17).

There is no data on the sTWEAK level in PD patients. The studies regarding sTWEAK levels in end stage renal disease is also limited. Most of the studies carried out on this subject were conducted on patients with heart failure but normal renal function. Gungor et al. reported in their study that sTWEAK levels were significantly higher in hemodialysis patients with coronary artery calcification score more than 400 than those with coronary artery calcification score below this level (27). Carrero et al. (13) compared sTWEAK levels of hemodialysis patients with the healthy control group. Although sTWEAK levels of the hemodialysis patients were lower than the control group, the mortality rate of patients with sTWEAK levels in the upper tertiles were significantly higher. These different results lead to the idea that sTWEAK metabolism is different in the presence of renal dysfunction. The lack of difference between the patient and control groups in our study may be due to these unkown factors related to peritoneal dialysis.

No data has been found in the literature about the relation between sTWEAK levels and echocardiographic findings. We detected a negative correlation between sTWEAK and EF. Jain et al. detected no correlation with any parameter related to left ventricular function in patients with normal renal functions (26).

Carrero et al. reported a negative correlation between sTWEAK levels and CRP, interleukin-6 and leukocyte count (13). We detected no correlation with hsCRP levels. This could be related with the small number of patients in our study.

There was no relation between comorbidities and sTWEAK levels in our study. Carrero et al. found no difference between diabetic and non-diabetic HD patients regarding sTWEAK levels (13). Kralisch et al. detected lower sTWEAK levels in diabetic uremic patients, and related this finding with CVD history and carotid atherosclerosis (21). Patients

with newly diagnosed hypertension were found to have lower sTWEAK levels compared with the normal population. sTWEAK levels were found to be negatively correlated with systolic and diastolic BP (27). We detected no correlation with BP. This may be related with the difference of pathophysiology of hypertension in PD patients.

Carrero et al. detected higher sTWEAK levels in patients using acetylsalicylic acid (13). The lack of this relation in our study may be related with the small number of patients.

There was a negative correlation between sTWEAK levels and residual urine volume in our study, although it did not reach statistical significance. Regarding the important role of residual renal functions on morbidity and mortality in dialysis patients, this issue deserves further studies for clarification.

Muñoz-Garcia et al. reported aggravated inflammation, vascular injury and renal damage after infusion of sTWEAK to mice, and showed regression of these pathologies after anti-sTWEAK antibody. They claimed that sTWEAK may be a new target for treatment (28). Schapira et al. showed that atherosclerotic plaque progression ceased after treatment of mice with Fn14-Fc that inhibits sTWEAK (29). Although animal studies can not be direct evidence for the pathophysiological role of sTWEAK in humans, it may be regarded as a clue.

The major limitations of our study are the cross-sectional nature, the small number of patients and the lack of HD patients, however it provides the first data about the relationship between sTWEAK levels and cardiac functions.

Level of sTWEAK is significantly high in PD patients with heart failure and IHD. sTWEAK may be a marker of cardiac functions in PD patients. It may be considered in the future as a target in the diagnosis, follow-up and treatment of IHD and heart failure in PD patients.

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