The Effects of Lifestyle Modification and HMG-Coa Reductase Inhibitor Treatment on Blood Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (TWEAK) Levels Among Patients with Isolated Hypercholesterolemia

İzole Hiperkolesterolemili Olgularda Terapötik Yaşam Şekli Değişikliği ve HMG-KoA Redüktaz İnhibitörü Tedavisinin Kan TWEAK (TNF-related weak inducer of apoptosis) Düzeyi Üzerine Etkisi

Gokhan OZGUR[1], Ilker TASCI[2], Serkan TAPAN[3], Gurkan CELEBI[4], Ali SELCUK[5], Battal ALTUN[6], Gurhan TASKIN[7], Alper SONMEZ[8], Bilgin Bahadir BASGOZ[2], Gokhan ERDEM[9]

[1]Gulhane Training and Research Hospital, Department of Hematology, Ankara
[2]University of Health Sciences, Gülhane Faculty of Medicine & Gulhane Training and Research Hospital, Department of Internal Medicine, Ankara
[3]Yuksek Ihtisas University, Medical Faculty, Department of Biochemistry, Ankara
[4]Gulhane Training and Research Hospital, Department of Gastroenterology, Ankara
[5]Erzurum Regional Training and Research Hospital, Department of Immunology and Allergic Diseases, Erzurum
[6]Kasımpasa Military Hospital, Department of Internal Medicine, Istanbul
[7]Kanuni Training and Research Hospital, Department of Intensive Care Unit, Trabzon
[8]University of Health Sciences, Gülhane Faculty of Medicine & Gulhane Training and Research Hospital, Department of Endocrinology and Metabolism, Ankara
[9]Health Sciences Universty, Gulhane School of Medicine, Department of Internal Medicine, Ankara

Abstract

Isolated hypercholesterolemia is a frequent condition in the general population. It is managed mostly by therapeutic lifestyle intervention and/or statin treatment. TWEAK is a cytokine from the TNF superfamily and plays a role in tissue regeneration in acute period; it is also involved in tissue damage in chronic period. In this study, we investigated plasma TWEAK levels of participants with isolated LDL cholesterol elevation in response to first 12 weeks of lifestyle modification, and 12 weeks of statin treatment. In conclusion, plasma sTWEAK level increased in dyslipidemia patients who were able to reach target LDL levels after therapeutic lifestyle modification. However, correcting dyslipidemia with statin was not associated with any change in plasma sTWEAK level.

Keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors, Hypercholesterolemia, Cytokine TWEAK, Lifestyle Modification

Öz

İzole hiperkolesterolemi genel popülasyonda sık görülen bir durumdur. Tedavide terapötik yaşam tarzı değişikliği ve/veya statin tedavisi altın standarttır. TWEAK, TNF süper familyasından bir sitokindir ve akut dönemde doku rejenerasyonunda rol oynar, ayrıca kronik dö-nemde doku hasarında da rol oynar. Bu çalışmada, ilk 12 haftalık yaşam tarzı değişikliği ve 12 haftalık statin tedavisine yanıt olarak izole LDL kolesterol yüksekliği olan hastaların plazma TWEAK düzeylerini araştırdık. Sonuç olarak, terapötik yaşam tarzı değişikliğinden sonra hedef LDL seviyelerine ulaşabilen dislipidemi hastalarında plazma sTWEAK düzeyi artmıştır. Bununla birlikte, dislipideminin statin ile düzeltilmesi, plazma sTWEAK seviyesinde herhangi bir değişiklik gözlenmemiştir.

Anahtar Kelimeler: Hidroksimetilglutaril KoA Redüktaz İnhibitörleri, Hiperkolesterolemi, Sitokin TWEAK, Yaşam Tarzı Değişikliği

Introduction

Inflammation is a crucial element of the atherogenesis from the early stages of plaque formation (1). One of the best characterized acute phase protein is the C- reactive protein (CRP), a member of pentraxin (pentameric proteins) family, is not only a marker of vascular inflamma-tion but also an active player in atherogenesis (2, 3). A number of well-designed studies have shown that treatment with statins decreases the level of CRP independent from LDL choles-terol lowering effect (4-6). Moreover, such a reduction in CRP was an independent predictor of reduced cardiovascular outcomes.

Pentraxin-3, also known as "long pentraxin", is another inflammatory marker and a member of pentraxin family. Its main role was defined as regulation of inflammatory reactions and cleansing of apoptotic cells (7). Elevation in pentraxin-3 levels demonstrates similarity with CRP in many pathologic conditions, such as infectious, autoimmune, and degenerative dis-eases. The most important and perhaps the only difference between CRP and pentraxin-3 is that unlike CRP, which is synthesized only in the liver as a response to IL-6 stimulation, pen-traxin-3 is synthesized in almost all

	ORCID No
Gokhan OZGUR	0000-0003-0357-0503
Ilker TASCI	0000-0002-0936-2476
Serkan TAPAN	0000-0002-7731-2120
Gurkan CELEBI	0000-0003-3433-8221
Ali SELCUK	0000-0003-4089-7564
Battal ALTUN	0000-0001-8714-1081
Gurhan TASKIN	0000-0002-6406-9221
Alper SONMEZ	0000-0002-9309-7715
Bilgin Bahadir BASGOZ	0000-0002-5795-533X
Gokhan ERDEM	0000-0003-3510-5905

Başvuru Tarihi / Received: 28.09.2018
Kabul Tarihi / Accepted : 17.10.2018

Adres / Correspondence : Gokhan OZGUR
Gulhane Training and Research Hospital, Department of Hematology, Ankara
e-posta / e-mail : gokhanozgur2010@hotmail.com

body cells, especially in vascular endothelial cells, vascular smooth muscle cells, adipocytes, macrophages and neutrophils (8). In healthy people, plasma pentraxin levels are very low. However, in conditions such as infectious, autoimmune, and degenerative diseases, its levels increase very rapidly (9, 10) and this elevation shows correlation with progression of the disease (11-13). Pentraxin–3 levels are also elevated in cardiovascular diseases such as acute myocardial infarction (14) and congestive heart failure (13). The fact that pentraxin-3 is an important marker for vascular inflammation suggests that it might be a better predictor for acute cardiovascular disease than CRP (14).

TNF-related Weak Inducer of Apoptosis (TWEAK) is a cytokine from the TNF superfa-mily known to contribute to the formation of unstable plaque by increasing the expression of many cytokines, such as adhesion molecules, proinflammatory cytokines, matrix metalloproteinases and tissue factors (15). The feature that carry TWEAK one-step forward in this cyto-kine family is its role in several biological activities such as stimulation of cell growth and angiogenesis, induction of inflammatory cytokines, and stimulation of apoptosis under some experimental conditions (16). While TWEAK plays a role in tissue regeneration in acute period, it is also involved in tissue damage in chronic period (17).

Isolated hypercholesterolemia is a frequent condition in the general population. It is managed mostly by therapeutic lifestyle change intervention (TLCI). However, subjects with increased risk of CV events may require pharmacological treatment after a failure to respond to lifestyle modifications. Blood levels of high sensitive (hs)-CRP, a more sensitive measure of blood CRP concentration, were also found increased in people with isolated hypercholeste-rolemia, an improvement was shown in response to both lifestyle modification and statin treatment (7, 8, 18). In this study, we investigated plasma TWEAK levels of participants with isolated LDL cholesterol elevation in response to first 12 weeks of lifestyle modification, and 12 weeks of statin treatment.

Material and Method

Baseline Characteristics:

The study was conducted in accordance with the Declaration of Helsinki. After ob-taining ethical approval by Local Ethical committee of Gulhane Military Medical Academy (15.05.2009/94) informed consent was obtained from all individual participants included in the study. In this observational study, subjects diagnosed with LDL-cholesterol elevation (>160 mg/dl) who were free of any known CVD or signs and symptoms of CVD were conse-cutively enrolled in an outpatient setting at a tertiary hospital. Detailed medical history includ-ing comorbid diseases and medications were collected. Physical examination and measure-ment of height, weight, waist circumference, and hip circumference were performed. All par-ticipants were informed about the study protocol and their written consent was obtained. In-clusion criteria were fasting glucose <100 mg/dL, blood pressure <140/90 mmHg, LDL cho-lesterol level >160 mg/dL, number of major risk factors ≤1 and low Framingham risk score, triglyceride level <200 mg/dL, body mass index (BMI)< 35 kg/m², stable body weight for the last 3 months, no ongoing medications. Exclusion criteria were proven coronary heart disease or equivalent, angina, diabetes mellitus, hypertension, renal and/or hepatic dysfunction and other metabolic or chronic diseases. Participants were excluded during follow-up after the onset of a disease.

Procedures:

Framingham risk score was calculated for each participant and those with a 10-year cardi-ovascular risk score of 20% or higher were considered as coronary heart disease equivalent and excluded. Participants with 0 or 1 cardiovascular risk factor and those with two or more cardiovascular risk factors but 10-year cardiovascular risk score less than 10% underwent the therapeutic lifestyle modifications as recommended in the NCEP ATP III guideline. This included an active session for information about exercise options and nutritional counselling.

In the second week of TLCI, a phone call was made to participants to encourage them about the program. By the end of a 12-week TLCI phase, all baseline data were reobtained as part of the routine follow-up. Those with reduced LDL-cholesterol level (<160 mg/dl) completed the observation period and were assigned to the TLCI group. As recommended by the guideline, other participants who did not achieve their target LDL-cholesterol level with the TLCI were prescribed rosuvastatin 10 mg/day by their physicians. After a 12-week statin treatment, data collection was repeated as part of the routine follow-up and these individuals were assigned to the statin treatment group (ST). The entire follow-up was completed in 24 weeks. Only individuals who underwent routine patient care for hypercholesterolemia were included in the study and no intervention was made except the phone calls in the second week of follow-up. Neither TLCI nor medical treatment was performed for research purposes.

Biochemical Analyses:

Serum and plasma samples were collected at baseline, 12th week and 24th week during rou-tine patient care as additional sample. Plasma and serum samples were stored in at -86ºC until the test time. Serum glucose, urea, creatinine, sodium, potassium, aspartate aminotrans-ferase (AST), alanine aminotransferase (ALT), total cholesterol,

triglyceride and HDL-cholesterol levels were determined by the enzymatic colorimetric method via The Olympus AU 600 auto analyzer (Olympus Diagnostics, GmbH, Hamburg, Germany) in the central lab of the institution as routine. LDL cholesterol levels were calculated by using the Fridewald's formula (LDL-cholesterol=Total cholesterol-(HDL-cholesterol+Triglyceride/5).
Plasma TWEAK level was determined by the ELISA (Lot Nr: Immundiagnostik AG, Bensheim, Germany). Plasma fasting insulin level was measured by radioimmunoassay. The homeostatic model assessment (HOMA) - Insulin resistance (IR) was calculated with following formula: Fasting plasma glucose (mg/dl) x immunoreactive insulin (μU/ml)/405 (19).

Statistical Analyses:

The descriptive data are given as mean ± standard deviation. Normality was tested by the Shapiro-Wilk test. To assess the difference between two sets of data T-test or the Mann-Whitney U test was used. Chi-square test was used to test for differences in categorical va-riables. Correlations were tested by the Pearson test or Spearman test. Exact p values were given and $p<0.05$ were considered as statistically significant.

Results

A total of 132 individuals with isolated LDL-cholesterol elevation were followed. By the end of the TLCI period, data were available for 118 individuals who attended to the second visit, at which LDL-cholesterol level was found lower than 160 mg/dl in 56 individuals. After exclusion of 6 of them due to missing blood samples, 50 subjects formed the TLCI. The TLCI group included 50 subjects. Data were available for 50 of 62 subjects that received a 12-week statin treatment. Baseline characteristics were similar in the two groups.

Changes in anthropometric and blood chemistry variables after 12 and 24 weeks are given in Table 2 and Table 3. In the TLCI group BMI, waist circumference and hip circumference were found significantly decreased after a 12-week TLCI (Table 2). Fasting plasma glucose, total cholesterol, LDL-cholesterol and non-HDL-cholesterol levels were also lower when compared with baseline (Table 2). Waist circumference, waist-to-hip ratio, total cholesterol, triglyceride, non-HDL cholesterol was found to decrease significantly also in the ST group by the end of the first 12–week period. Total cholesterol, LDL-cholesterol, and non-HDL cholesterol levels were lower in the ST group by the end of the 24th week. HDL-cholesterol level showed no significant difference after the TLCI or statin period.

Table 1. Baseline characteristics of the study population.

	TLCI group Mean±SD (n=50)	**ST group** Mean±SD (n=50)
Age (years)	45.27±8.96	48.84±9.67
Gender, female	%52*	%54*
BMI	27.17±2.55	27.48±2.9
Waist Circumference (cm)	89.14±9.29	88.21±9.39
Male	92.23±7.22	90.65±8.67
Female	87.63±11.12	84.78±8.82
Hip Circumference (cm)	100.68±7.39	101.84±8.77
Male	99.62±5.26	98.30±6.53
Female	103±8.94	103.59±8.42
Waist /Hip Circumference	0.88±0.08	0.85±.08718
Male	0.93±0.054	0.9233±.07751
Female	0.85±0.09	0.82±0.06
Systolic Blood Pressure (mmHg)	124.6±10.68	124.50±12.46
Diastolic Blood Pressure (mmHg)	81.4±7.15	78.5±8.35
Creatine kinase (IU/L)	97.91±41.71	108±15.89
Total-cholesterol (mg/dl)	253.21±19.02	273.66±26.37
LDL-cholesterol (mg/dl)	174.12±15.16	188.26±21.67
HDL-cholesterol (mg/dl)	50.34±10.29	51.66±11.27
Triglyceride (mg/dl)	145.73±36.98	162.39±54.41
Non-HDL- cholesterol	204.68±18.97	220.42±22.54
Total-cholesterol/HDL-cholesterol	5.21±0.87	5.35±.97
LDL-cholesterol/HDL-cholesterol	3.61±0.71	3.74±0.75
Fasting blood glucose (mg/dl)	93.82±6.55	92.70±6

SD: standard deviation *Chi-square test

Mean plasma insulin level was found reduced after TLCI for 12 weeks in both groups, further decreasing during the medical treatment in the ST group. HOMA-IR score, however, was found reduced in the initial 12 weeks only in the TLCI group, but 24th week HOMA-IR score was significantly low (Table 4).

Mean TNF-α level was lower by the 12th week in the TLCI group but it was significantly higher compared to baseline value in the ST group. However, mean TNF-α level was found significantly reduced by the end of the statin treatment (Table 4). Mean pentraxin-3 level was similar either after the TLCI or statin treatment periods, showing no change at observations (Table 4). By the end of the 12th week mean level of sTWEAK was significantly increased in TLCI group but no change was observed in the ST group. After the statin period, sTWEAK level was higher not only in the whole group but in females (Table 4).

In the TLCI group, sTWEAK levels correlated with both diastolic blood pressure ($r=-0.408$, $p=0.005$), LDL-cholesterol level ($r=0.392$, $p=0.008$), and BMI ($r=-0.339$, $p=0.023$) in the first 12 weeks. In the ST group, sTWEAK levels correlated with both systolic ($r=0.382$, $p=0.049$) and diastolic ($r=0.321$, $p=0.018$) blood pressure in the first 12 weeks but these were lost between the 12th to 24th weeks.

Table 2. Therapeutic lifestyle intervention group

	Baseline	12-week	P
Age (years)	45.27±8.96		
Sex (male/ female)	24 / 26*		
BMI (kg/m^2)	27.17±2.55	26.63±2.82	<0.001**
Waist Circumference (cm)	89.14±9.29	86.71±8.82	<0.001**
Male	92.23±7.22	89.54±7.7	<0.001**
Female	87.63±11.1	85±9.51	0.008**
Hip Circumference (cm)	100.68±7.39	98.86±7.18	<0.001**
Male	99.62±5.26	97.69±5.48	<0.001**
Female	103±8.94	101.25±8.63	0.001**
Waist /Hip Circumference	0.88±0.08	0.89±0.08	0.055**
Male	0.93±0.05	0.92±0.05	0.112**
Female	0.85±0.09	0.84±0.08	0.237**
SBP (mmHg)	124.6±10.6	121.5±11.2	0.054**
DBP (mmHg)	81.4±7.15	79.3±6.93	0.103**
Creatine kinase (IU/L)	97.91±41.7	121.72±62.1	0.768**
Total-cholesterol (mg/dl)	253.21±19.0	217.27±13.8	<0.001**
LDL-cholesterol (mg/dl)	174.12±15.1	139.26±12.8	<0.001**
HDL-cholesterol (mg/dl)	50.34±10.2	48.68±9.03	0.096***
Triglyceride (mg/dl)	145.73±36.9	144.64±33.3	0.458**
Non-HDL-cholesterol	204.68±18.9	167.26±14.6	<0.001**
Total- cholesterol/HDL-cholesterol	5.21±0.87	4.56±0.8	<0.001**
LDL- cholesterol/HDL-cholesterol	3.61±0.71	2.94±0.68	<0.001**
Fasting blood glucose (mg/dl)	93.82±6.55	86.96±9.8	<0.001***

SBP: systolic blood pressure, DBP: diastolic blood pressure
* Chi-square test, p=0.572, ** t-test, *** 2-related samples test

Table 3. Statin treatment group

	Baseline	12-week	24-week	P1	P2
Age (years)		48.84±9.67			
Sex (male/ female)		23 / 27*			
BMI (kg/m^2)	27.48±2.9	27.06±2.80	26.96±2.84	0.063**	0.387**
Waist Circumference (cm)	88.21±9.39	86.6579±9.62	86.16±9.99	0.002**	0.280**
Male	90.65±8.67	88.74±8.11	88.39±8.56	0.018**	0.304**
Female	84.78±8.82	83.15±9.13	82.8148±9.03	0.044**	0.518**
Hip Circumference (cm)	101.84±8.77	101.47±8.54	100.84±8.59	0.712**	0.032**
Male	98.30±6.53	98.35±6.66	97.65±6.49	0.954**	0.299**
Female	103.59±8.42	103.85±8.24	102.96±8.22	0.606**	0.030**
Waist /Hip Circumference	0.85±.087	0.85±0.08	0.87±0.09	0.004**	0.489**
Male	0.92±.077	0.90±.079	0.91±0.07	0.067**	0.758**
Female	0.82±0.06	0.80±0.06	0.80±0.06	0.025**	0.526**
SBP (mmHg)	124.50±12.4	122.3±10.1	120.1±9.82	0.259**	0.195**
DBP (mmHg)	78.5±8.35	78.4±7.38	76.52±6.49	0.888**	0.050**
Creatine kinase (IU/L)	108±15.8	130.84±89.7	121.56±60.1	0.356**	0.325**
Total-cholesterol (mg/dl)	273.66±26.3	266.34±28.4	189.±20.8	0.049**	<0.001**
LDL-cholesterol (mg/dl)	188.26±21.6	187.05±24.2	108.71±22.3	0.114**	<0.001**
HDL-cholesterol (mg/dl)	51.66±11.2	52.18±10.2	51.55±11.4	0.515***	0.671**
Triglyceride (mg/dl)	162.39±54.4	137.68±33.8	135.21±46.9	0.009***	0.961**
Non-HDL- cholesterol	220.42±22.5	211.9±26.8	139.18±24.6	0.035**	0.000**
Total- cholesterol /HDL- cholesterol	5.35±.97	5.10±.86	3.8167±.97	0.036**	0.000**
LDL- cholesterol /HDL- cholesterol	3.74±0.75	3.58±0.74	2.23±0.74	0.103**	0.000**
Fasting blood glucose (mg/dl)	92.70±6	93.29±11.5	90.97±10.7	0.817***	0.252**

SBP: systolic blood pressure, DBP: diastolic blood pressure; * Chi-square test, p=0.572, ** t-test, *** 2-related samples test

Table 4. Markers of inflammation at 12 and 24-weeks

	Baseline	12-week	24-week	P1	P2
TLCI group					
Insulin (μU/ml)	14.58±7.66	12.29±7.51	-	0.007***	
HOMA-IR	3.41±1.88	2.67±1.78	-	0.001***	
TNF-α	7.25+1.66 (4.18-10.88)	5.26+3.99 (0.11-20.98)	-	0.001***	
Pentraxin-3	1.92+0.94 (0.61-4.40)	1.88+0.77 (0.82-3.82)	-	0.595	
TWEAK (pg/ml)	679.69±230	928.3±369.49	-	<0.001**	
Male	656.49±261	959.10±366	-	<0.001**	
Female	714.98±189	905.50±352.97	-	0.014**	
ST group					
İnsulin (μU/ml)	11.89±9.27	8.88±3.77	7.89±3.23	0.007***	0.039***
HOMA-IR	2.67±2.02	2.08±1.01	1.78±0.75	0.21***	0.047***
TNF-α	7.19+3.39 (368-20.16)	8.29+1.44 (4.57-10.81)	7.35+3.42 (3.28-19.58)	0.013	0.010
Pentraxin-3	2.04+0.99 (0.53-4.66)	2.05+1.16 (0.32-5.18)	1.91+0.83 (0.33-3.81)	0.898	0.421
TWEAK (pg/ml)	860.58±287.24	784.48±270.99	869.28±329.31	0.148**	0.091**
Male	890.07±281.20	860.35±275.46	888.77±316.23	0.272**	0.582**
Female	835.46±277.2	748.19±275.04	869.40±313.31	0.356**	0.044**

SBP: systolic blood pressure, DBP: diastolic blood pressure; * Chi-square test, p=0.572, ** t-test, *** 2-related samples test

Discussion

The importance and efficacy of therapeutic lifestyle modification in the treatment of dyslipi-demia patients is well known (20-22). However, response to diet and exercise varies among individuals and expected targets may not be achieved in all individuals (23, 24). This variability is tried to be explained by both demographic characteristics and genetic factors (25, 26). In addition, relationship between diet, exercise and inflammatory mediators have been reported by several researchers (27, 28).

By the end of the first 12 weeks, we observed a significant increase in plasma sTWEAK level only in subjects with LDL-cholesterol level fell below 160 mg/dl. Cholesterol reduction was not observed in another group of patients after lifestyle modification, and these individu-als also showed no significant change in sTWEAK levels. This observation suggests that re-sponse to TLCI in terms of LDL-cholesterol reduction determines changes in inflammatory mediators. However, because, significant changes were observed in basic determinants of metabolic changes including arterial blood pressure, BMI, waist and hip circumference in both groups during the initial 12 weeks, no significant increase in plasma sTWEAK level in the ST group needs to be explained. Waist circumference showed no change in the ST group but decreased in the TLCI group, suggesting less severe and/or shorter-term chronic inflammation in these individuals. The concordance of changes in waist circumference and sTWEAK levels corroborate this hypothesis.

Medical treatment options for chronic diseases such as hypertension and diabetes have al-ways been investigated for their additional effects on inflammation. In patients with type 2 diabetes mellitus who receive antihypertensive treatment, mean plasma sTWEAK level was found increased while mean pentraxin-3 level was decreased (29). In our study, we observed meaningful increases in sTWEAK level only in female individuals receiving statin. Interes-tingly, baseline sTWEAK level was higher in subjects unresponsive to TLCI who underwent statin treatment thereafter. This might suggest that a compensatory increase in synthesis and secretion of sTWEAK occurs in subjects with dyslipidemia who have significant chronic in-flammation as well. Lower final mean sTWEAK level in the ST group may also suggest the presence of higher level of inflammation. Due to our study design mimicking real life dyslipi-demia management, the initial phase of TLCI in the first 12 weeks might have influenced res-ponses in the second 12 weeks.

The involvement of sTWEAK in atherogenesis has not been consistently shown in studies so far. ApoE-knockout mice fed with hyperlipidemic diet showed accelerated athereosclerotic plaque formation after recombinant TWEAK administration; this was abolished by anti-TWEAK blocking mAb administration (30). In the other

study, however, ApoE-knockout mice treated with TWEAK inhibiting fusion protein (Fn14-Fc) and blocking TWEAK resulted in little improvement in lesion initiation, macrophage accumulation and plaque progression (31). In an in vitro study, increased Fn14 expression in human aortic smooth muscle cell cultures in response to the administration of proinflammatory cytokines was neutralized following atorvastatin administration (32). These findings suggest some action of statins on TWEAK/Fn-14 interaction but we could observe marginal changes in circulating form TWEAK limited to female patients. It is possible that functions of TWEAK/Fn-14 at cellular level may not always be evident in the circulation (33).

TNF-α and TWEAK both have very similar biological activities (34). In our study, blood levels of TNF-α and sTWEAK were found to change in opposite directions in the ST group, suggesting that increased synthesis of this mediator is associated with reduced state of in-flammation. On the other hand, production of TWEAK may differ depending on the acute phase or chronic phase of damage. Mean sTWEAK level did not change markedly in our ST Group, possibly related to the fact that this inflammatory mediator is less involved in the chronic process of inflammation and tissue damage. As shown in Table 4, TNF-α level also increased in the ST group despite TLC intervention in the first 12 weeks.

In conclusion, we observed in this study that plasma sTWEAK level increased in dys-lipidemia patients who were able to reach target LDL cholesterol goals after therapeutic lifestyle modification. However, correcting dyslipidemia with statin in TLC non-responders was not associated with any change in plasma sTWEAK level. We also found weak similarities between blood TNF-α and sTWEAK level, suggesting not all individuals with dyslipidemia are similar and those who are unresponsive to TLC may actually have different degree and duration of systemic inflammation.

Ethics Committee Approval: Local Ethical committee of Gulhane Military Medical Academy (15.05.2009/94).

References

1. Tracy RP. Inflammation in cardiovascular disease: cart, horse or both--revisited. Arterioscler Thromb Vasc Biol. 2002;22(10):1514-5.
2. Bienvenu J WJ, Aguzzi F. C-reactive protein. In: Ritchie RF NO, editor. Serum proteins in clinical medicine. Portland: Maine Printing Group; 1996. p. 7.01.–7..6.
3. Pepys MB. C-reactive protein fifty years on. Lancet (London, England). 1981;1(8221):653-7.
4. Kinlay S, Schwartz GG, Olsson AG, et al. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation. 2003;108(13):1560-6.
5. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. Jama. 2004;291(9):1071-80.
6. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation. 2003;108(19):2292-7.
7. Okutani D. The role of long pentraxin 3, a new inflammatory mediator in inflammatory responses. Nihon Rinsho Men'eki Gakkai kaishi = Japanese journal of clinical immunology. 2006;29(3):107-13.
8. Mantovani A, Garlanda C, Bottazzi B, et al. The long pentraxin PTX3 in vascular pathology. Vascul Pharmacol. 2006;45(5):326-30.
9. Ortega-Hernandez OD, Bassi N, Shoenfeld Y, Anaya JM. The long pentraxin 3 and its role in autoimmunity. Semin Arthritis Rheum. 2009;39(1):38-54.
10. Kotooka N, Inoue T, Fujimatsu D, et al. Pentraxin3 is a novel marker for stent-induced inflammation and neointimal thickening. Atherosclerosis. 2008;197(1):368-74.
11. Tong M, Carrero JJ, Qureshi AR, et al. Plasma pentraxin 3 in patients with chronic kidney disease: associations with renal function, protein-energy wasting, cardiovascular disease, and mortality. CJASN. 2007;2(5):889-97.
12. Imamura M, Kawasaki T, Savchenko AS, et al. Lipopolysaccharide induced expression of pentraxin 3 in human neutrophils and monocyte-derived macrophages. Cell Immunol. 2007;248(2):86-94.
13. Kotooka N, Inoue T, Aoki S, Anan M, Komoda H, Node K. Prognostic value of pentraxin 3 in patients with chronic heart failure. Int J Cardiol. 2008;130(1):19-22.
14. Peri G, Introna M, Corradi D, et al. PTX3, A prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. Circulation. 2000;102(6):636-41.
15. Kim SH, Lee WH, Kwon BS, Oh GT, Choi YH, Park JE. Tumor necrosis factor receptor superfamily 12 may destabilize atherosclerotic plaques by inducing matrix metalloproteinases. Jpn Circ J. 2001;65(2):136-8.
16. Wiley SR, Winkles JA. TWEAK, a member of the TNF superfamily, is a multifunctional cytokine that binds the TweakR/Fn14 receptor. Cytokine Growth Factor Rev. 2003;14(3-4):241-9.
17. Burkly LC, Michaelson JS, Hahm K, Jakubowski A, Zheng TS. TWEAKing tissue remodeling by a multifunctional cytokine: role of TWEAK/Fn14 pathway in health and disease. Cytokine. 2007;40(1):1-16.
18. Tasci I, Erdem G, Ozgur G, Tapan S, Dogru T, Genc H, et al. LDL-cholesterol lowering increases plasma apelin in isolated hypercholesterolemia. Atherosclerosis. 2009;204(1):222-8.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
20. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. 2001;285(19):2486-97.
21. Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD. Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. Sports Med. 2001;31(15):1033-62.
22. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet (London, England). 2004;364(9438):937-52.
23. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation. 2000;102(18):2284-99.

24. Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. J Clin Endocrinol Metab. 2003;88(6):2445-61.
25. Williams PT. The relationships of vigorous exercise, alcohol, and adiposity to low and high high-density lipoprotein-cholesterol levels. Metabolism. 2004;53(6):700-9.
26. Rice T, Despres JP, Perusse L, et al. Familial aggregation of blood lipid response to exercise training in the health, risk factors, exercise training, and genetics (HERITAGE) Family Study. Circulation. 2002;105(16):1904-8.
27. Lakka TA, Lakka HM, Rankinen T, et al. Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study. Eur Heart J. 2005;26(19):2018-25.
28. Jenkins DJ, Kendall CW, Marchie A, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. Jama. 2003;290(4):502-10.
29. Yilmaz MI, Carrero JJ, Martin-Ventura JL, et al. Combined therapy with renin-angiotensin system and calcium channel blockers in type 2 diabetic hypertensive patients with proteinuria: effects on soluble TWEAK, PTX3, and flow-mediated dilation. CJASN. 2010;5(7):1174-81.
30. Munoz-Garcia B, Moreno JA, Lopez-Franco O, et al. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) enhances vascular and renal damage induced by hyperlipidemic diet in ApoE-knockout mice. Arterioscler Thromb Vasc Biol. 2009;29(12):2061-8.
31. Schapira K, Burkly LC, Zheng TS, et al. Fn14-Fc fusion protein regulates atherosclerosis in ApoE-/- mice and inhibits macrophage lipid uptake in vitro. Arterioscler Thromb Vasc Biol. 2009;29(12):2021-7.
32. Munoz-Garcia B, Martin-Ventura JL, Martinez E, et al. Fn14 is upregulated in cytokine-stimulated vascular smooth muscle cells and is expressed in human carotid atherosclerotic plaques: modulation by atorvastatin. Stroke. 2006;37(8):2044-53.
33. Sanz AB, Sanchez-Nino MD, Izquierdo MC, et al. TWEAK, the facilitator of acute kidney injury. Nefrologia. 2008;28(6):587-92.
34. Chicheportiche Y, Bourdon PR, Xu H, et al. TWEAK, a new secreted ligand in the tumor necrosis factor family that weakly induces apoptosis. J Biol Chem. 1997;272(51):32401-10.