ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Proportional Serum Lipid Parameters in Coronary Slow Flow Phenomenon

Koroner Yavaş Akım Fenomeninde Oransal Serum Lipid Parametreleri

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ABSTRACT Objective: The association between serum lipid parameters and coronary slow-flow (CSF) phenomenon has been searched previously. The aim of our study was to determine the association between proportional serum lipid parameters and CSF. **Material and Methods:** We enrolled 93 stable patients randomly who had undergone coronary angiography and had near-normal coronary arteries with normal and slow coronary flow. Demographic, clinical and laboratory data were recorded retrospectively. Coronary flow velocity was evaluated by TIMI frame count (TFC). CFS phenomenon was defined as a TFC greater than 27 frames. Corrected TFC was calculated for the left anterior descending coronary artery. **Results:** Fifty four patients were in CSF group and 39 patients were in control group. The mean age of the patients in CSF group was significantly higher than control group (55.4±9.5 vs. 50.5±9.8 years, p= 0.019). Triglyceride (TG) levels was found higher in CSF group than control group (187.3±103.4 mg/dl, 125.3±63.8 mg/dl, p<0.001). Total cholesterol to high density lipoprotein cholesterol ratio (TC/HDL-c), TG/HDL-c, low density lipoprotein cholesterol to HDL-c ratio (LDL-c/HDL-c) and non-HDL-c levels were significantly higher in CSF group (p=0.007, p=0.004, p=0.044, p=0.018, respectively). TG and TG/HDL-c were found correlated with TFC (r=0.280, r=0.262, respectively). In multivariate logistic regression analysis age, smoking and TG were found statistically significant to predict of CSF. TG was found most associated with the presence of CSF (OR: 7.516, p=0.001). **Conclusion:** Higher TG, TC/HDL-c, TG/HDL-c, LDL-c/HDL-c and non-HDL-c levels were related with CSF phenomenon.

Keywords: Dyslipidemia; HDL-triglyceride; triglycerides; coronary slow flow; lipid ratio

ÖZET Amaç: Serum lipid parametreleri ve koroner yavaş akım (KYA) fenomeni arasındaki ilişki daha önce araştırılmıştır. Bizim çalışmamızın amacı oransal lipid parametreleri ile KYA arasındaki ilişkiyi araştırmaktır. **Gereç ve Yöntemler:** Biz çalışmaya koroner anjiyografi yapılan ve normale yakın koroner arterleri olan, normal ve yavaş koroner akıma sahip 93 stabil hastayı randomize dahil ettik. Demografik, klinik ve laboratuvar verileri retrospektif olarak yerel veri tabanından bulunarak kaydedildi. Koroner akım velositesi miyokard infarktüsünde tromboliz kare sayısı (TFC) ile değerlendirildi. KYA fenomeni TFC'nin 27 kare üzerinde olması olarak tanımlandı. Sol ön inen koroner arter için düzeltilmiş TFC hesaplandı. **Bulgular:** KYA grubunda 54 hasta, kontrol grubunda 39 hasta vardı. KYA gubunda ortalama yaş, kontrol grubuna göre anlamlı olarak daha fazla saptandı (55,4±9,5 yıl, 50,5±9,8 yıl, p=0,019). Trigliserit (TG) seviyesi KYA grubunda kontrol grubuna göre yüksek bulundu (187,3±103,4 mg/dl, 125,3±63,8 mg/dl, p<0,001). Total kolestrolün yüksek yoğunluklu lipoprotein kolestrolüne oranı (TC/HDL-c), TG/HDL-c, düşük yoğunluklu lipoprotein kolestrolün HDL-c'e oranı (LDL-c/HDL-c) ve non-HDL-c seviyesi KYA grubunda anlamlı olarak yüksek saptandı (sırayla, p=0,007, p=0,004, p=0,044, p=0,018). TG ve TG/HDL-c TFC ile korele bulundu. Çok değişkenli lojistik regresyon analizinde yaş, sigara ve TG değeri KYA'ı öngörmede istatistiksel olarak anlamlı bulundu (r=0,280, r=0,262, sırasıyla). TG değeri KYA ile en fazla ilişkili parametre olarak bulundu (OR: 7,516, p=0,001). **Sonuç:** Yüksek TC/HDL-c, TG/HDL-c, LDL-c/HDL-c, TG ve non-HDL-c seviyeleri KYA fenomeni ile ilişkilidir.

Anahtar Kelimeler: Dislipidemi; HDL-trigliserit; trigliseritler; koroner yavaş akım; lipit oranı

Coronary slow-flow (CSF) such a phenomenon as known as delayed contrast passage to the distal part of the angiographically normal epicardial coronary arteries.[1] The frequency of CSF is declared as 1-7% of coronary angiograms by Wang et al.[2] The definite etiology and pathogenesis of SCF are unclear, yet many of underlying mechanisms have been asserted including endothelial dysfunction, small vessel disease, microvascular dysfunction, increased inflammation and latent atherosclerosis.[3-7] CSF phenomenon also seems to be associated with some of the clinical conditions, such as acute myocardial ischemia, arrhythmias, and finally sudden cardiac death.[8]

Dyslipdemia is a conventional risk factor for coronary artery disease. In previous studies demonstrated that low high-density lipoprotein cholesterol (HDL-c) and high triglyceride (TG) levels were associated with CSF.[9-11] Besides low- density lipoprotein cholesterol (LDL-c) was found associated with CSF.[12] As an "atherogenic index of plasma" LDL-c to HDL-c ratio (LDL-c/HDL-c) and TG to HDL-c (TG/HDL-c) are also associated with increased cardiometabolic risk, acceleration on the atherosclerotic plaque progression and worse cardiovascular events.[13-16] Alike, non-HDL-c and some of proportional serum lipid parameters such as TG/HDL-c, LDL-c/HDL-c may be associated with CSF phenomenon. In this study, we aimed to investigate the relationship between proportional serum lipid parameters and CSF phenomenon.

MATERIAL AND METHODS

STUDY POPULATION

In our study was observational and cross-sectional. We selected the study patients who had undergone elective coronary angiography for suspected ischemic heart disease who have normal or nearly normal coronary arteries in May 2017-August 2017. We enrolled the 93 patients randomly the patients with normal coronary arteries or coronary slow flow. Demographic variables, clinical features and laboratory data were collected retrospectively from the local database. The following classical cardiovascular risk factors were recorded: hypertension (blood pressure >140/90 mmHg or using of an antihypertensive drug), diabetes mellitus (fasting glucose >126 mg/dL, or using of oral hypoglycemic agents or insulin), dyslipidemia (low-density lipoprotein >130 ng/dL, total cholesterol >200 ng/dL) and smoking. Medications used by patients were also recorded.

The exclusion criteria were as follows: < 18 years old, decompensated heart failure, the presence of left ventricular ejection fraction < 40%, severe renal and/or hepatic disease, acute infection and active malignancy and the history of an acute coronary syndrome, percutaneous coronary intervention or cardiac surgery. The study patients provided written informed consent. This study was approved by the Institutional Review Board.

This study was approved by Zonguldak Bülent Ecevit University Hospital Ethics Committee (approval No: 2015-95-21/10). All procedures have been applied in accordance with the principles of the Declaration of Helsinki.

CORONARY ANGIOGRAPHY

Indication for coronary angiography was based on documented coronary ischemia on an exercise stress test or myocardial perfusion imaging. Patients underwent coronary angiography (Siemens Artis Zee, Germany) using the standard Judkins technique with 6 Fr Judkins diagnostic catheter. Iohexol (Omnipaque; Nycomed Ireland Ltd, Cork, Ireland) was used as the choice of contrast agent for the procedures. The coronary arteries were visualized in the right and left oblique positions using caudal and cranial view, at 30 frames/s. The dye injection speed was the same in all of the study patient. Administration of nitrates, which cause enlargement of the artery and the volume to be filled with dye significantly, increases the TFC by approximately 6 frames. Therefore none of the study patients was used of nitrates. We excluded the patients with pacemaker cause of pacing may alter the epicardial flow velocity.

The coronary angiograms were evaluated by two invasive cardiologists blindly. Coronary flow velocity was evaluated by thrombolysis in my-

ocardial infarction (TIMI) frame count (TFC) method as defined by Gibson et al.[17] CFS phenomenon was defined as a TFC greater than 27 frames. TFC was measured for each coronary vessels respectively. Corrected TFC (cTFC) was calculated for the left anterior descending (LAD) coronary artery that divided by 1.7 to find cTFC for LAD's longer length.[17] Thus, the study population was divided into two groups according to TFC. The inter-observer variability of the TFC measurement was 2.8%.

LABORATORY MEASUREMENTS

Blood samples were taken from all patients on the morning of the coronary angiography for measurement of biochemistry panel, plasma glucose and lipid parameters after a fasting period. LDL-c levels were calculated by the Friedewald formula.[18] Only one patient has TG concentration >500 mg/dL. LDL-c level was directly measured in this patient. Non-HDL-c levels were calculated as total cholesterol (TC) minus HDL-c.

STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS 19.0 software (SPSS Inc, Chicago, Illinois, USA). Shapiro-Wilk test was used to assess normality of distribution. Continuous variables were expressed as mean ± standard deviation and categorical variables as number and percent. Continuous variables were compared with the independent sample t test or Mann-Whitney *U* test and categorical variables were compared using Yates's Corrected Chi-square test or Fisher Exact Chi-Square test. Pearson's or Spearman's correlation analysis was performed to determine the relationship between continious variables. A receiver operating characteristic (ROC) analysis was constructed to determine the best cut-off value to predict the outcome. Age, diabetes mellitus, smoking, metabolic syndrome, urea, TG, TG/HDL-c, TC/HD-c, LDL-c/HDL-c and non-HDL-c were taken into multivariable logistic regression analysis was performed to determine the risk factors of CSF phenomenon by Backward LR method. Results were considered statistically significant at P<0.05.

RESULTS

A total of 93 patients were enrolled in this study (n=54 patients in CSF group and n=39 patients in control group). Among our study population, 37 patients (39.8%) were female and 56 patients (60.2%) were male. Baseline clinical and demographic data of the study groups were presented in Table 1.

There was no statistically significant difference regarding sex, body mass index, waist circumference, hypertension, systolic and diastolic blood pressure among the groups. The mean age of the patients in the CSF group was significantly higher than control group (55.4±9.5 vs. 50.5±9.8 years, p=0.019). The prevalence of diabetes mellitus, hyperlipidemia, and metabolic syndrome was significantly higher in CSF group. Similarly, the rate of smoking was higher in CSF group (72% vs 41%, p=0.005). Antiplatelet, beta blocker and statin usage were more common in CSF patients.

Table 2 represents the laboratory data of the patients. Serum TC, LDL-c and HDL-c levels were similar between the groups. Also especially TG levels higher in CSF group than control group (187.3±103.4, 125.3±63.8, p<0.001). The analysis of proportional lipid parameters also showed in Table 2. According to this, TC/HDL-c, TG/HDL-c, LDL-c/HDL-c and non-HDL-c levels were significantly higher in CSF group (p=0.007, p=0.004, p=0.044, p=0.018, respectively).

We performed correlation analysis between mean TFC and lipid parameters shown in Table 3. As a result, TG and TG/ HDL-c were found a weak and positive correlation with mean TFC (r=0.280, r=0.262, respectively).

In the ROC curve analysis, the AUC (area under the curve) value of TG was 0.698 for the patients in the CSF group and the test was found to have 53% sensitivity and 87% specificity at values above 165 mg/dl (95% CI: 0.594-0.789, *p*=<0.001) in Figure 1.

The AUC value of TG/HDL was 0.694 for the patients in the CSF group, and the test was found to have 72% sensitivity and 61% specificity at values above 2.84 (95% CI: 0.590-0.785, *p*=<0.001) in Figure 2.

TABLE 1: Comparison of baseline demographic and clinical characteristics of the groups.[a,b]

Variables	CSF group (N=54)	Control group (N=39)	P value
Age (year)	55.4±9.5	50.5±9.8	0.019
Female gender, n (%)	17 (31.5)	20 (51.3)	0.087
Hypertension, n (%)	26 (48.1)	20 (51.3)	0.930
Diabetes mellitus, n (%)	20 (37.0)	5 (12.8)	0.018
Smoking, n (%)	39 (72.2)	16 (41.0)	0.005
Hyperlipidemia, n (%)	26 (48.1)	8 (20.5)	0.012
BMI (kg/m^2)	29.7±3.6	29.4±5.7	0.735
Waist circumference (cm)	106±12.1	104±14.6	0.504
Metabolic syndrome n (%)	29 (53.7)	11 (28.2)	0.025
Blood pressure (mmHg)			
Systolic	129.8±19.0	128.6±17.5	0.757
Diastolic	77.7±10.3	78.4±13.0	0.771
Medications, n (%)			
Antiplatelet	28 (73.7)	10 (26.3)	0.020
Beta blocker	21 (38.9)	5 (12.8)	0.011
Calcium canal blocker	9 (16.7)	5 (12.8)	0.827
ACEI	9 (16.7)	3 (7.7)	0.337
ARB	10 (18.5)	7 (17.9)	1.000
Statin	16 (29.6)	4 (10.3)	0.047
Nitrate	5 (9.3)	1 (2.6)	0.395

[a] ACEI indicates angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; BMI: Body-mass index; CSF: Coronary slow-flow.

[b] Data are presented as means ± SD or n (%)

TABLE 2: Comparative analysis of laboratory parameters between two groups.[a,b]

Variables	CSF group (N=54)	Control group (N=39)	P value
Urea (mg/dL)	32.2±9	27.6±8.7	0.016
Creatinine (mg/dL)	0.87±0.19	0.80±0.17	0.064
Glucose (mg/dL)	123.6±53.3	105.6±32.0	0.047
TC (mg/dL)	201.7±44.3	184.2±44.1	0.064
LDL (mg/dL)	122.1±37.8	111.8±35.2	0.185
cxHDL (mg/dL)	44.8±10.5	47.5±12.8	0.256
Triglyceride (mg/dL)	187.3±103.4	125.3±63.8	<0.001
TC/HDL-c	4.65±1.11	4.02±1.05	0.007
TG/HDL-c	4.43±2.72	2.93±1.96	0.004
LDL/HDL-c	2.81±0.89	2.44±0.84	0.044
Non-HDL-c (mg/dL)	156.8±40.5	136.6±38.7	0.018
LAD TFC	24±6	17±3.7	<0.001
CX TFC	30±6.3	22±2.6	<0.001
RCA TFC	28±7.8	20±2.8	<0.001
Mean TFC	27±4.2	20±2.2	<0.001

[a] CSF indicates coronary slow-flow; CX: Circumflex; HDL: High-density lipoprotein; LAD: Left anterior descending ; LDL: Low-density lipoprotein; RCA: Right coronary artery; TFC: TIMI frame count; TC: Total cholesterol; TG: Triglyceride.

[b] Data are presented as mean ± SD.

TABLE 3: Correlation analysis between lipid parameters and TFC.

Variables	r	P value
TG	0.280	0.007
TC/HDL-c	0.179	0.086
TG/HDL-c	0.262	0.011
LDL/HDL-c	0.101	0.335
Non-HDL-c	0.136	0.195

HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; TFC: TIMI frame count; TC: Total cholesterol; TG: Triglyceride.

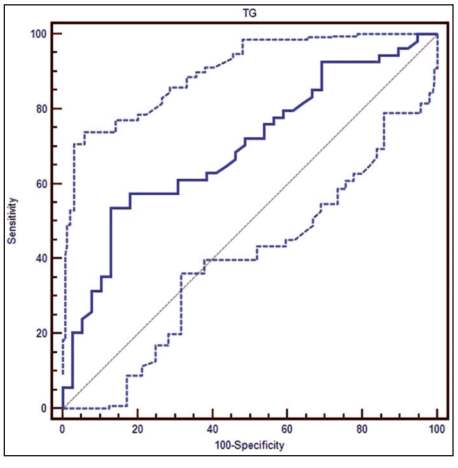

FIGURE 1: The ROC curve anaylsis of the trigliseride (TG). AUC=0.698, p=<0.001.

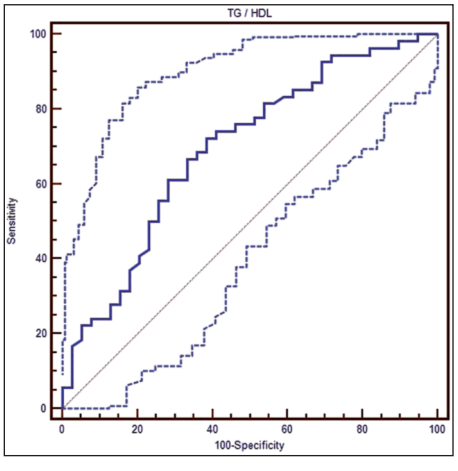

FIGURE 2: The ROC curve anaylsis of the trigliseride to HDL-c (TG/HDL-c). AUC=0.694, p=<0.001.

Multivariable logistic regression analysis was performed to determine the risk factors of CSF phenomenon. Indicators were selected among the significantly different parameters in CSF group that were age, diabetes mellitus, smoking, metabolic syndrome, urea, TG, TG/HDL-c, TC/HD-c, LDL-c/HDL-c and non-HDL-c values. Age, smoking and TG were found statistically significant to predict of CSF in Table 4. TG was found as the most associated indicator with the presence of CSF (OR: 7.516, 95% CI: 2.323-24.323, p=0.001).

DISCUSSION

The pathological mechanisms of CSF are not fully understood yet. The main hypothes for the etiology of CSF is microvascular dysfunction. Inflammation and diffuse atherosclerosis may contribute to the development of CSF phenomenon. Some inflammatory biomarkers were found associated with CSF in recent studies.[19,20] However the data about association between CSF and lipid parameters are limited.

We thought that there may be an association between CSF phenomenon and lipid parameters and proportional serum lipid parameters. As our literature review, we did not find any previous study about the relationship between CSF and proportional serum lipid parameters. In our study, we have shown that there were a significant association between CSF phenomenon and higher TG, TG/HDL-c, TC/HD-cL, LDL-c/HDL-c and non-HDL-c. There are several studies about the association between LDL-c levels and CSF. According to these studies LDL-c level was not related with CSF.[11,21] Alike we were also found that LDL-c level was similar in two groups in our study. Further Fan et al. demonstrated that statin usage provide a benefit in patients with CSF and reduced coronary flow reserve.[22] As a primary target of statin therapy, LDL-c is well-known and more atherogenic lipid fraction widely used in laboratory analyzes. This condition may be explain with different ef-

TABLE 4: Multivariate logistic regression analysis of independent predictors for the presence of coronary slow flow.

Indicators*	OR	%95 CI	P value
Age	1.095	1.033-1.161	0.002
Smoking	4.739	1.593-14.102	0.005
Trigliserid	7.516	2.323-24.323	0.001

*Age, diabetes mellitus, smoking, metabolic syndrome, urea, TG, TG/HDL-c, TC/HD-c, LDL-c/HDL-c and non-HDL-c were taken into multivariable logistic regression analysis.

fects of statin other than LDL-c lowering. In our study the usage of statin was higher in CSF group that may cause the high number of high-risk patients for atherosclerosis in CSF group. The similar LDL-c level between two groups may explain the higher usage of statin in CSF group. The higher usage of statin and beta blocker in CSF group may affect our findings and this condition was one of the limitations of the study.

Yokoyama et al. showed that hypertriglyceridemia is associated with impaired coronary vasodilatation in the absence of evident coronary stenosis.[23] Sezgin et al. also reported that low HDL and high TG levels might be contributed to endothelial dysfunction in CSF patients.[11] In two studies, low HDL-c level seems to be an independent predictor for CSF phenomenon.[10,24] In our study we found high TG levels in CSF group like previous studies. However we did not found a significant difference with HDL-c in two groups. In our study the similarity of HDL-c level in two groups may be due to differences in statin use, smoking or daily exercise time. According our findings we can say TG was more important than LDL-c and HDL-c in coronary slow flow pathogenesis.

As it is known, LDL/HDL-c was an important predictor of atherosclerotic plaque vulnerability and lipid content.[13] However the importance LDL/HDL-c to predict CSF remains uncertain and have limited data. In our study LDL/HDL-c was higher in CSF group than control group.

According to a recent study, the correlation analysis of the TG/HDL-c with the remainder of the lipid parameters revealed that a higher TG/HDL-c was associated with an increasingly atherogenic lipid profile.[25] Similarly TC/HDL-c seems provide further information to classical atherogenic lipid parameters.[26] In this study, we found that both parameters significantly higher in CSF group. Besides TG/HDL-c was correlated with mean TFC like TG level.

In conjunction with previous studies, we aimed to research the relationship between some of proportional serum lipid parameters and presence of CSF phenomenon. To the best of our knowledge, there was no study hitherto has evaluated the association of proportional lipid parameters with the CSF phenomenon. In our study, we found a significant relationship between the presence of CSF and TC/HDL-c, TG/HDL-c, LDL-c/HDL-c, serum TG level, non-HDL-c levels. Furthermore TG level and TG/HDL-c were correlated with mean TFC value in correlation analysis. The higher TG/HDL-c may cause of higher TG level. Because TG level was higher in CSF group and HDL-c level was similar between two groups.

Our study has some limitations that should be referred. The major limitation of the study was retrospective design. Another limitation was the heterogeneity in the clinical characteristic of the study population. The groups were different in respect to age, diabetes mellitus, smoking, metabolic syndrome and medication. This might affect the results. We performed multivariate logistic regression analysis to demonstrate the effect of heterogeneity in the clinical characteristic. According our findings the effect of age was so few compared with triglyceride value (OR= 1.095 vs OR=7.516).

Smoking was also higher in CSF group rather than the control group and smoking was found as one of independent predictors for CSF (OR: 4.739). Arbel and colleagues demonstrate that current smoking is the most strong predictor for CSF.[27] Especially smoking might effect the level of HDL-c and proportional lipid parameters.

Urea and fasting blood glucose levels were higher in CSF group. However urea levels were in normal limits between groups. Besides we used a single blood sample for our analysis provides no information about a temporal trend. Higher fasting blood glucose level may also explain with frequent diabetes mellitus rate in CSF group. The difference of the presence of diabetes mellitus might affect the lipid parameters.

The other limitation was excess use of statins and beta blocker in the CSF group. These medications might affect all lipid parameters and the study results. Further we did not recorded daily exercise

time. Exercise affects all lipid parameters, in particular HDL-c. It was an another limitation of our study.

CONCLUSION

In conclusion, our findings showed that higher TG, TG/HDL-c, TC/HD-c, LDL-c/HDL-c and non-HDL-c levels were significantly associated with the presence of CSF phenomenon. Besides TG and TG/HDL-c were found correlated with TFC. Furthermore TG was found statistically significant to predict of CSF in multivariate logistic regression analysis. So we can say TG was most important lipid parameters than the other lidip parameters and proportional serum lipid parameters in coronary slow flow pathogenesis. These parameters are readily available at no extra cost, permits sustained monitoring with longitudinal follow-up for clinical events. Nevertheless further prospective investigations required in a large-scale prospective design to demonstrate stronger correlation.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Belma Kalaycı;* ***Design:*** *Belma Kalaycı, Süleyman Kalaycı, Fürüzan Köktürk;* ***Control/Supervision:*** *Süleyman Kalaycı, Belma Kalaycı;* ***Data Collection and/or Processing:*** *Belma Kalaycı, Süleyman Kalaycı;* ***Analysis and/or Interpretation:*** *Fürüzan Köktürk;* ***Literature Review:*** *Belma Kalaycı;* ***Writing the Article:*** *Belma Kalaycı, Süleyman Kalaycı, Fürüzan Köktürk;* ***Critical Review:*** *Belma Kalaycı, Süleyman Kalaycı, Fürüzan Köktürk;* ***Statistical Analysis:*** *Fürüzan Köktürk.*

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