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

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Body

: 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 (less than 5.2 mmol/L), borderline raised cholesterol group (5.2-6.3 mmol/L) and hypercholesterolemia (greater than 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 (less than 4.0 mmol/L) to highest (greater than 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.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 approaches in medicine are the emergence of various anti-platelet and anti-lipids medications for both primary and secondary prevention of cardiovascular diseases5, 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 January2011 to May 2012. Based upon non-probability convenience sampling, all subjects who presented in medical fasting status i.e., overnight fast of 10+2 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 of867 subjects were finally selected for study after explanation of study purpose and signing of the consent Performa. 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 less than 1.6 mmol/L), Group-2 (Serum triglyceride results between1.6 to 2.3 mmol/L) Group-3 (Serum triglyceride resultsgreater than 2.3 mmol/L)

2) Total cholesterol: Groups were made as: Group-1(Serum total cholesterol less than 5.2 mmol/L), Group-2 (Serum total cholesterol between 5.2-6.3 mmol/L) Group-3 (Serum total cholesterol results greater than 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 07groups 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, posthoc 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 (less than 4.5 mmol/L) and hypercholesterolemia (greater than 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 between4.5 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 Lower bound	95% CI Upper bound		Mean	95 % CI Lower bound	95 % CI Upper bound	
1	less than 25 years	4.07	3.71	4.43		1.61	1.16	2.06	
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	
			less than 0.001					less than 0.001	
4	45-54 years	5.00	4.87	5.13		2.25	2.12	2.39	
5	greater than 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	

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

S.No	Total cholesterol	Triglycerides

	Parameter	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	0.056	0.104	0.029	0.397

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

S. No	Parameter	Group	n	Mean	95% Confidence interval Lower bound	Upper bound	Sig. (One way ANOVA)
1.	Platelet count	Total cholesterol less than 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 greater than 6.3 mmol/L	41	254	230	278	
2.	Platecrit (PCT)	Total cholesterol less than 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 greater than 6.3 mmol/L	41	0.23	0.20	0.26	
3.	Mean platelet volume (MPV)	Total cholesterol less than 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 greater than 6.3 mmol/L	41	9.66	9.17	10.15	
4.	Platelet distribution width (PDW)	Total cholesterol less than 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 greater than 6.3 mmol/L	41	14.06	13.90	14.22	

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

S. No	Parameter	Group	n	Mean	95% Confidence interval Lower bound	Upper bound	Sig. (One way ANOVA)
		Triglyceride level less than 1.6					

			315	257	248	265	
		mmol/L					
	Platelet	Triglyceride level 1.6 2.29					
1.			243	265	254	276	0.426
	count	mmol/L					
		Triglyceride level greater than 2.29					
			282	260	252	269	
		mmol/L					
		Triglyceride level less than 1.6					
			333	0.23	0.22	0.24	
		mmol/L					
	Platecrit	Triglyceride level 1.6 2.29					
2.			247	0.24	0.23	0.25	0.492
	(PCT)	mmol/L					
		Triglyceride level greater than 2.29					
			286	0.23	0.23	0.24	
		mmol/L					
		Triglyceride level less than 1.6					
			314	9.47	9.33	9.62	
		mmol/L					
	Mean plate-						
		Triglyceride level 1.6 2.29					
3.	let volume		241	9.53	9.37	9.69	0.491
		mmol/L					
	(MPV)						
		Triglyceride level greater than 2.29					
			280	9.60	9.44	9.77	
		mmol/L					
		Triglyceride level less than 1.6					
			326	13.91	13.83	14.00	
		mmol/L					
	Platelet						
		Triglyceride level 1.6 2.29					
4.	distribution		247	13.89	13.80	13.99	0.337
		mmol/L					
	width (PDW)						
		Triglyceride level greater than 2.29					
			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 hypocholestrolemia 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 hypocholestrolemia as important entity which results in subject's predisposition towards a higher adverse outcome12, 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 Santimore 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 resistance18, 19. Thus the likely conclusion at our end is that triglyceride don 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-pint 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 (greater than 6.0 mmol/L) and hypocholestrolemia (less than 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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