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Original article

ASSESSMENT OF THE RELATIONSHIP BETWEEN SERUM TWEAK LEVELS AND THE DEGREE OF VASCULAR INVOLVEMENT IN PATIENTS WITH STABLE ANGINA PECTORIS

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Abstract: **Introduction:** This study investigates the relationship between serum TWEAK levels and the degree of vascular involvement in patients with stable angina pectoris, offering insights beyond conventional cardiovascular risk factors.

Materials and Methods: This study involved 88 patients (33 women, 55 men) diagnosed with stable angina pectoris. Patients were classified based on angiographic findings. Comprehensive demographic and medical history data were collected, and morning blood samples were analyzed, focusing on TWEAK and IL-6 levels. To assess the severity of coronary artery lesions, a modified version of the Gensini scoring system was employed.

Results: Analyses revealed no significant correlation between TWEAK levels and the severity of coronary artery disease. Although some variations in biochemical markers were observed based on gender and diabetic status, these differences did not exhibit a statistically significant relationship with the degree of vascular involvement.

Conclusion: The findings indicate that serum TWEAK levels do not have a significant association with the severity of vascular involvement in patients with stable angina pectoris. These results highlight the limited efficacy of TWEAK as a sole biomarker in assessing the severity of coronary artery disease, emphasizing the complexity of its role.

Keywords: TWEAK, Angina pectoris, Gensini score.

INTRODUCTION

Cardiovascular diseases continue to rank among the leading causes of morbidity and mortality worldwide. Understanding the underlying causes of these diseases is of paramount importance for developing more effective treatment strategies and prevention. Beyond traditional risk factors such as metabolic syndrome, hypertension, and hyperlipidemia, recent years have witnessed significant findings pointing to the contributions of inflammation, particularly adipokines, to the pathogenesis of these diseases (1, 2). In this context, TWEAK (a member of the TNF superfamily) and its impact on cellular mechanisms have emerged as a novel research area in the understanding and management of cardiovascular diseases (3).

TWEAK, a member of the TNF superfamily and originally synthesized as a transmembrane protein with 249 amino acids, was first identified as a trigger of apoptosis (4). Subsequent studies have revealed that TWEAK is involved in various inflammatory and immune processes (5). Its action occurs through interaction with its only known receptor, fibroblast growth factor-inducible 14 (Fn14), which when activated can stimulate the release of cytokines such as TNF-α, IL-1, IL-6 and granulocyte colony-stimulating factor (G-CSF) and interferon-γ. In addition, TWEAK is involved in the secretion of other inflammatory mediators, including monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) (6, 7). Macrophages and monocytes, particularly in inflamed tissues, have been identified as major producers of soluble TWEAK, highlighting the importance of the TWEAK/Fn14 signaling pathway in its contribution to the inflammatory environment and suggesting that its upregulation may influence the

pathogenesis of certain inflammatory and infectious diseases (8). The role of TWEAK is increasingly recognized in the progression of atherosclerosis, a disease characterized by inflammatory processes within the vessel wall (4). Studies of endothelial cells, macrophages, and other components of the vascular wall have increased our understanding of both chronic inflammation and acute responses to vascular injury. Furthermore, ongoing research on markers of oxidative stress, including IL-6, NO, and ROS, highlights their importance in the pathogenesis of cardiovascular disease and their potential as targets for therapeutic interventions (3, 4, 9). The association between TWEAK/Fn14 signaling and macrophage-mediated inflammation is a critical factor in the development of atherosclerotic plaques, with implications for the broader spectrum of cardiovascular disease.

This study aims to explore the relationship between TWEAK and cardiovascular diseases and potential correlations with oxidative stress markers like IL-6, NO, and ROS. By investigating the clinical and demographic relationships between TWEAK levels and these oxidative stress markers in patients with stable angina pectoris, this study seeks to contribute to the understanding of the use of biomarkers in the diagnosis, treatment, and management of coronary artery disease.

MATERIALS AND METHODS

Patients and Grouping

This study enrolled 88 patients (33 women, 55 men) diagnosed with stable angina pectoris who underwent coronary angiography. Patients were stratified into two groups based on the severity of observed coronary lesions: Group 1 included patients with non-significant lesions or a Gensini score below 50, while Group 2 consisted of patients with substantial vessel involvement or a Gensini score above 50. Detailed demographic profiles and comprehensive medical histories, encompassing gender, age, smoking status, diabetes, hypertension, dyslipidemia, coronary artery disease, family medical history, and current medication regimens, were meticulously documented through extensive survey forms. Height and weight data were also collected. Body Mass Index (BMI) was calculated using the formula: BMI = weight (kg) / height^2 (meters). The study was initiated following ethical approval from the local ethics committee (decision no: 2011-714190).

Inclusion and Exclusion Criteria

Inclusion Criteria: The inclusion criteria consisted of patients diagnosed with stable angina pectoris who had undergone coronary angiography.

Exclusion Criteria: The exclusion criteria encompassed patients with a history of myocardial infarction (MI) or prior coronary artery bypass surgery, individuals with significant valvular heart disease, active thyroid dysfunction, severe liver or kidney failure, systemic infectious or malignant diseases, and those who did not provide informed consent for participation in the study.

Laboratory Samples

Morning blood samples taken from the patients after 10-12 hours of fasting were used for biochemical analyses. Creatinine, glucose, lipid profile, hs-CRP, IL-6, ROS, and NO levels were measured. Serum Tweak and IL-6 levels were measured using East Biopharm brand ELISA kits with the sandwich ELISA method.

Angiography and Gensini Scoring

After comprehensive clinical and laboratory risk factor assessments, coronary angiography was performed on each patient by an experienced operator using the Judkins technique. Patients adhered to a twelve-hour fasting protocol for this procedure. Both the right and left coronary arteries were imaged in multiple angles in detail, to provide a comprehensive analysis. The assessment of angiographic images and scoring of lesions were independently carried out by two operators.

The coronary arteries were divided into 27 segments, and each segment was scored based on the degree of narrowing, ranging from 0.5 to 5.0. The Gensini score was calculated by multiplying these values, facilitating the classification of patients into two groups based on the prevalence of vascular lesions observed in angiography. In our Gensini scoring approach, the degree of angiographic stenosis was quantified as follows: 1 point for 0-25% narrowing, 2 points for 25-50% narrowing, 4 points for 50-75% narrowing, 8 points for 75-90% narrowing, 16 points for 90-99% narrowing, and 32 points for 100% occlusion. Specific coefficients were applied for each main coronary artery and the identified segments. These coefficients were as follows: 5 points for a left main coronary lesion, 2.5 points for proximal left anterior descending and left circumflex artery, 1.5 points for mid left anterior descending artery lesions, 1 point for the first diagonal branch, obtuse marginal branches, and the right coronary artery, and 0.5 points for the second diagonal and posterolateral branches of the left circumflex artery.

Statistical Analysis

In this study, statistical analyses were conducted using SPSS Version 20.0 (SPSS Inc., Chicago, IL,

USA) and R software (Version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria). The Shapiro-Wilk test was employed to evaluate the normality of the distribution of continuous variables, which are presented as mean ± standard deviation (SD). Categorical variables are reported as frequencies and percentages (%). The Independent Sample T-test or Mann-Whitney U Test was utilized for comparisons of continuous variables between groups, while the Chi-Square test was applied for the comparison of categorical variables. To investigate the relationships between clinical and demographic characteristics, Pearson or Spearman correlation analyses were performed. Univariate logistic regression was carried out to identify potential predictors of outcomes, and Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of the identified predictors. The level of statistical significance was established at $p < 0.05$.

RESULTS

In this comprehensive study, 88 participants were evaluated; of these, 34 were women (38.6%) and 54 were men (61.4%). The average age of the participants was 61.2 (age range 33-77). Half of the patients (50%) had a history of smoking. The most common comorbidities were hypertension (69.3%), Diabetes Mellitus (40.9%), and hyperlipidemia (34.1%). A family history of coronary artery disease was present in 38.6% of the participants.

In terms of vascular involvement, 21 patients (23.9%) had single-vessel involvement, 20 patients (22.7%) had two-vessel, 13 patients (14.8%) had three-vessel involvement, while 34 patients (38.6%) had no vessel involvement. The average Gensini score was calculated as 43.67 (range 0-268).

Patients were divided into two groups based on their Gensini score: Group 1 consisted of 50 patients (57%), and Group 2 consisted of 38 patients (43%). The demographic, comorbid disease, and laboratory findings of these groups are presented in Table 1.

In the analysis of IL-6 levels according to gender, the average was 119 ± 251 ng/L in women and 151±276 ng/L in men; this difference was not statistically significant ($p = 0.61$). Statistically significant differences were observed in ROS and NO levels when analyzed by gender (ROS $p = 0.054$, NO $p = 0.024$). When comparing Tweak values by gender, they were found to be 336.24 ± 137.09 ng/L in men and 323.42 ± 94.13 ng/L in women; this difference was also not statistically significant ($p = 0.988$). Comparisons related to gender are provided in Table 2.

Table 1. *Demographic and biochemical parameters of the patients*

	Total	Group 1 (n = 58)	Group 2 (n = 30)	P-value
Age (years)	61.2 ± 9.8	59.8 ± 10.1	63.7 ± 8.8	0.077
Sex (F/M)	34/54	30/28	4/26	< 0.001
Family History of CAD (%)	38.6	43.1	30.0	0.23
Smoking History (%)	50	55.2	40.2	< 0.001
DM (%)	40.9	43.1	36.7	0.56
HT (%)	69.3	70.7	66.7	0.70
Hyperlipidemia (%)	34.1	31.0	40.0	0.40
BMI (kg/m²)	29.19 ± 4.97	29.5 ± 5.6	28.6 ± 3.3	0.42
Glucose (mg/dl)	122 ± 47	123 ± 49	121 ± 45	0.865
HDL (mg/dl)	45 ± 12	45 ± 14	44 ± 10	0.645
hsCRP (mg/dl)	2.5 ± 1.9	2.43 ± 1.90	2.71 ± 2.1	0.52
Creatinine (mg/dl)	0.95 ± 0.15	0.95 ± 0.14	0.96 ± 0.19	0.88
LDL (mg/dl)	124 ± 37	121 ± 33	130 ± 43	0.31
Leukocytes (10^3/mm³)	6.9 ± 1.3	6.82 ± 1.26	7.30 ± 1.5	0.118
IL6 (ng/L)	139 ± 265	144 ± 282	129 ± 238	0.814
Tweak (ng/L)	354.27 ± 161.82	307,14 ± 95,50	354,27 ± 161,82	0.346
NO (ng/L)	3689 ± 1910	3861 ± 2043	3357 ± 1602	0.243
ROS (ng/L)	0.38 ± 0.2	0.37 ± 0.23	0.40 ± 0.3	0.654

Note: CAD - Coronary Artery Disease, DM - Diabetes Mellitus, HT - Hypertension, HDL - High-Density Lipoprotein, hsCRP - High-Sensitivity C-Reactive Protein, LDL - Low-Density Lipoprotein, IL-6 - Interleukin-6, NO - Nitric Oxide, ROS - Reactive Oxygen Species, BMI - Body Mass Index.

Table 2. *Comparison of Tweak, ROS, NO, and IL-6 levels by gender*

Indicator	Female	Male	P-value
IL-6 (ng/L)	119 ± 251	151 ± 276	0.61
ROS (ng/L)	0.4307 ± 0.026	0.3526 ± 0.24	0.054
NO (ng/L)	4220 ± 2038	3354 ± 1762	0.024
Tweak (ng/L)	323.42 ± 94.13	336.24 ± 137.09	0.988

Note: TWEAK - Tumor Necrosis Factor-like Weak Inducer of Apoptosis, ROS - Reactive Oxygen Species, NO - Nitric Oxide, IL-6 - Interleukin-6.

Table 3. *Comparison of Tweak, ROS, NO, and IL-6 levels by Diabetes Status*

Indicator	Non-Diabetic Mean ± SD	Diabetic Mean ± SD	P-value
Tweak (ng/L)	334.90 ± 120.11	329.27 ± 129.60	0.992
ROS (ng/L)	0.33 ± 0.20	0.45 ± 0.30	0.035
NO (ng/L)	3500 ± 600	3400 ± 650	0.43
IL-6 (ng/L)	150 ± 75	160 ± 80	0.52

Note: TWEAK - Tumor Necrosis Factor-like Weak Inducer of Apoptosis, ROS - Reactive Oxygen Species, NO - Nitric Oxide, IL-6 - Interleukin-6.

Table 4. *Univariate analyses of variables associated with significant vessel involvement or Gensini score exceeding 50*

Indicator	Odds Ratio	95% CI (Lower, Upper)	P-value
Age	0.991	0.946, 1.037	0.69
Sex	1.30	0.45, 3.79	0.63
Family History of CAD	0.42	0.16, 1.09	0.07
Smoking History	0.77	0.31, 1.87	0.56
DM	0.81	0.31, 2.11	0.67
HT	0.80	0.33, 1.96	0.62
Hyperlipidemia	0.62	0.25, 1.54	0.30
BMI	1.13	0.98, 1.30	0.08
Glucose	1.00	0.99, 1.01	0.85
HDL	1.03	0.98, 1.07	0.23
hsCRP	0.97	0.78, 1.20	0.76
Creatinine	0.41	0.05, 3.67	0.42
LDL	1.00	0.99, 1.01	0.73
Leukocytes	1.13	0.85, 1.52	0.40
IL6	1.00	0.998, 1.002	0.70
TWEAK	1.00	0.998, 1.004	0.45
NO	1.00	0.999, 1.000	0.33
ROS	1.45	0.28, 7.52	0.66

Note: CAD - Coronary Artery Disease, DM - Diabetes Mellitus, HT - Hypertension, HDL - High-Density Lipoprotein, hsCRP - High-Sensitivity C-Reactive Protein, LDL - Low-Density Lipoprotein, IL-6 - Interleukin-6, NO - Nitric Oxide, ROS - Reactive Oxygen Species, BMI - Body Mass Index.

When Tweak values were examined according to the presence of diabetes, they were 334.90 ± 120.11 ng/L in non-diabetic patients and 329.27 ± 129.60 ng/L in diabetic patients; this difference was not statistically significant (p = 0.992; Table 3). Finally, when evaluating the relationship between the number of affected vessels and TWEAK, ROS, NO, and IL-6 levels, no significant correlation was found among these parameters (p-values respectively 0.75, 0.27, 0.43, 0.52).

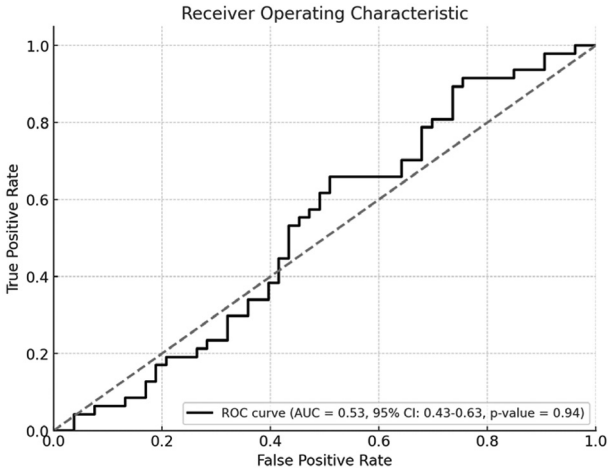

Figure 1. *ROC Curve Analysis of TWEAK for Predicting Significant Vessel Involvement or Gensini Score Above 50*

Univariate logistic regression analyses were conducted to evaluate potential predictors of inclusion in Group 2, considering factors such as age, gender, family history of coronary artery disease (CAD), smoking status, DM, HT, hyperlipidemia, BMI, glucose levels, HDL, hsCRP, creatinine, LDL, leukocytes, IL6, TWEAK, NO, ROS. The results showed that odds ratios and 95% confidence intervals for these variables were generally close to one, with all p-values being non-significant ($p > 0.05$), indicating that none of the variables studied were strong predictors of classification into Group 2, (Table 4). Additionally, the ROC curve analysis for TWEAK levels in Group 2 revealed an AUC of approximately 0.53(95%CI: 0.43-0.63). This underlines that TWEAK levels do not reliably discriminate between the presence and absence of the condition under investigation (Figure 1). These findings provide significant insights into the biological markers associated with coronary artery disease and establish a foundation for further research in this area.

DISCUSSION

Cardiovascular diseases hold a leading position among global causes of death, and numerous factors contributing to their etiology have been identified. Alongside common risk factors such as metabolic syndrome, the roles of inflammation and adipokines, particularly TWEAK, in the atherosclerotic process are drawing increasing interest (10). TWEAK, a member of the serine protease inhibitor family associated with adipose tissue dysfunction and insulin resistance, is currently under study for its connection to cardiovascular diseases (11). In this investigation, we examined the relationship between TWEAK levels and the degree of vascular involvement in patients with stable angina pectoris. Our findings indicate no significant correlation between the number or severity of vascular involvements and TWEAK levels. Furthermore, no significant differences were observed in the levels of inflammatory and oxidative stress indicators such as IL-6, NO, and ROS, between genders or in the presence of diabetes. These results suggest that TWEAK alone is not a sensitive marker for the presence or severity of coronary artery disease.

Recent studies have provided valuable insights into the relationship between TWEAK levels and cardiovascular diseases, aligning with our findings of no significant correlation between TWEAK levels and disease severity. In peripheral arterial disease, soluble TWEAK and the CD163/TWEAK ratio have been identified as predictors of long-term cardiovascular mortality (12). This highlights the prognostic importance of TWEAK in specific conditions rather than its direct correlation with disease progression. Similarly, while soluble TWEAK levels are linked to the presence of carotid atherosclerotic plaques in asymptomatic individuals, this does not necessarily indicate a progression towards severe cardiovascular conditions (13).

In patients with chronic kidney disease, soluble TWEAK levels are associated with major adverse cardiovascular events (14). This finding suggests a role for TWEAK in cardiovascular health that may not directly reflect disease severity. The observation of elevated soluble TWEAK levels in patients with ST-elevation myocardial infarction, which are related to adverse short-term outcomes, supports the idea of TWEAK being involved in specific cardiovascular events rather than indicating overall disease severity (15). Additionally, a study demonstrating that soluble TWEAK predicts hemodynamic impairment and functional capacity in pulmonary arterial hypertension underlines TWEAK's broader role in cardiovascular outcome prediction, independent of disease severity (16). These findings from diverse patient populations and conditions emphasize TWEAK's potential as a diagnostic or prognostic marker in cardiovascular diseases, rather than a direct indicator of disease severity. The evidence positions TWEAK as a key molecule in the complex interplay of inflammatory and cardiovascular processes, necessitating further investigation to fully understand its role in cardiovascular pathology.

Hypotheses regarding the mechanisms underlying the lack of association between TWEAK (tumor necrosis factor-like weak inducer of apoptosis) levels and the degree of vascular involvement suggest that this molecule's effects on the cardiovascular system may be modulated by various cofactors. Specifically, TWEAK's influence on the osteogenic transition and calcification of vascular smooth muscle cells (VSMCs) has been observed under both non-calcific and pro-calcific conditions. TWEAK increases the expression of markers

such as bmp2 mRNA (bone morphogenetic protein 2 messenger RNA), enhancing TNAP (tissue-nonspecific alkaline phosphatase) activity, thereby promoting calcification. However, it does not significantly alter MMP2 (matrix metalloproteinase 2) mRNA expression or activity, while it does increase both the expression and activity of MMP9 (matrix metalloproteinase 9). These findings indicate that TWEAK's effects on the vascular system are modulated by a range of factors including cell type, microenvironment, and disease stage, thus explaining the lack of a direct association between TWEAK levels and the degree of vascular involvement (6, 7, 17–19). Additionally, our demographic and biochemical analyses highlight that factors such as gender and smoking status are not associated with serum TWEAK levels. Research indicates that smoking affects the human serum metabolite profile, and these effects may be gender-specific. These studies show that the effects of smoking and cessation on serum metabolites are reversible, potentially reducing cardiovascular disease risks. However, these studies do not directly address serum TWEAK levels. Thus, specific relationships between serum TWEAK levels, gender, and smoking require further research for clarification (20).

There are several limitations to this study that warrant consideration. The sample size and demographic diversity of our study are limited, which may restrict the generalizability of the findings. Additionally, the design of the study precludes establishing causality, and the results are interpretative only in a correlative manner. The sensitivity and specificity of the methods used to measure TWEAK levels could also impact the outcomes. Moreover, the study did not evaluate other potential biomarkers and risk factors alongside TWEAK levels, limiting the scope of our findings.

CONCLUSION

This study marks a significant step in evaluating the potential roles of TWEAK and other biomarkers in the diagnosis and management of cardiovascular diseases. Our findings indicate that TWEAK levels do not show a significant relationship with the degree of vascular involvement in patients with stable angina pectoris nor are they associated with inflammatory and oxidative stress markers in the context of gender or the presence of diabetes. These results can guide further understanding of the potential use of TWEAK and other biomarkers in cardiovascular disease diagnosis and management. They also underscore the importance of tailoring the clinical use of biomarkers to specific patient populations and clinical scenarios. Comprehensive and multifaceted research in this field will advance the integration of these markers into clinical practice and refine strategies for the management of cardiovascular diseases.

Authorship: Conception and design of the study: Savaş Öztürk; Acquisition of data: Vehbi Şirikçi; Analysis and interpretation of data: Hüseyin Avni Fındıklı; Drafting the article: Vehbi Şirikçi; Critical revising: Vehbi Şirikçi; Final approval: Hüseyin Avni Fındıklı.

Ethical Standards:The study was conducted according to the Declaration of Helsinki and approved by the Research Ethics Committee at the Istanbul University Faculty of Medicine (decision no: 2011-714190).

Informed Consent: Written informed consent was obtained from all the participants prior to inclusion in the study online.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

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Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

PROCENA ODNOSA IZMEĐU NIVOA TWEAK-a U SERUMU I STEPENA VASKULARNE UKLJUČENOSTI KOD PACIJENATA SA STABILNOM ANGINOM PEKTORIS

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Uvod: Ova studija istražuje odnos između serumskih nivoa TWEAK i stepena vaskularne uključenosti kod pacijenata sa stabilnom anginom pektorisom, pružajući uvide izvan konvencionalnih faktora rizika za kardiovaskularne bolesti.

Materijali i metode: U ovoj studiji učestvovalo je 88 pacijenata (33 žene, 55 muškaraca) dijagnostikovanih sa stabilnom anginom pektorisom. Pacijenti su klasifikovani na osnovu angiografskih nalaza. Prikupljeni su sveobuhvatni demografski i medicinski podaci, a

analizirani su uzorci jutarnje krvi, fokusirajući se na nivoe TWEAK i IL-6. Za procenu težine lezija koronarnih arterija korišćena je modifikovana verzija Gensini skale.

Rezultati: Analize nisu pokazale značajnu korelaciju između nivoa TWEAK i težine koronarne bolesti. Iako su primećene neke varijacije u biološkim markerima na osnovu pola i statusa dijabetesa, ove razlike nisu pokazale statistički značajnu povezanost sa stepenom vaskularne uključenosti.

Zaključak: Rezultati ukazuju da nivoi serumskog TWEAK nemaju značajnu povezanost sa težinom vaskularne uključenosti kod pacijenata sa stabilnom anginom pektorisom. Ovi rezultati ističu ograničenu efikasnost TWEAK kao jedinog biomarkera u proceni težine koronarne bolesti, ističući kompleksnost njegove uloge.

Ključne reči: TWEAK, Angina pektoris, Gensini skala.

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