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Original Article

Insights into Cardiovascular Disease Risk Based on Platelet Indices and Lipid Ratios in Reference to Glycemic Control and Duration of Diabetes

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Abstract

Background

Diabetic patients are at the risk of untimely atherosclerotic cardiovascular disease. The level of blood lipids, their ratios, glycosylated hemoglobin, and platelet indices are potential markers for the assessment of cardiovascular disease risk in diabetic patients. This study aims to insights into cardiovascular disease risk among diabetic patients in reference to glycemic control and duration of diabetes on the basis of lipid ratios and platelet indices by comparing with healthy controls.

Materials and Methods

A case control study was carried out among the patients, diagnosed as type 2 diabetes mellitus at Dhulikhel hospital-Kathmandu University hospital. Socio-demographic questionnaire, anthropometric measurements, and biochemical tests was performed. Descriptive analysis and independent samples T-test for the testing relationship between categorical variables along with correlation was done.

Results

Nearly one-third of diabetic patients were under poor glycemic control with high risk of cardiovascular diseases on the basis of blood lipid ratios and platelet indices. Cardiac risk ratio, Atherogenic Index of Plasma, and Atherogenic Coefficient was found to be significantly high in diabetic compared to the control group (5.22±1.54 vs. 3.71±0.99, p <0.05), (0.33±0.18 vs. 0.22±0.14, p <0.05), (4.22±1.54 vs. 2.71±0.99, p <0.05) respectively. Similarly Mean Platelet Volume was also significantly higher in diabetic compared to the control group (10.16±1.43 vs. 9.06±0.81, p <0.05).

Conclusion

Poor glycemic control seems riskier than prolonged diabetes on the basis of blood lipids, their ratios and platelet indices.

Keywords: *Cardiovascular disease, Glycemic control, Lipid*

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Introduction

It is found that patient of type 2 diabetes mellitus (T2DM) are at the risk of untimely (nearly 14.6 years early) atherosclerotic cardiovascular disease [1]. Thrombocytes play a crucial role in the development of atherothrombosis in diabetic and non-diabetic patients and aggregation and adhesion properties of these cells are responsible for cardiovascular events [2, 3]. Blood lipids are established biomarkers for the risk of cardiovascular disease (CVD) more prominently than others [4].

Laboratory medicine play crucial role in the diagnosis and management of various diseases, [5] however, reporting of lipid ratios and platelet indices are neglected [6] and study focused on laboratory parameter based CVD risk for diabetic patients are lacking in Nepal.

This study aims insights into CVD risk among T2DM in reference to glycemic control and duration of diabetes based on platelet indices and lipid ratios to reflect the importance of reporting blood lipid ratios and platelet indices in T2DM patients.

Materials and Methods

This case-control study was conducted in 2018-2019 at Dhulikhel Hospital-Kathmandu University Hospital (DH-KUH), Nepal. Ethical approval was obtained from Kathmandu University School of Medical Sciences Institutional Review Committee (KUSMS-IRC). Previously diagnosed type 2 diabetic (T2DM) patients were selected. Sample size was calculated by using https:// www.surveymonkey.com/mp/ sample-size-calculator/, where population size of Kavre district was 381937, confidence level 99% and margin of error was 10%. 172 T2DM patients under oral hypoglycemic medication were enrolled and 86 (50% of cases) apparently healthy (without a history of diabetes and other chronic diseases) people were selected as a control. T2DM patients visiting Dhulikhel Hospital who agreed to participate in this study with written consent were selected as case group. Apparently healthy hospital staffs or other patient's visitor ready to participate voluntarily with written consent were enrolled as control group. Patients having any other known metabolic or chronic disease like renal failure, hypertension, hepatitis, and thyroid dysfunction along with diabetes were excluded. Pregnant women, participants on oral anticoagulants, under the medication of hypertension, and lipid-lowering drugs were excluded. Along with this, history of blood transfusion within less than one month and participants having blood hemoglobin level <12.0gm/dL (in the female) and <14.0gm/dL (in the male) were also excluded in both case and control groups. Weight was measured on a weighing scale in kilograms with no shoes and using minimum clothing by a modern digital weighing scale (Omron HBF-400, USA). Height was measured with the person erect, barefooted, feet together, back, and heels against the wall and head upright. Waist circumference was measured using a measuring tape in centimeter with the subject's feet shoulder-width apart and arm crossed over the chest keeping the measuring tape around the top of the iliac crest. Semi-structured questionnaires were implemented to know participant's socio-demographic characters such as age, sex, and health status such as duration of diabetes diagnosis, along with habits of smoking and alcohol consumption. Blood pressure was measured in a sitting posture on the right arm over loose clothes using a standard digital blood pressure measuring (BP) machine (Microlife, Switzerland). Overnight fasting blood was collected from the median cubital vein of all participants by trained phlebotomist using aseptic technique in sterile tubes. 3.0 ml of blood was collected in a yellow capped gel activator tube 2.0 ml in Ethylenediaminetetraacetic acid (EDTA) tube. Collected blood samples transported within 30 minutes to the Department of Clinical Biochemistry Laboratory of DH-KUH. Yellow capped, gel activator tube with blood samples were allowed to clot and centrifuged at 4000 rpm for 7 minutes. Obtained serum was analyzed for biochemical parameters such as lipid profile tests, high sensitive C - reactive protein (hs-CRP) and blood glucose in a fully automatic biochemistry analyzer (BA 400 Biosystems, Spain) after validation of internal quality control. In the lipid profile test, Total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol and Triacylglycerol were directly measured in serum. The cardiac risk ratio was calculated by dividing the total cholesterol by HDL while non HDL cholesterol was calculated by subtracting HDL from total cholesterol. Atherogenic index of plasma (AIP) was obtained by Log (Triacylglycerol/HDL) and the atherogenic coefficient was obtained dividing non-HDL cholesterol by HDL.

EDTA containing blood sample in lavender capped tubes placed in a sample rotator for uniform mixing. After 5-10 minutes of mixing HbA1c was measured in a fully automated High-Performance Liquid Chromatography (HPLC) analyzer (Hb-Vario, Erba Mannheim, UK). After noting the results for HbA1c, that blood sample was immediately transported to the Hematology Unit

of the Pathology Department of DH-KUH. EDTA samples were mixed well and inserted in a fully automated 5 part hematology analyzer (Bene-Sphera H51, India) to obtain complete blood count. Hemoglobin below our inclusion criteria was excluded and criteria matched patient's platelets indices were analyzed.

Value of fasting blood glucose, lipids, HbA1c, and platelet indices were entered in Microsoft excel 2010 along with all answers of a semi-structured questionnaire related to all participants. The baseline variables were compared by descriptive analysis and independent samples T-test. The box plot was obtained to analyze the difference in median, interquartile range, lower quartile and whiskers of mean platelet volume (MPV) and cardiac risk ratio in reference to glycemic control and duration of diabetes in study group and to non-diabetic control group. The rho correlation was analyzed to assess the relationship between calculated lipid ratios and MPV with glycemic control and duration of diabetes in IBM SPSS Statistics version 23.

Results

The mean age of diabetic patients was 55.37± 10.71years among them 52.9% (91) were males and 47.1% females (81).Similarly, the mean age of the control group was 47.85±6.51 years with 47.7% (41) males and 52.3 % (45) females. In diabetic patients group, based on the duration of diabetes diagnosis,19.25% were newly diagnosed (<1 year), 52.3% were in between 1-5 years, 21.5% were in between 6-10 years and 7% were having more than 11 years of diabetic history.

Out of the 172 diabetic patients, 43.0% had good glycemic control (HbA1c level below 7%), 26.7% were under fair glycemic control (HbA1c level 7.1 to 8%) while 30.2% had poor glycemic control (HbA1c level >8%). In the control group, 75.6% have HbA1c level is below 5.6% while 24.4 % fall under the diabetic risk group or pre-diabetic group having the HbA1c level between 5.7 to 6.4%.

Table 1: Lipid ratios and platelet indices in diabetic and control participants

	Diabetic Patients	Control Group	*P*-Value*
Total Cholesterol (mg/dL)	191.32±44.13	152.53±36.86	<0.005
HDL Cholesterol (mg/dL)	38.06±8.36	41.71±5.93	<0.005
LDL Cholesterol (mg/dL)	132.23±35.66	87.35±27.21	<0.005
Non-HDL Cholesterol (mg/dL)	153.26±44.33	110.83±36.53	<0.005
Cardiac Risk Ratio	5.22±1.54	3.71±0.99	<0.005
Atherogenic Index of Plasma	0.33±0.18	0.22±0.14	<0.005
Atherogenic Coefficient	4.22±1.54	2.71±0.99	<0.005
Mean Platelet Volume (fL)	10.16±1.43	9.06±0.81	<0.005
Platelet Count (10^9/L)	279.88±93.58	272.97±77.21	0.055
PWD %	16.42±0.74	16.09±0.59	<0.005

*Independent samples T-test was performed to obtain P value

When independent samples T-test was analyzed, (Table 1) statistically significant difference was found in blood lipids, their ratios, and mean platelet volume between diabetic patients and non-diabetic control participants but there was no significant association of platelet counts. Age is strongly associated with diabetes. We also observed that there was a significant difference in BMI and waist-hip ratio between diabetic patients and control participants. Smoking and alcohol drinking habits were also significantly associated with diabetic patients but there was no significant association of diabetes and gender.

Obtained data also plotted in a simple-box plot to analyze mean platelet volume against glycemic control of the study group and control group. The middle quartile (median) of the mean platelet volume was below 9.5 fL in all diabetic groups and non-diabetic control except the poor glycemic group (Figure 1). The median of MPV in poor glycemic diabetic patients was 11 to 11.5 fL. The upper quartile of MPV in the pre-diabetic category from control participants and fair glycemic status from the diabetic study group was almost the same around 10.0fL but the upper quartile of MPV was below 9.5 fL and around 10.5 fL in non-diabetic and good glycemic patients respectively. The lower whisker of non-diabetic, good glycemic, and fair glycemic control was almost the same in between 7.0 to 7.5 fL.

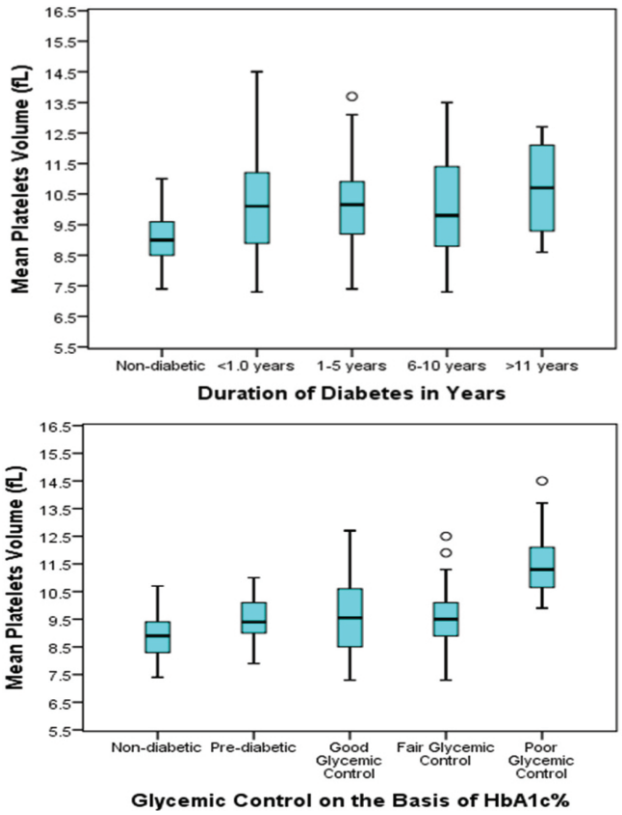

Figure 1: Box plot of Mean Platelet Volume against glycemic control and duration of diabetes

However, the lower whisker for MPV was slightly higher in the pre-diabetic group but very high in the poor glycemic control group, which was above of middle quartile of other categories. Similarly, lower quartile of the poor glycemic group was more than the upper quartile of other categories and upper whisker was highest in poor glycemic status patients followed by a good glycemic group. When MPV was compared with glycemic control and duration of diabetes, the median MPV in the Poor glycemic control patients seems higher than prolonged duration of diabetes.

The calculated cardiac risk ratio was plotted in clustered box plots and analyzed against the duration of diabetic and glycemic control for male and female participants (Figure 2).

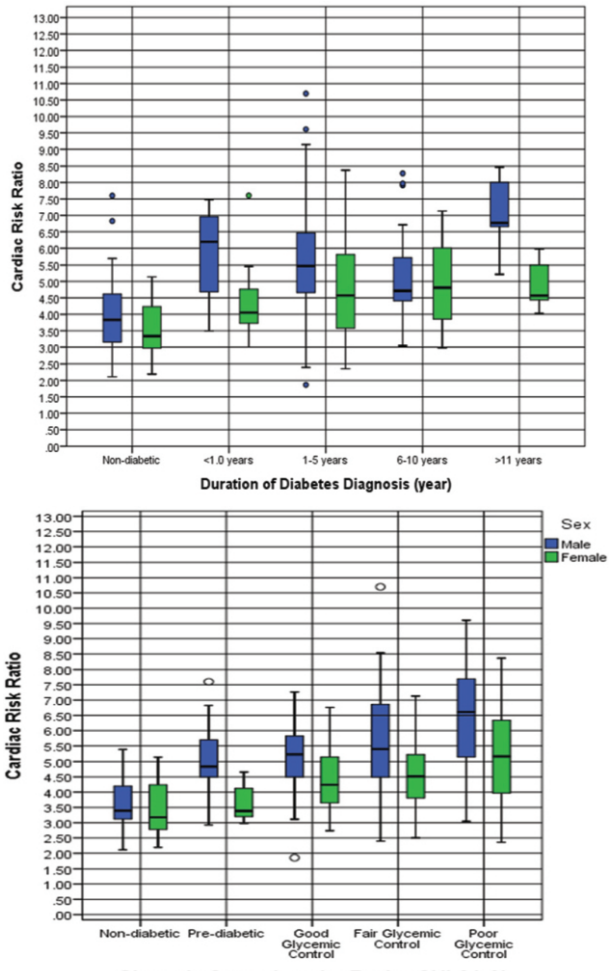

Figure 2: Clustered Box plot of cardiac risk ratio against the duration of diabetes and glycemic control in male and female

The median of the calculated cardiac risk ratio was strikingly high in male participants than females in all groups except in 6-10 years of diabetic history. The minimum and maximum value of the calculated cardiac risk ratio was very close in the control group, 1 to 5 years, and 6 to 10 years of diabetic history in males and females. However, there was a marked difference in males and females of recently diagnosed diabetic patients (< 1.0 years) and >11.0 years of diabetic history. The median of calculated cardiac risk was between 6 and 7, which was strikingly high in male patients compared to females belongs to recently diagnosed (<1.0 years) and having >11.0 years of diabetic history.

Table 2: The rho correlation of lipid ratios and MPV with glycemic control and duration of diabetes

		Correlations						
		HbA1c %	Duration of Diabetes (Years)	Mean Platelets Volume (fL)	Cardiac Risk Ratio	Atherogenic Index of Plasma	Non HDL Cholesterol	High-sensitivity-C-Reactive Protein
HbA1c %	Correlation Coefficient	1.000	.148	.606**	.533**	.352**	.480**	.610**
	Sig. (2-tailed)	.	.053	.000	.000	.000	.000	.000
		258	172	258	258	258	258	258
Duration of Diabetes (Years)	Correlation Coefficient	.148	1.000	.225**	.212**	.038	.248**	.123
	Sig. (2-tailed)	.053	.	.003	.005	.624	.001	.107
Mean Platelets Volume (fL)	Correlation Coefficient	.606**	.225**	1.000	.355**	.299**	.321**	.493**
	Sig. (2-tailed)	.000	.003	.	.000	.000	.000	.000
Cardiac Risk Ratio	Correlation Coefficient	.533**	.212**	.355**	1.000	.591**	.884**	.429**
	Sig. (2-tailed)	.000	.005	.000	.	.000	.000	.000
Atherogenic Index of Plasma	Correlation Coefficient	.352**	.038	.299**	.591**	1.000	.369**	.274**
	Sig. (2-tailed)	.000	.624	.000	.000	.	.000	.000
Non HDL Cholesterol	Correlation Coefficient	.480**	.248**	.321**	.884**	.369**	1.000	.405**
	Sig. (2-tailed)	.000	.001	.000	.000	.000	.	.000
High-sensitivity-C-Reactive Protein (hs-CRP)	Correlation Coefficient	.610**	.123	.493**	.429**	.274**	.405**	1.000
	Sig. (2-tailed)	.000	.107	.000	.000	.000	.000	.

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

The glycemic control (HbA1c) level showed fairly positive and statistically significant correlation with mean platelet volume, cardiac risk ratio, atherogenic index of plasma non-HDL cholesterol and hs-CRP. Duration of diabetes also showed positive correlation with MPV, cardiac risk ratio and non-HDL cholesterol but the correlation with atherogenic index of plasma and hs-CRP was not statistically significant. AIP showed statistically insignificant correlation with duration of diabetes while there was statistically significant positive correlation with MPV, cardiac risk ratio, non-HDL cholesterol and hs-CRP.

Non-HDL cholesterol reflects strong positive and statistically significant correlation with cardiac risk ratio but fairly positive correlation with glycemic control, duration of diabetes, AIP and hs-CRP.

Discussion

We found that nearly one third (30.2%) of diabetic patients were under poor glycemic control category and one fourth (24.4%) healthy control people were in diabetic risk or pre-diabetic conditions. This study exhibited significant elevation in blood lipids, their ratios, and mean platelet volume in poor glycemic control diabetic patients group in comparison to the non-diabetic control group. The exact biochemical mechanism of diabetic dyslipidemia is not well understood, [7] however available evidence suggested that

insulin resistance is associated with over-expression cytokines by adipose tissue which contributes for inflammation and accumulation of lipids on the blood vessels leading to the development of endothelial dysfunction and diabetic dyslipidemia [8-13].

We found the duration of diabetes and poor glycemic control are independent risk factor for the cardiovascular disease based on the blood lipid ratios and MPV but poor glycemic control is more risky for CVD in diabetic patients. Our findings are similar with a study conducted in the Chinese Han population found that AIP is an independent predictor of cardiovascular disease [14]. Several studies conducted in different countries, suggested that lipid ratios can aid additional values to assess CVD even when lipid profile tests are apparently normal [15-18] and our finding are similar to those studies. We found that 6.5%, 71.2%, and 22.4% of diabetic patients have a low, intermediate, and high risk of CVD respectively based on hs-CRP and several studies also showed a positive and significant association of hs-CRP with diabetes mellitus, [19-22], however a cohort study showed no association of hs-CRP with vascular inflammation in diabetic patients [23].

A study conducted in Nepal reported significant correlation between MPV and rising fasting blood glucose level [24] similarly this study find poor glycemic control has a strong association with MPV than the prolonged duration of good glycemic control study groups. A cross-sectional study conducted in South Korea also found that MPV is strongly associated with severity of glycemic control [25] and a bunch of other studies also show that MPV increased with severity of diabetes mellitus and size of MPV decreased after improvement in glycosylated hemoglobin [26-29]. Even These strong evidences, these cost effective markers for CVD risk are neglected [6] and researchers having less interest on these easy and inexpensive measurements but engaged in developing expensive tools and technologies [30].

Conclusion

Poor glycemic control is more risky for CVD in T2DM patients. Blood lipid ratios and platelet indices can play crucial role to notice possibly missing CVD risk in diabetic patient. It is very important especially in LMICs where the clinician are limited and under pressure to see many patients in short duration. Clinical laboratories have to adopt and practice of adding lipid ratios in lipid profile test and platelet indices on complete blood count report.

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Conflicts of interests: None

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