

RELATIONSHIP BETWEEN PLATELET INDICES AND LIPIDEMIAS: A CROSS-SECTIONAL STUDY AT KARACHI

Sikandar Hayat Khan¹, Syed Azhar Ahmad²

¹ Department of Pathology
PNS Rahat, Karachi - Pakistan.

² Baqai Medical and Dental
University, Karachi - Pakistan.

Address for correspondence:

Dr. Sikandar Hayat Khan

Department of Pathology PNS
Rahat, Karachi - Pakistan.

E-mail: sik_cpsp@yahoo.com

Date Received:

July 11, 2013

Date Revised:

February 10, 2014

Date Accepted:

February 17, 2014

ABSTRACT

Objective: To compare platelet indices among patients with low and high levels of cholesterolemia and triglyceridemia

Methodology: This cross-sectional study was conducted from January 2011 to May 2012 at the departments of pathology, PNS Rahat and Baqai medical and dental university, Karachi. A total of 867 subjects presenting for estimation of fasting triglycerides and total cholesterol were selected after excluding patients receiving anti-platelet or lipid medication, pregnancy, acute infectious disorders. They were interviewed, examined and sampled for measurement of total cholesterol, triglycerides and platelet indices including total platelet count, mean platelet volume (MPV), platelet distribution width (PDW) and platecrit (PCT).

Results: The results of platelet count and mean platelet volume were found to be significantly different among subjects with normal cholesterolemia (<5.2 mmol/L), borderline raised cholesterol group (5.2-6.3 mmol/L) and hypercholesterolemia (>6.3 mmol/L); however, post-hoc comparison did not show any significant difference between all groups. Using age as a variable and segregating total cholesterol results into 7 groups, starting from very low cholesterol values (<4.0 mmol/L) to highest (>6.5 mmol/L), in a univariate general linear model, higher mean platelet volume were observed at the extremes of cholesterolemia groups [p=0.039]. A similar trend was observed for platelet count after adjusting for age, where low levels of platelet levels were associated with hypocholesterolemia and hypercholesterolemia (p=0.021).

Conclusion: Higher MPV and low total platelet counts were associated with the observed extremes of cholesterol range. No significant differences were observed for platelet indices across various groups formulated based upon fasting triglycerides.

Key Words: Platelet count, Platecrit (PCT), Mean platelet volume (MPV), Platelet distribution width (PDW), Total cholesterol, Triglycerides.

This article may be cited as: Khan SH, Ahmad SA. Relationship between platelet indices and lipidemias: A cross-sectional study at Karachi. *J Postgrad Med Inst* 2014; 28(2):121-7.

INTRODUCTION

The role of platelets in health and disease cannot be underestimated. Physiologically the platelets are primed to induce the formation of primary homeostatic plug, and later to ensure coagulation by repairing the endothelial vessel repair¹. The pathological dimensions about the platelet's role are simply an extension of their physiological function in health and include exaggerated atherogenesis and thrombus formation¹. The available evidence highlights that certain morphological changes do appear before these platelets get consumed in the accelerated process of atherosclerosis including coronary artery disease, stroke and others².

These morphological changes in the platelets and possibly their numerical counts may indicate the possible platelet activation in such situations³. So changes could be possible in both platelet numbers and morphological appearance once they encounter an atherogenic environment in the plasma. Alongside, the current risk stratification strategies rely heavily upon the measurement of lipids in blood⁴. Raised levels of cholesterol or triglycerides may indicate an underlying possibility of enhanced fat deposition in vasculature with risk for cardiovascular disease⁴. Thus, varied or enhanced platelet lipid interactions should possibly lead to accelerations in atherosclerosis with ultimate outcome in the shape of cardiovascular diseases⁵. Present day management ap-

proaches in medicine are the emergence of various anti-platelet and anti-lipids medications for both primary and secondary prevention of cardiovascular diseases^{5, 6}.

Considering the role of platelet and lipid interactions in the formation and then rupture of atherosclerotic plaque as fundamental, following aspects prompt us to evaluate the role of available platelet indices with lipidemia: Firstly, platelet indices including numerical counts, mean platelet volumes (MPV), platelet distribution width (PDW), and platecrit (PCT) are now routinely measured on commonly used hematological cell counters in most developing countries. An establish link between lipids and platelet indices can provide commonality of targets for both in vogue therapeutic use, and also the diagnostic side can be better used for monitoring patients. Secondly, literature review albeit sparse, does highlight studies not linking cardiovascular disease progression with morphological platelet changes. Kalay et al during their evaluation of progression of coronary artery disease did not find changes in mean platelet volumes as different while showed at that the same time factors like cholesterol being significant between progressive and non-progressive groups⁷. Thirdly, most studies evaluating the link between platelet indices and cholesterol have confined their roles to platelet counts and mean platelet volume; while less data is available to demonstrate the relationship between platelet parameters and triglycerides. Finally, multiple studies have identified the ethnicity and racial aspects to be a very important determinant in the development of cardiovascular diseases especially in Asians⁸. While studies have identified multiple reasons to this ethnic predisposition, still other factors remain there to be explored⁹. Further exploration into platelet to lipid interaction could be one area which may further identify the association between our ethnicity to peaking prevalence of cardiovascular diseases.

Keeping this background in mind the study was planned to evaluate the platelet indices as generated on a common hematological analyzers with those patient's cholesterol levels for possible association.

METHODOLOGY

This was a cross-sectional study planned at the departments of pathology, PNS Rahat in liaison with Baqai Medical and Dental College, Karachi between January 2011 to May 2012. Based upon non-probability convenience sampling, all subjects who presented in medical fasting status i.e., overnight fast of 10-12 hours after excluding the state of stress like acute ailment or apparent anxiety, for analysis of their lipid status were considered for inclusion into the study. The several exclusions were pregnancy, having an acute infectious disorder,

admitted patients, on anti-platelet or other cholesterol lowering medications, not observing an exact medical fasting status or collected sample being rendered unfit due to marked hemolysis, or other reasons. A total of 867 subjects were finally selected for study after explanation of study purpose and signing of the consent Per-forma. Enrolled individuals were interviewed, clinically examined and then sent to the phlebotomy station for collection of 7 ml of blood as per standard procedure. 4 ml of blood collected in heparinized vacutainer tubes was sent to chemical pathology workstation for analysis of total cholesterol and serum triglycerides. 3 ml of blood collected in EDTA bottle was sent to hematology workstation for analysis of platelet indices including platelet counts, mean platelet volume (MPV), platelet distribution width (PDW) and platecrit (PCT). Total cholesterol was analyzed by CHOD-PAP methodology, and triglycerides were measured by GPO-PAP technique on clinical chemistry analyzer (Hitachi-902). Platelet indices were measured on automated hematology analyzer.

Grouping of results:

1) Triglyceridemia status: The results were grouped as: Group-1 (Serum triglyceride results < 1.6 mmol/L), Group-2 (Serum triglyceride results between 1.6 to 2.3 mmol/L) Group-3 (Serum triglyceride results > 2.3 mmol/L)

2) Total cholesterol: Groups were made as: Group-1 (Serum total cholesterol < 5.2 mmol/L), Group-2 (Serum total cholesterol between 5.2-6.3 mmol/L) Group-3 (Serum total cholesterol results > 6.3 mmol/L)

Later we further segregated the subject's cholesterol and triglyceride results into seven groups in order to understand the differences between the groups as highlighted by post-hoc comparisons.

Data analysis was done by using SPSS version 15. First mean and SD/95% confidence intervals were calculated for age. Frequencies were calculated for gender. The results of total cholesterol and triglycerides were compared between various age groups by one way ANOVA. Correlation between total cholesterol and triglycerides with platelet indices and age were calculated by Pearson's correlation. The differences for platelet counts and other platelet parameters among various groups formulated based upon their total cholesterol and triglycerides were measured by one way ANOVA along with post-hoc comparisons. Later Univariate General linear model (GLM) was utilized, keeping the effect of age as a co-variate to measure the effect of platelet counts and mean platelet volumes among total cholesterol groups, which were further segregated into 07

groups to understand which groups had the most differences as highlighted by post-hoc analysis.

RESULTS

The mean age among our data set was 43.41 +11.51 years. 52.7 % were male while 47.3 % were female. The results of total cholesterol and fasting triglycerides remained significantly different among various age groups. [Table-1] Overall correlations between platelet indices with total cholesterol and triglycerides are shown in table-2. The results of platelet count and mean platelet volume were found to be significantly different among cholesterolemia group (Table-3); however, post-hoc comparison did not show these results to be significantly different between all the groups. Adjusting age and with further segregation of total cholesterol levels into seven groups in a univariate general linear model showed higher mean platelet volume at both extremes of cholesterol i.e., hypocholesterolemia (< 4.5 mmol/L)

and hypercholesterolemia (> 6.0 mmol/L). [Figure-1] A similar trend was observed for platelet count after adjusting age, where low levels of platelet levels were linked (P=0.021) with hypocholesterolemia and hypercholesterolemia. [Figure-2] Cholesterol levels between 4.5 mmol/L to 6.5 mmol/L were not found with lower platelet levels. Table-4 showed a no association between platelet indices and serum fasting triglycerides.

DISCUSSION

Our study is the pioneer local study which has attempted to demonstrate the relationship between various platelet indices with cholesterol and triglycerides. The relationship between cholesterol remained only significant for mean platelet volume and platelet counts. However, a deeper dissection of our data by post-hoc comparisons and by further segregating cholesterol into smaller groups suggested that only hypo and hyper cholesterolemia were related to depressions in platelet

Table 1: Comparison of total cholesterol and serum triglycerides among various age groups (n=867)

S.No	Age group	Total cholesterol (mmol/L)			Sig.*	Fasting triglycerides(mmol/L)			Sig.*
		Mean	95% CI			Mean	95 % CI		
			Lower bound	Upper bound			Lower bound	Upper bound	
1	< 25 years	4.07	3.71	4.43	< 0.001	1.61	1.16	2.06	< 0.001
2	25-34 years	4.48	4.34	4.63		1.66	1.53	1.80	
3	35-44 years	4.80	4.71	4.89		2.28	2.15	2.40	
4	45-54 years	5.00	4.87	5.13		2.25	2.12	2.39	
5	> 54 years	4.83	4.67	4.98		1.93	1.78	2.07	
6	Total	4.79	4.73	4.85		2.10	2.03	2.17	

*Significance calculated by One way ANOVA

Table 2: Bivariate Pearson’s correlations between fasting blood glucose and different platelet parameters (n= 867)

S.No	Parameter	Total cholesterol		Triglycerides	
		Correlation co-efficient (r2)	Significance	Correlation co-efficient (r2)	Significance
1.	Age in years	0.129**	0.000	0.031	0.353
2.	Platelet count	0.010	0.780	0.096**	0.005
3.	Platecrit (PCT)	0.034	0.317	0.041	0.228
4.	Mean platelet volume (MPV)	-0.088*	0.011	0.081*	0.019
5.	Platelet distribution width (PDW)	0.056	0.104	0.029	0.397

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

Table 3: Differences of platelet indices among subjects with different levels of cholesterol

S. No	Parameter	Group	n	Mean	95% Confidence interval		Sig. (One way ANOVA)
					Lower bound	Upper bound	
1.	Platelet count	Total cholesterol < 5.2 mmol/L	570	254	248	260	0.001
		Total cholesterol from 5.2 - 6.3 mmol/L	256	275	265	284	
		Total cholesterol > 6.3 mmol/L	41	254	230	278	
2.	Platecrit (PCT)	Total cholesterol < 5.2 mmol/L	570	0.23	0.22	0.24	0.260
		Total cholesterol from 5.2 - 6.3 mmol/L	256	0.24	0.23	0.25	
		Total cholesterol > 6.3 mmol/L	41	0.23	0.20	0.26	
3.	Mean platelet volume (MPV)	Total cholesterol < 5.2 mmol/L	570	9.62	9.50	9.74	0.020
		Total cholesterol from 5.2 - 6.3 mmol/L	256	9.33	9.18	9.47	
		Total cholesterol > 6.3 mmol/L	41	9.66	9.17	10.15	
4.	Platelet distribution width (PDW)	Total cholesterol < 5.2 mmol/L	570	13.89	13.83	13.96	0.153
		Total cholesterol from 5.2 - 6.3 mmol/L	256	13.97	13.99	14.06	
		Total cholesterol > 6.3 mmol/L	41	14.06	13.90	14.22	

Figure 1: Univariate General linear model (GLM) with MPV (dependent variable) and Cholesterol groups (Fixed factor) keeping age as co-variates. [Model significance: p = 0.039]

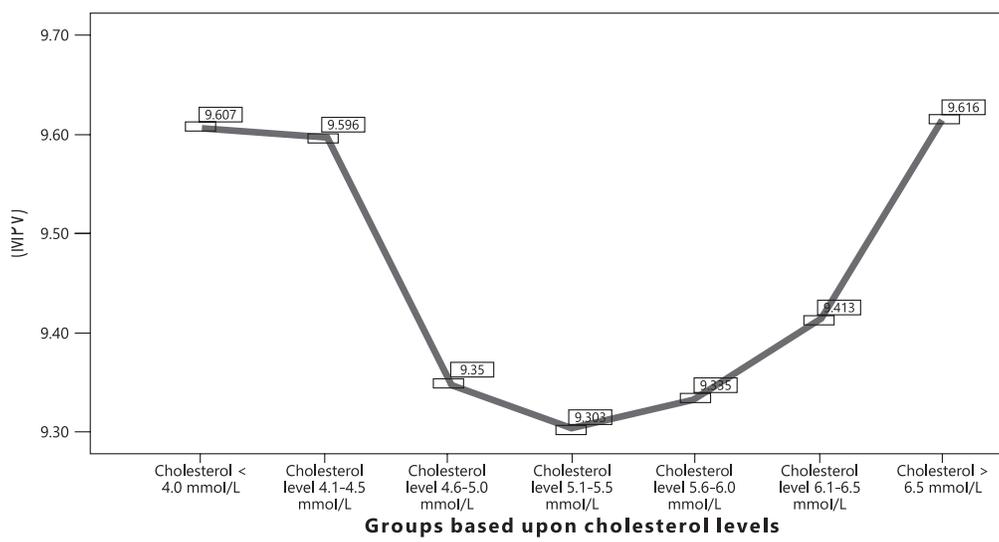


Figure 2: Univariate General linear model (GLM) with platelet count (dependent variable) and Cholesterol groups (Fixed factor) keeping age as co-variates. [Model significance: p= 0.043]

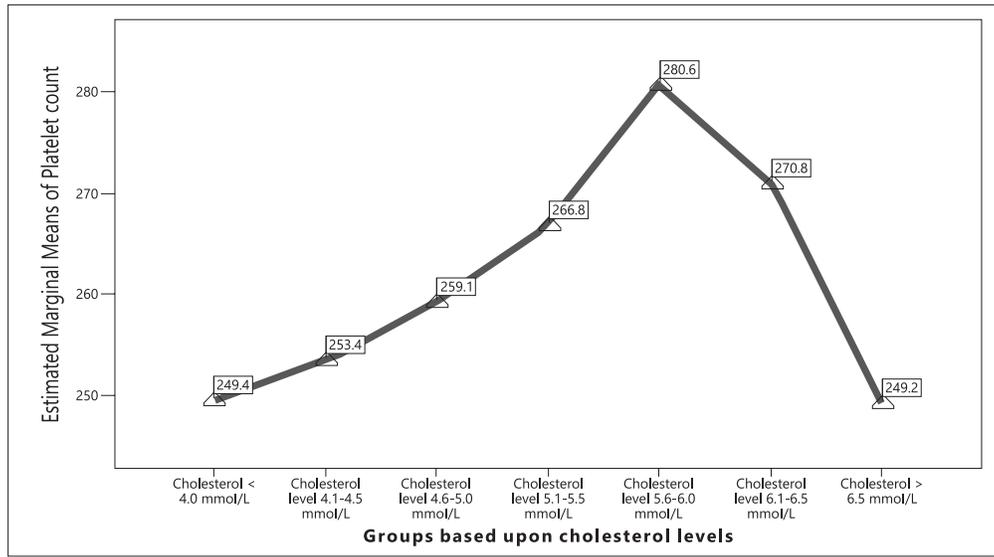


Table 4: Differences of platelet indices among subjects with different levels of triglycerides

S. No	Parameter	Group	n	Mean	95% Confidence interval		Sig. (One way ANOVA)
					Lower bound	Upper bound	
1.	Platelet count	Triglyceride level < 1.6 mmol/L	315	257	248	265	0.426
		Triglyceride level 1.6 - 2.29 mmol/L	243	265	254	276	
		Triglyceride level > 2.29 mmol/L	282	260	252	269	
2.	Platecrit (PCT)	Triglyceride level < 1.6 mmol/L	333	0.23	0.22	0.24	0.492
		Triglyceride level 1.6 - 2.29 mmol/L	247	0.24	0.23	0.25	
		Triglyceride level > 2.29 mmol/L	286	0.23	0.23	0.24	
3.	Mean platelet volume (MPV)	Triglyceride level < 1.6 mmol/L	314	9.47	9.33	9.62	0.491
		Triglyceride level 1.6 - 2.29 mmol/L	241	9.53	9.37	9.69	
		Triglyceride level > 2.29 mmol/L	280	9.60	9.44	9.77	
4.	Platelet distribution width (PDW)	Triglyceride level < 1.6 mmol/L	326	13.91	13.83	14.00	0.337
		Triglyceride level 1.6 - 2.29 mmol/L	247	13.89	13.80	13.99	
		Triglyceride level > 2.29 mmol/L	286	13.98	13.90	14.06	

counts and rises in platelet volumes. Literature review suggests minimal evidence relating the data regarding platelet indices with lipid relationship. Whatever, data we do have in this connection is marked by considerable variability.

In this regard Santimone et al have shown a significant relationship between both raised cholesterol and triglycerides levels with platelet levels¹⁰. MPV readings were not found to be significantly raised with hypercholesterolemia in the same study. Moreover, the authors did acknowledge that the results only explained minimally the variability which surrounds the platelet results. Our findings depicted both hypocholesterolemia and hypercholesterolemia as associated with lower platelet levels and higher MPV. The probable explanations for our findings are suggested as: Apart from hypercholesterolemia, we did find raised MPV and low platelets with hypocholesterolemia. Hypercholesterolemia in literature is well known identified direct risk factor for cardiovascular disease¹¹; however, there is available evidence which also points out towards the role of hypocholesterolemia as important entity which results in subject's predisposition towards a higher adverse outcome^{12,13}.

Another study by Reuben et al have highlighted that lower cholesterol results are associated with inflammation that could lead to higher patient mortality¹⁴. Similarly a regional study by Okamura et al have also identified a cholesterol level of less than 4.1 mmol/L to be associated with higher all cause mortality¹⁵. Thirdly, the possibility that the U-curve for MPV and inverted V in case of platelets in our graphs as observed could be a random finding as post-hoc comparisons in actual did provide statistical significance between few groups only. However, keeping in view the sample size, methodology and the aforementioned evidence we consider our results to be significant and makes us feel that more controlled trials in general population may be done to augment or disapprove our findings. Finally, the clinically available platelet parameters may not be predictive of underlying cardiovascular disease risk as Beyan et al did not find any correlations between the anatomic platelet indices like platelet, MPV and others with functional platelet markers for activation, suggesting that such markers cannot depict underlying platelet activation¹⁶. Similarly, another Italian study attempting to demonstrate a relationship between platelet parameters (MPV and platelet counts) and thrombotic events did not prove a stronger link between the two, while showing a significant relationship with cholesterol at the same time¹⁷.

The relationship between fasting triglycerides and platelet parameters was not found to be significant in

our study. Apart from the study by Santimone et al, not much data is available to negate or augment our conclusions¹⁰. Moreover, a lot of evidence is there which only demonstrate triglycerides as dependent risk factors for cardiovascular diseases or identified it as a metabolic cluster with associated findings of insulin resistance^{18,19}. Thus the likely conclusion at our end is that triglyceride do not affect platelet indices.

LIMITATIONS

Our study may have limitations some due to its inherent design as a cross-sectional one, and being a study carried out in clinical settings. An epidemiological study incorporating subjects from different sections of life may provide a better tool to further evaluate the lipid platelet relationship. Secondly, the subject of lipidology is further evolving which may yield further insight into the aforementioned relationship. However, in a clinical set up our utilized markers are the ones which on account of their feasible measurements and cost may become a better investigative tool after more clinical research.

However, the study may be important clinically as it has provide a direct insight into the lipid-platelet link which has been attributed as common end-point in the development of atherosclerotic plaque. The data our study provides the shifting dynamics between established cardiovascular predispositions like cholesterol levels with candidate markers of accelerated atherosclerosis i.e., platelet indices. Future may allow better refining of platelet parameters through further research and technology improvement and for their routine clinical use.

CONCLUSION

Platelet parameters differ including their number and volumes i.e., higher MPV and low platelet counts in subjects with hypercholesterolemia (> 6.0 mmol/L) and hypocholesterolemia (< 4.5 mmol/L). No significant differences were observed for platelet indices across various groups formulated based upon individual's fasting triglyceridemia status

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CONTRIBUTORS

SHK planned the study, did data analysis and wrote manuscript. SAA helped in manuscript writing. Both authors contributed significantly to the final manuscript.