RESEARCH ARTICLE

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Platelet Large Cell Ratio Levels in Smoking

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Objective: It was reported that smoking promotes endovascular thrombosis by increasing platelet adherence to endothelium and platelet aggregation. It is known that platelet volume indices (PVI) can indicate to increased platelet activity. Therefore, we aimed to evaluate effects of smoking on PVI values in healthy smokers.

Materials and Methods: Two hundred and ninety eight consecutive current smoking, healthy male subjects and two hundred and six age-matched, non-smoking healthy male subjects were enrolled to the study. Complete blood count parameters (especially PVI values), and lipid profile were analyzed in all study participants and persons' smoking habits were calculated as pack-years.

Results: The study showed that platelet large cell ratio was (PLC-R) significantly higher by smokers compared to the non-smokers. PLC-R and PLCC (Platelet large cell count) values have a moderate degree of positive correlation with pack-year. In multivariate logistic regression analysis it was found that PLC-R levels were independent predictors of smoking (*β*=0.384, P: 0.03, 95% CI: 0.134 to 2.071). There were no statistically significant differences between two group in terms of other PVI parameters**.**

Conclusion: Elevated PLC-R level is correlated with cigarette smoking positively and may be a useful indicator of coagulation activity in the smokers.

Key words: *Smoking, platelet volume indices, platelet large cell ratio*

Sigara İçiciliğinde Büyük Hücreli Trombosit Oranı Düzeyleri

Amaç: Sigara içiciliğinin, trombositlerin agregasyonunu ve endotele tutunmasını arttırmak suretiyle endovasküler trombozu arttırdığı bildirilmiştir. Trombosit hacim indexleri (THİ)'nin artmış trombosit aktivitesini belirlemede kullanılabildiği bilinmektedir. Bu nedenle biz bu çalışma ile sigara içiciliğinin THİ üzerine olan muhtemel etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya sağlıklı, aktif sigara içicisi 298 erkek olgu ve sigara içmeyen sağlıklı 206 erkek olgu dahil edildi. Tam kan sayımı (özellikle PHİ değerleri) ve lipid profili analiz edildi. Bireylerin sigara içiciliği paket-yıl olarak hesaplandı.

Bulgular: Bu çalışma, büyük hücreli trombosit oranı (PLC-R) değerlerinin sigara içen bireylerde içmeyenlere kıyasla daha yüksek olduğunu göstermektedir. Ayrıca PLC-R and PLCC (büyük hücreli trombosit sayısı) değerleri paket-yıl ile orta derecede pozitif korele olarak değerlendirildi. Yapılan multivariate regresyon analizi ile PLC-R'nin sigara içiciliği için bağımsız bir öngördürücü olduğu belirlendi (*β*=0.384, P: 0.03, %95 CI: 0.134 to 2.071). Diğer PHİ parametreleri açısından iki grup arasında fark gözlenmedi.

Sonuç: Yüksek PLC-R seviyesi sigara içiciliği ile pozitif koreledir ve sigara içen bireylerde gözlenebilecek koagülasyon aktivitesi artışı için kullanışlı bir belirteç olabilir.

Anahtar Kelimeler: *Sigara içiciliği, trombosit hacim indexleri, platelet large cell ratio*

Introduction

Apart from causing cardiovascular disease, smoking can lead to cancer, respiratory and neurological diseases and may affect all systems (1). Cigarette smoking is one of the leading causes of morbidity and mortality in cardiovascular disease and has been implicated in the pathogenesis of atherosclerosis and thrombotic events (2, 3). It has suggested that smoking increases the risk of venous thrombosis and is considered one of the major risk factors for atherothrombotic disease (4).

Platelet volume indices (PVI) can be considered as indicators of increased platelet activity and include platelecrit (Pct), platelet large cell ratio (PLC-R), mean platelet volume (MPV), mean platelet volume-to-platelet count ratio, platelet distribution width (PDW) and platelet distribution width-to-platelet count ratio (PDW/P) (5, 6).

While there are many studies about PVI in many areas, there are very few reports on the effect of smoking on PVI and we are unaware of a study evaluating the effect of smoking on PLC-R, mean platelet volume-to-platelet count ratio (MPV/P) and PDW/P (7-9).

Materials and Methods

Study Population: This cross-sectional, observational study included two hundred and ninety eight consecutive male participants with current smoking and two hundred and six age-matched healthy male subjects with no history of smoking who admitted to

the outpatient clinics of Elazig Education and Research Hospital and Harput State Hospital, Elazig, Turkey, between April 2016 and January 2017. Participants are aged between 17-75 haven't any systemic disease or atherosclerotic risk factors (except from hyperlipidemia). The study was performed in accordance with Helsinki principles and approved by the local Ethics Committee (Presidency of T.C. Fırat University Ethics Committee).

Participants who smoked one or more cigarettes per day were accepted as smokers. Pack-year were calculated as number of cigarettes smoked per day x number of years smoked/20.

Participants whose BMI>30 kg/m^2 were excluded from the study.

Laboratory Measurements: All Blood samples (6 mL for full biochemistry, 5 mL for complete blood count) were obtained from ante-cubital vein after 12 hours of fasting. Samples were drawn into vacuum tubes containing 15% K3 ethylene diamine tetraacetic acid (EDTA)-anticoagulation tubes (Sarstedt, Essen, Belgium) and analyzed. CBC parameters were assessed using a Sysmex XN-1000 hematology analyzer (Sysmex Europe GmbH, Sysmex Corporation, Hamburg, Germany) according to the manufacturer's instructions. PVI were evaluated using a 3 mL sample of venous blood collected in EDTA-containing anticoagulation tubes. We analyzed the blood samples of two groups using an automatic blood counter after half an hour of venipuncture. The half hour waiting period was allowed for the stabilization of platelet shape changes. Glucose, urea, creatinine, total cholesterol, triglycerides, high-density lipoprotein colesterol (HDL-C), and low-density lipoprotein colesterol (LDL) levels were measured with a Cobas®8000 (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) auto-analyzer equipment using chemiluminescence method.

Statistical evaluation: Statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows. The Kolmogorov–Smirnov test was used to evaluate whether the variables were normally distributed. Continuous data were analyzed by Student's *t*-test for normally distributed variables and Mann–Whitney *U* test for non-normally distributed variables. Normally distributed variables were presented with mean and standard deviation, non-normally distributed variables were presented with median and 25th-75th precentiles. Multivariate regression analysis was performed to determine which clinical variables would independently predict smoking. Pack-year was used in the model as a dependent variable. Platelet counts, MPV, PLR(Total platelet count/ Total lymphocyte count ratio), PLC-R, PDW, PCT, triglycerides, haemoglobin, sodium, potassium, and creatinine were treated as independent variables. Results were presented as beta coefficients and 95% confidence intervals (CIs). Correlation analyses were performed using Pearson's correlation test. All P-values were two-tailed, and values <0.05 were considered to indicate statistical significance.

Results

The study included 504 consecutive male subjects. There were 298 smokers and 206 nonsmokers. It was observed that PLC-R values for the smokers group were significantly higher compared to the non-smokers group (32.35±6.37 and 30.33±7.85, P=0.03) (Table 1, Figure 1, Figure 2). Wight blood cell (WBC), haematocrit, haemoglobin values and triglycerides for the smokers group were significantly higher than the non-smokers group (respectively, P=0.001, P=0.02, P=0.01, P<0.0001) (Table 1). On the other hand, high density lipoprotein cholesterol (HDL-C) levels for the non-smokers were significantly higher than the smokers group (P<0.0001). Although there were no statistically significant differences between the two groups with regard to PDW, PLCC (Platelet large cell count), total platelet counts, total cholesterol, low density lipoprotein cholesterol (LDL-C), triglycerides levels, there was a positive correlation between pack-year and these parameters in the smokers group in addition to PLC-R values (Table 2).

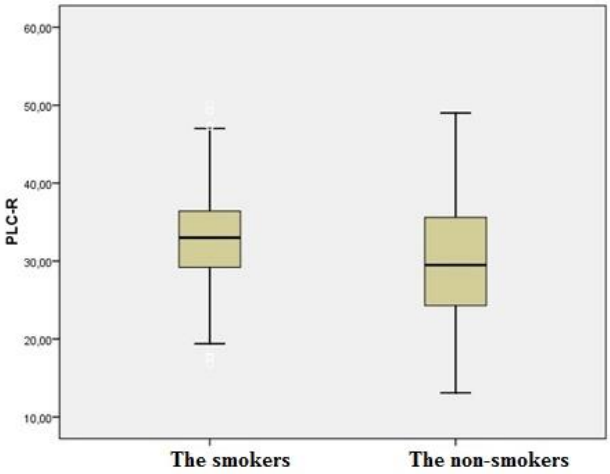

Figure 1. Comparison of PLC-R between the smokers and The non-smokers

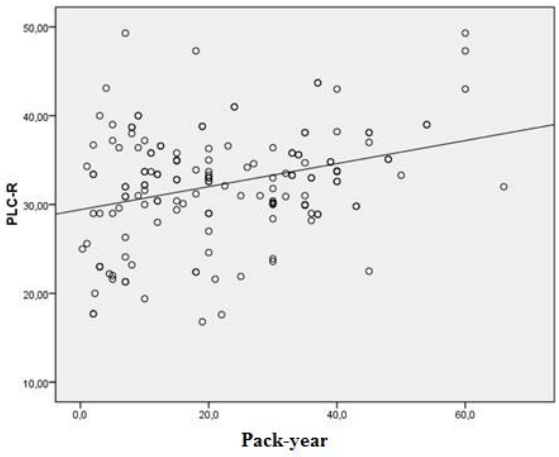

Figure 2. Schematic illustration of the correlation analysis between PLC-R and Pack-Year

Multivariate logistic regression analysis results showed that PLC-R levels were independent predictors of smoking (β=0.384, P: 0.03, 95% CI: 0.134 to 2.071) (Table 3).

There were no statistically significant differences between the smokers group and the non-smokers group in terms of hyperlipidemia, age and other investigated laboratory parameters (Table 1).

Table 1. Inter-group comparison of demographical data

	The Smokers (298)	The Non-smokers (206)	P value
Age (year)	35	36.2	0.36
Hyperlipidemia, n (%)	38(12.8)	20(9.7)	0.36
Platelet (10^3/mm^3)	257.5±50.8	259.8±58.2	0.65
Platelecrit (%)	0.28±0.11	0.26±0.10	0.07
Mean Platelet Volume (fL)	10.6±5.01	10.4±1.04	0.38
PDW (fL)	11,96±2.1	11.91±2.2	0.8
PLC-R (%)	32.35±6.37	30.33±7.85	0.03*
PLCC (10^3/mm^3)	84.8±21.21	79.6±21.61	0.06
MPV/P Ratio (%)	4.34±2.63	4.24±1.23	0.6
PDW/P Ratio (%)	4.86±1.49	4.88±1.68	0.9
PLR (%)	129.5±57.37	131.9±50.79	0.6
Glucose (mg/dL)	93.9±13.41	95.4±14.76	0.26
Triglycerides (mg/dL)	150.7 (95.0-156.0)	131.6 (75.5-151.5)	<0.0001#
Low density lipoprotein cholesterol (mg/dL)	102.5±32.7	99.4±33.3	0.31
Total cholesterol (mg/dL)	173.4±40.9	171.5±36.7	0.6
HDL cholesterol (mg/dL)	42.1±10.2	47.0±11.6	<0.0001**
Hemoglobin (g/dL)	15.2±2.7	13.9±3.6	0.01*
Hematocrit (%)	44.3±6.7	42±9.1	0.02*
White blood cell (10^3/mm^3)	7.53±2.1	7.0±1.6	0.001**
Urea (mg/dL)	28.0±7.63	27.1±7.64	0.12
Creatinine (mg/dL)	0.65±0.37	0.68±0.38	0.28
Sodium (mmol/L)	138.0± 2.91	139.4± 3.01	0.10
Potassium (meq/L)	4.4± 0.46	4.3± 0.41	0.17
Calcium (mg/dL)	9.51± 0.61	9.42± 0.55	0.14

PDW: Platelet distribution width, PLC-R: Platelet large cell ratio, PLCC: Platelet large cell count, MPV/P Ratio: Mean platelet volume/Total platelet count ratio, PDW/P Ratio: Platelet distribution width/Total platelet count ratio, PLR: Total platelet count/Total lymphocyte count ratio

Mann–Whitney *U* test#.

Statistically significant (*P<0.05, **P<0.01)

Table 2. Pearson correlation analysis between smoking (as pack-year), Platelet volume indices and some laboratory measurements

	Pack-year	
	r	P
Platelet (10^3/mm^3)	0.160	0.007**
Platelecrit (%)	0.118	0.140
Mean platelet volüme (fL)	-0.013	0.822
PDW (fL)	0.316	<0.0001**
PLC-R (%)	0.310	<0.0001**
PLCC (10^3/mm^3)	0.349	<0.0001**
PLR (%)	-0.076	0.203
MPV/P Ratio (%)	-0.062	0.298
PDW/P Ratio (%)	0.076	0.204
WBC (10^3/mm^3)	0.252	<0.0001**
Hemoglobin (g/dL)	0.162	0.142
Hematocrit (%)	0.231	0.035*
Triglycerides (mg/dL)	0.098	0.100
Total cholesterol (mg/dL)	0.207	<0.0001**
LDL-C (mg/dL)	0.202	0.001**

PDW: Platelet distribution width, PLC-R: Platelet large cell ratio, PLCC: Platelet large cell count, MPV/P Ratio: Mean platelet volume/Total platelet count ratio, PDW/P Ratio: Platelet distribution width/Total platelet count ratio, PLR: Total platelet count/Total lymphocyte count ratio, WBC: White blood cell, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol,

Statistically significant (*P<0.05, **P<0.01)

Table 3. Multivariate Logistic Regression Analysis Results in The Smokers Group

	β	P	95% Confidence Interval	
PLC-R	0.384	0.03	0.134	2.071
PLR	0.031	0.84	-0.102	0.124
MPV	-0.482	0.06	-19.806	0.397
PCT	-0.129	0.40	-99.442	40.882
PDW	0.257	0.31	-2.068	6.340
Triglycerides	0.101	0.52	-0.053	0.103
Sodium	0.122	0.40	-0.799	1.987
Hemoglobin	0.154	0.39	-0.996	2.498
Creatinine	0.188	0.25	-15.194	55.898

Discussion

The important findings of our study is that PLC-R was significantly higher in the smokers compared to the non-smokers (Table 1, Figure 1). In addition, PLC-R and PLCC values have a moderate degree of positive correlation with pack-year (Table 2, Figure 2). There were no statistically significant differences between the two groups in terms of other PVI parameters (Table 1).

Smoking has serious affects on atherosclerosis and promotes coronary artery thrombosis by increasing platelet adherence to endothelium and platelet aggregation (10). It was reported that smoking may increase platelet aggregation and promote endovascular thrombosis through various mechanisms (11). One of the most important mechanism is that platelet survival half-life is shortened by smoking in healthy persons (from 4 days to less than 92 hours) (12). This situation causes to enhancement in reproductibility and aggregability in platelet actions (10).

Larger platelets have more granules and receptors, and prone tend clot more rapidly than smaller ones. Therefore, the platelet's activity is more accurately exemplified via their size, not count (13). Platelet size can be evaluated from the PVI, including the PLC-R, MPV, Pct, PDW, PDW/P, and MPV/P (6,14-17).

The MPV is a machine-calculated measurement of the average size of platelets found in blood and is typically included in blood tests as part of the CBC (18). When platelet production is decreased, young platelets become bigger and more active, thus MPV levels increase. Increasing in MPV infers increased platelet diameter, which can be handled as a marker of production rate and platelet activation (19). It is calculated by the following formula, MPV (fL) = [(plateletcrit (%)/platelet count ($\times 10^9$/l)] $\times 10^5$ (20).

The Pct is the ratio of the platelet volume to the whole blood volume (reported as a %) and can be accepted analogous to the hematocrit (20, 21). Pct is an effective screening tool for detecting platelet quantitative abnormalities. It is calculated according to the formula Pct = Platelet count × MPV / 10,000 (18, 22-24). Normal platelet count has a Plateletcrit within the range of % 0.22 to % 0.24 (19, 25).

PLC-R is an indicator of circulating larger platelets (> 12 femtoliter: fL), which is presented as percentage and calculated according to the formula PLC-R = Large platelet cell counts(>12 FL) / Total platelet counts. It has also been used to monitor platelet activity (26). P-LCC is the number of platelets that are greater than 12 fL. P-LCC is the multiplication of Plt× P-LCR (27).

The platelet distribution width (PDW) is the width of distribution of platelets related to the different sizes produced by these cells (28). Inflation in PDW is an indication for the anisocytosis of platelets. Therefore, PDW is an indicator of volume variability in platelets size (19). PDW is a simple platelet index, which is accepted as a specific marker of platelet activation, since it does not increase during simple platelet swelling (29). Briefly, it was accepted that PDW directly measures variability in platelet size, changes with platelet activation, and reflects the heterogeneity in platelet morphology (25, 29). In recent study, although PDW and platelet values were not statistically significant between smokers and non-smokers groups, in the correlation analysis performed within the smokers group, it was observed that the pack-year and platelet values were correlated with a weak level and the PDW values were correlated with a moderate level. We think this situation may be because of some PVI values between the two groups are close to each other due to the fact that many cases included in the smokers group have a very low pack-year amount.

Previous studies demonstrated the inverse relationship between MPV and platelet count in normal populations which suggests the need to interpret MPV and platelet counts as a ratio rather than as independent variables (30-32). In the light of this information, we investigated MPV/P Ratio (Mean platelet volume/Total platelet count ratio), PDW/P Ratio (Platelet distribution width/Total platelet count ratio) and PLR (Total platelet count/Total lymphocyte count ratio) in addition to the PVI.

Chronic cigarette smoking results in a increase in platelet activation (33). The platelet function can be detecteded easily by PVI which does not require advanced or expensive technology (5-7). In the present study, we found elevated PLC-R values in smokers than non-smokers and a moderate degree of positive correlation observed between PDW, PLC-R, PLCC values and pack-year. Additionally, a weak but significant correlation observed between platelet counts and pack-year. Possible explanation for why smoking leads to increment in some PVI may be related to chemicals such as carbon monoxide and nicotine in cigarette smoke, which increase platelet activity (34).

The present study showed that smoking is associated with a statistically significant increase in

WBC (White blood cell), hemoglobin, hematocrit and triglycerides. On the other hand, lipid profile analysis (total cholesterol, and LDL-C) in our study, did not significantly different between two groups and this finding is inappropriate with previous findings that showed higher serum levels of total cholesterol, and LDL-C concentrations in smokers (35). There isn't any difference between smokers and non–smokers with regard to hyperlipidemic cases included in our study and this situation may be responsible for lipid profile results. Secondly, this may be due to dietary differences between the two groups. Last, triglycerides and HDL-C analysis in our study groups were significantly different between the two groups. These findings are consistent with previous findings that showed higher serum levels of triglyceride concentrations and lower plasma concentrations of HDL-C in smokers (35-37).

The harmful effects of cigarette smoking with regard to arterial cardiovascular diseases are well known (38). Plausible mechanisms by which smoking can increase the risk of stroke and heart disease are numerous and include carboxyhaemoglobinemia, increased platelet aggregability, increased fibrinogen levels, reduced HDL-cholesterol (39). Larger platelets are haemostatically more active and are a risk factor for developing coronary thrombosis (40). Some PVI values we observed coincide with the previous research conducted on cigarettes and support the thesis of that healthy smokers are prone to arterial thrombus formation (3, 10, 33, 34, 41).

Previous studies have reported that platelet activation increases with age (42). It has also been shown that age is associated with an increase in platelet aggregability (43). Recent studies reported platelet counts and some PVI are positively correlated with obesity as well (44-46). On the other hand, some authors declared refuting findings on these areas (47-48). In our study, participants whose BMI>30 kg/m^2 were excluded and there were no statistically significant differences between the smokers and non-smokers group in terms of age. That is why, analyzing of the study results focused on just smoking. The present study revealed that PLC-R is significantly higher in the smokers group compared to the non-smokers group (Table 1, Figure 1, Figure 2). Furtheremore, although there were no statistically significant differences between the two groups with regard to PDW, PLCC (Platelet large cell count), total platelet counts and there were a positive correlation between pack-year and these parameters in addition to PLC-R values (Table 2, Figure 2). Therefore, it is reasonable to say elevated PLC-R level may be a useful indicator of coagulation activity in the smokers.

Conclusions: PVI are important, simple, effortless, and cost effective tools that should be used for predicting the possibility of impending acute thrombotic events. Cases with larger platelets can easily be identified during routine complete blood count analysis and could possibly benefit from preventive treatment. Therefore, more attention should be paid to these indices in the examinaton of a smoker case.

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