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Relationships Between Glycemic Control and Platelet Indices, Atherogenic Index of Plasma and Vitamin D in Patients with Type 2 Diabetes

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Abstract

Objectives: Vitamin D deficiency, increased platelet indices and abnormal lipid profile are closely associated with increased vascular complications in type 2 diabetes mellitus (T2DM) patients. We investigated the relationship between glycemic control and platelet indices, vitamin D, atherogenic index of plasma (AIP) and other lipid components in T2DM patients.

Materials and Methods: Diabetic subjects were divided into the groups 1 (good glycemic control, n=59 patients), 2 (moderate glycemic control, n=71 patients), and 3 (poor glycemic control, n=95 patients) according to the HbA1c levels of <7%, 7-9%, and >9%, respectively. We retrospectively analyzed serum lipid profile, platelet count, platelet indices, calcium, phosphorus, vitamin D and HbA1c levels in all patients. The AIP values of the subjects were calculated as follows: AIP=[log triglyceride/high density lipoprotein cholesterol (HDLc)].

Results: In group 1, the mean platelet volume (MPV), platelet distribution width (PDW), platelet large cell ratio (P-LCR), triglyceride and AIP levels were lower, and the HDLc levels were higher than in group 3. Platelet indices, lipid profile, and AIP values of group 2 did not differ from those of group 1 or group 3. There was no difference among the three groups in terms of vitamin D levels. HBA1c levels were positively correlated with the duration of diabetes, triglycerides, AIP, PDW, MPV, and P-LCR, and negatively correlated with HDLc.

Results: Increased platelet indices (MPV, PDW and P-LCR) and AIP values were observed in poor glycemic controlled diabetics. Accordingly, these parameters may be helpful in assessing increased cardiovascular risk in diabetics.

Keywords: Glycemic control, platelet indices, vitamin D, atherogenic index of plasma.

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Introduction

Cardiovascular diseases (CVDs) are a serious complication of type 2 diabetes mellitus (T2DM) and the primary cause of death and disability in diabetics[1]. Abnormal metabolic conditions (such as chronic hyperglycemia, dyslipidemia and insulin resistance) accompanying diabetes may contribute to increased platelet activation and platelet hyperreactivity[2]. Platelet activation, which is known to be associated with cardiovascular risk factors that accelerate atherogenesis[3], can easily be estimated by measuring platelet indices, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and platelet large cell ratio (P-LCR) in automatic complete blood count profiles[4]. MPV, PCT, and PDW levels are reported to be higher in diabetic patients compared to healthy controls[5].

Changes in lipid profiles (increased triglycerides and low-density lipoprotein cholesterol (LDLc) levels and decreased high-density lipoprotein cholesterol (HDLc) levels) are associated with increased cardiovascular event rates in diabetic patients[6]. Increasing evidence indicates that atherogenic index of plasma (AIP), which is defined as log (triglycerides/HDLc), is superior to other lipid parameters in predicting CVD risk[7,8]. It has also been reported that AIP can be used to evaluate the risk of T2DM[9].

The function of vitamin D is not limited to the maintenance of mineral homeostasis and skeletal health but also includes physiological functions in extraskeletal tissues[10]. Substantial evidence suggests that vitamin D affects the mechanisms associated with the pathophysiology of T2DM, including pancreatic beta cell function, insulin action, and secretion[11,12]. Additionally, vitamin D deficiency may increase the risk of cardiovascular disease in diabetics[13,14].

Accumulating evidence has shown a close association between poor glycemic control and the development and progression of diabetes-related complications such as CVD, nephropathy and retinopathy[15,16]. Platelet indices, vitamin D, AIP, and other lipid parameters have been evaluated separately in T2DM patients. Here, we examined the relationship between glycemic control and levels of these parameters in patients with T2DM.

Materials and Methods

This retrospective study was conducted between January 2015 and March 2016 at the Department of Internal Medicine of Mustafa Kemal University Hospital in Hatay Province, Turkey. A total of 225 diabetic subjects were divided into three groups according to their hemoglobin A1c (HbA1c) levels. There were 59 patients with HbA1c <7% (group 1), 71 patients with HbA1c 7-9 % (group 2), and 95 patients with HbA1c >9% (group 3). Group 1, group 2 and group 3 were defined as having good, moderate and poor glycemic control, respectively[17]. Vitamin D (25-hydroxyvitamin D) level of less than 20 ng/mL was considered as hypovitaminosis D[12]. Patients with hematological diseases, active inflammation, infection, liver problems, end stage renal failure and other endocrinology disorders (other than T2DM), pregnancy and malignancy were excluded from the study. None of the patients used anticoagulant medications, vitamin D supplements or lipid-lowering drugs.

Demographic characteristics and laboratory results including lipids, complete blood count, calcium, phosphorus, vitamin D and HbA1c levels of the subjects were obtained from hospital records. Complete blood count analyses were carried out in tubes containing K2 ethylenediamine tetraacetic acid (EDTA) on a Sysmex XN1000 instrument (Sysmex Corp., Kobe Japan) within 2 hours. Serum lipid parameters (total cholesterol, HDLc, LDLc, and triglyceride), calcium and phosphorus levels were run by standard methods on the ARCHITECTc8000 (Abbot, Lake Forest, Illinois, USA). Vitamin D levels were analyzed on an ADVIA Centaur XP Immunoassay System (Siemens, Munich, Germany). HbA1c values of patients were measured by ion-exchange chromatography in a Bio-Rad Variant II system (Bio-Rad, Hercules, CA, USA). Daily quality control was carried out with commercial quality control materials to ensure the

precision and accuracy of measurements in our laboratory. The AIP values of patients with T2DM were calculated as follows: AIP=(log triglyceride/HDLc)[18].

Statistical Analysis

Statistical analyses were performed by using SPSS (Version 20, Chicago IL, USA). The normality test of variables was evaluated by using the Kolmogorov-Smirnov test. Differences among the groups in terms of gender distribution were determined using the chi-square test. ANOVA and post-hoc Tukey tests were used to compare normally distributed variables. When the variables were not normally distributed, Kruskal-Wallis test was utilized and pairwise comparisons were performed by using Mann-Whitney U test with Bonferroni correction. Correlations were determined using Spearman and Pearson correlation tests. Significance was accepted at $p<0.05$ ($p<0.0167$ for Mann-Whitney U test with Bonferroni correction).

Results

Demographic and laboratory data of the study groups are provided in Table 1. There were no differences among the three groups according to age, gender distribution, and diabetes duration.

LDLc and total cholesterol levels were similar among the three groups. The triglyceride and AIP values were significantly higher and the HDLc levels were significantly lower in group 3 than in group 1. The triglyceride, HDLc, AIP values of group 2 did not differ from group 1 or group 3.

Platelet count and PCT values were similar in all groups. MPV, PDW, and P-LCR levels were significantly higher in group 3 than in group 1. MPV, PDW and P-LCR levels of group 2 did not differ from those of group 1 or group 3.

The prevalence of hypovitaminosis D was 85.3% (n=192), and that of vitamin D sufficiency was 14.7% (n=33) in patients with T2DM. There were no differences in vitamin D, calcium, and phosphorus levels among groups.

The correlations between HBA1c and other parameters (age, lipid profile, atherogenic index, platelet indices, calcium, phosphorus and vitamin D) are presented in table 2. The levels of HBA1c were positively correlated with the duration of the diabetes, triglycerides, AIP, PDW, MPV and P-LCR, and inversely with HDLc. In addition, vitamin D level was inversely correlated with triglycerides ($r=-0.224$, $p=0.001$) and AIP ($r=-0.202$, $p=0.004$). There was no correlation between platelet indices and AIP and vitamin D levels ($p>0.05$).

Discussion

Accumulating research suggests that dyslipidemia[6], vitamin D deficiency[13,14] and increased platelet indices[19,20] are closely associated with increased cardiovascular events in diabetic populations. Platelet activation is increased in diabetic subjects due to factors such as hyperglycemia, hyperinsulinemia, and atherogenic dyslipidemia[21]. Platelet activation contributes to the increased risk of atherothrombotic events in these patients[2] and can easily be estimated by measuring platelet indices[4].

Many studies have shown that MPV, PCT, PDW, and P-LCR levels are higher in diabetics than in non-diabetic individuals[22-24]. Several authors have also suggested that increased MPV and PDW are associated with the presence of diabetes-related complications in T2DM patients[24-26]. On the other hand, it has been observed that platelet indices tend to decrease in patients with good glycemic control[5,27,28]. Similarly, we determined that MPV, PDW, and P-LCR levels were lower in T2DM patients with good glycemic control compared to the poor glycemic control group, and a positive correlation was observed between HbA1c and these parameters. These results suggest that poor glycemic control contributes to increased platelet activation, thereby increasing cardiovascular events in diabetics.

Patients with T2DM tend to have abnormal lipid profiles that increase cardiovascular event rates[29]. AIP, a newly developed lipid index, is closely associated with

the risk of T2DM[9]. Furthermore, high AIP is closely associated with an increased risk of microvascular complications in diabetics[30]. On the other hand, Kocak et al.[31] found that serum cholesterol, LDLc, and TG levels were higher, and HDLc levels were lower, in unregulated diabetic patients (HbA1c ≥7%) compared to regulated diabetics (HbA1c <7%). Another study has emphasized that HbA1c is a good indicator of lipid profile[32]. In the present study, high AIP and triglyceride levels and low HDL levels were observed in the unregulated group (HbA1c >9%) compared to the regulated group (HbA1c <7%). HBA1c levels were positively correlated with triglycerides and AIP, and inversely correlated with HDLc. Collectively, these results showed that in diabetics, lipid

Table 1. Characteristics and laboratory data of study groups

	Group 1 (HbA1c <7%)	Group 2 (HbA1c 7-9%)	Group 3 (HbA1c >9%)	p	Multiple comparisons
Gender (Males; %)	12; 20.3%	21; 29.6%	31; 32.6%	0.251[a]	-
Age (years)	56 (20-75)	59 (23-78)	56 (21-82)	0.342[b]	-
Duration of diabetes (years)	6 (1-30)	7 (1-29)	7 (1-34)	0.081[b]	-
HbA1c (%)	6.3 (5.8-6.9)	7.7 (7-9)	10.5 (9.1-16.5)	**<0.001[b]**	**P_1= <0.001 P_2= <0.001 P_3= <0.001**
LDLc (mg/dL)	139.9±39.5	128.7±43.1	130.8±40.6	0.284[c]	-
HDLc (mg/dL)	44.9 (26.8-72.9)	38.6 (24-77.6)	38.8 (22.4-72)	**0.006[b]**	P_1=0.021 **P_2=0.001** P_3=0.544
Cholesterol (mg/dL)	218.5±43.8	204.8±52.1	214.4±46.6	0.267[c]	-
Triglyceride (mg/dL)	132.1 (69.3-358.2)	142.5 (51.5-490.6)	189.8 (59.2-603.8)	**0.005[b]**	P_1=0.333 **P_2=0.002** P_3=0.021
AIP	0.50±0.27	0.58±0.30	0.68±0.29	**0.001[c]**	P_1=0.262 **P_2=0.001** P_3=0.081
Platelet (103/µL)	304±70.8	298.8±83.4	295.9±84.9	0.838[c]	-
PDW (fL)	12.2 (9.6-18)	13.3 (8.3-23)	13.2(8.9-23.4)	**0.002[b]**	P_1=0.032 **P_2= <0.001** P_3=0.271
MPV (fL)	10.4 (9-12.9)	10.8 (8.4-14.2)	10.9 (7.2-14.4)	**0.002[b]**	P_1=0.022 **P_2= <0.001** P_3=0.371
PCT (%)	0.32±0.07	0.32±0.08	0.32±0.08	0.913[c]	-
P-LCR (%)	28.2 (16.9-47.1)	32.1 (15.5-57.7)	33.1 (14-57)	**0.001[b]**	P_1=0.026 **P_2= <0.001** P_3=0.216
Calcium (mg/dL)	9.32±0.55	9.55±0.55	9.41±0.51	0.162[c]	-
Phosphorus (mg/dL)	3.39±0.56	3.53±0.63	3.59±0.58	0.359[c]	-
Vitamin D (ng/mL)	7.5 (4.2-33.9)	10.5 (4.2-52.5)	6.2 (4.2-45.1)	0.177[b]	-

LDLc: Low-density lipoprotein cholesterol, HDLc: High-density lipoprotein cholesterol, AIP: Atherogenic index of plasma, PDW: Platelet distribution width, MPV: Mean platelet volume, PCT: Plateletcrit, P-LCR: Platelet large cell ratio, HbA1c: Hemoglobin A1c

[a]Chi square ($\chi 2$) test, [b]Kruskal-Wallis test, [c]Analysis of variance (ANOVA) test. Post-hoc Tukey test was used for multiple comparisons of AIP, Mann-Whitney U test with Bonferroni correction was used for multiple comparisons of HbA1c, HDLc, triglyceride, PDW, MPV and P-LCR.Significance was accepted at p<0.05 (p<0.0167 for Mann-Whitney test with Bonferroni correction). Bold values indicate statistical significance

P_1 between group 1 and group 2

P_2 between group 1 and group 3

P_3 between group 2 and group 3

Table 2. Correlation between HBA1c levels and other variables in diabetic patients

	HBA1c	
	r	p
Age	0.052	0.437
Duration of diabetes	0.160	**0.016***
LDLc	-0.043	0.537
HDLc	-0.191	**0.006***
Cholesterol	0.038	0.591
Triglyceride	0.274	**<0.001***
AIP	0.290	**<0.001***
Platelet	-0.036	0.596
PDW	0.216	**0.001***
MPV	0.221	**0.001***
PCT	0.011	0.872
P-LCR	0.240	**<0.001***
Calcium	0.017	0.842
Phosphorus	0.167	0.057
Vitamin D	-0.117	0.079

LDLc: Low-density lipoprotein cholesterol, HDLc: High-density lipoprotein cholesterol, AIP: Atherogenic index of plasma, PDW: Platelet distribution width, MPV: Mean platelet volume, PCT: Plateletcrit, P-LCR: Platelet large cell ratio, HbA1c: Hemoglobin A1c
**p<0.05*

profile and blood glucose should be controlled to prevent or slow the progression of diabetic complications.

Low vitamin D levels have been shown to be associated with decreased insulin sensitivity and increased risk of developing T2DM[33,34]. For example, Chiu et al.[12] found that vitamin D levels were positively correlated with insulin sensitivity and inversely with glucose. Another study examined the relationship between vitamin D and HBA1c in diabetic patients between November 2016 and June 2017. They found that vitamin D levels were higher in the well-controlled group (HbA1c <8%) than in the poorly controlled group (HbA1c ≥8%)[35]. In contrast, we did not identify differences in vitamin D levels between diabetic groups. This discrepancy may be attributed to the fact that seasonal changes in vitamin D determinations were ignored, and that vitamin D deficiency was present in 85.3% of our diabetic patients. We also found a negative correlation between vitamin D level and triglycerides and AIP. Consistent with our own findings, an observational study showed that vitamin D was inversely related to total cholesterol/HDLc or LDLc/HDLc ratios and triglyceride levels, and that high vitamin D concentrations were related to a favorable lipid panel[36].

The main limitation of this study is that it was a single-center retrospective study. Consequently, we found an association between improved glycemic control in T2DM and decreased MPV, PDW, P-LCR, triglycerides and AIP levels and increased HDLc. Future studies should be conducted to confirm these findings.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Mustafa Kemal University Ethics Committee (Protocol code: 09/05/2016/100).

Informed Consent: Since the study was a retrospective study, informed consent was not obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.M.Ç., Concept: G.Ç., M.M.Ç., Design: G.Ç., M.M.Ç., Data Collection or Processing: G.Ç., M.M.Ç., Analysis or Interpretation: G.Ç., M.M.Ç., Literature Search: G.Ç., Writing: G.Ç., M.M.Ç.

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