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MEAN PLATELET VOLUME IS DECREASED IN HIV INFECTED WOMEN

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Abstract

Objectives—HIV infection is associated with higher than expected cardiovascular event rates and lowered platelet counts. These conditions are associated with an elevation of mean platelet volume (MPV). The present study compares MPV in HIV-infected and uninfected women and identifies factors influencing MPV values in HIV-infected women.

Methods—A total of 234 HIV-infected and 134 HIV-uninfected participants from the Women's Interagency HIV Study (WIHS) had MPV values obtained. HIV-infected women were older, more likely to have diabetes, and have higher triglyceride levels than HIV-uninfected women.

Results—The mean platelet count was lower in HIV infected vs. uninfected women (249/ μ l 95% CI 238, 259 vs. 276/ μ l 95% CI 265, 287, $p < 0.01$). Adjusted mean MPV values were lower in the HIV- infected than in the uninfected group (8.66 fl 95% CI 8.52, 8.79 vs. 9.05 fl 95% CI 8.87, 9.24). In multiple regression analysis after adjusting for other covariates, MPV was positively associated with platelet count, and negatively with HIV infection (model $R^2 = 0.20$ $p < 0.01$). In multiple regression analysis confined to HIV-infected women, a lower MPV was independently associated with history of AIDS defining illness ($R^2 = 0.28$ $p = 0.03$), but not with CD4 nadir count or HAART use.

Conclusions—HIV-infected women have lower MPV values than-uninfected women suggesting impaired production rather than increased destruction. Higher than expected cardiovascular event rates, cannot be attributed to greater platelet reactivity as measured by MPV.

Keywords

HIV; mean platelet volume; WIHS

Introduction

Mean platelet volume (MPV) is a laboratory measure of platelet size that has long been routinely reported as part of complete blood counts.¹⁻⁴ Historically, this measure has been used to help differentiate the various causes of thrombocytopenia. Since the size of immature platelets is larger than that of senescent platelets, decreased MPV generally indicates marrow underproduction including aplastic anemia, whereas higher MPV generally signifies high destruction in diseases such as immune thrombocytopenic purpura, preeclampsia, and sepsis.¹⁻⁴

MPV has also been implicated as a marker of platelet reactivity as larger platelet size has been correlated with greater activation, measured by a variety of techniques including: aggregation, thromboxane synthesis and beta-thromboglobulin release.⁵⁻⁸ MPV is inversely correlated with platelet phospholipid (PL) PUFA composition and Glycoprotein IIb-IIIa receptor number.^{9,10} The role of platelet activation and aggregation contributing to thrombus formation after plaque rupture has lead to multiple studies examining the prognostic value of MPV with regard to cardiovascular and cerebrovascular disease states.¹¹⁻¹³ MPV is increased in the presence of atherosclerosis and cardiovascular risk factors.¹⁴⁻¹⁶ Larger MPV is increased in the presence of acute stroke, myocardial infarction, and acute coronary syndromes.¹⁷⁻¹⁹ Higher MPV is predictive of greater left ventricular dysfunction as well as secondary cardiovascular events and poorer outcomes following myocardial infarction.^{11-13,20} Accordingly, MPV has been implicated as a marker of cardiovascular risk.

Over the past decade, there has been growing concern over an increased risk of cardiovascular events in HIV infected patients.^{21,22} HIV- infected persons have been observed to have higher than expected rates of myocardial infarction and stroke.^{21,22} While the use of highly active retroviral therapy (HAART) has resulted in improved survival, various diseases have been reported to worsen cardiovascular risk factors including: hypertension, diabetes, hyperlipidemia, and metabolic syndrome, and to contribute to higher cardiovascular risk. Also, platelet counts are lowered in the setting of HIV infection even during treatment.²³ Despite both cardiovascular disease and thrombocytopenia being common in this patient population, there are few data pertaining to MPV in the setting of HIV infection. Accordingly, the objectives of the present study were to compare MPV in HIV-infected and uninfected women and to identify those factors associated with alterations in MPV in these patients.

Materials and Methods

Study population

The study was conducted in a sample of participants from the Women's Interagency HIV Study (WIHS), an ongoing multicenter observational cohort study of HIV disease in women. From the original cohort of HIV-infected and high-risk HIV-uninfected women recruited at 6 centers across the United States (Brooklyn, Bronx, Chicago, Los Angeles, San Francisco, and Washington, DC) between 1994 and 2011, 368 women from SUNY Downstate Medical Center in Brooklyn were included in this analysis. The study was approved by the Institutional Review Board. Women eligible for enrollment into the WIHS were 13 years of age or older, gave informed consent, completed an interviewer-assisted questionnaire in English or Spanish, had a physical and gynecological examination, blood collection and attended study visits every 6 months. The standardized interview-based questionnaire collected information regarding sociodemographics, access to care information, chronic illness, behaviors associated with HIV acquisition, medications, HIV treatment, and disease characteristics. Data were collected in a cross-sectional manner between WIHS visits 20-33

(4/2004-3/2011). Since MPV values had not been routinely entered into the WIHS database, individual MPV values were retrieved from archived laboratory records available from this time period. Laboratory values were obtained in concordance to each patient's visit and a single lab value for each parameter was included in the statistical analysis for every patient.

Outcome classification

Laboratory tests conducted using standard WIHS protocols on blood collected at the study visit were used to generate values for HIV serostatus, fasting glucose, low density lipoprotein cholesterol, platelet and CD4 count. HIV serostatus was determined using the Food and Drug Administration (FDA)-approved enzyme-linked immunosorbent assay testing and, if reactive, confirmed with the FDA approved Western blot HIV-1 confirmatory assay. Diabetes was defined as either a fasting blood glucose of >126 mg/dl or a self-reported diagnosis of diabetes or treatment of diabetes with medications. Low-density lipoprotein cholesterol (LDL-C) was estimated from the Friedewald equation.²⁴

Platelet measurements were performed by an automated laser-optical Siemens ADVIA 2120 (Siemens, Germany) counter that provided platelet count, MPV (fl). The Siemens ADVIA 2120 counters perform a 2-dimensional platelet analysis. Volume and refractive index of effectively spheroid individual platelets are simultaneously determined on a cell-by-cell basis by measuring 2 angles of laser light scatter. These 2 scatter measurements are converted into volume (platelet size) using the Mie theory of light scattering for homogeneous spheres. EDTA was used as an anticoagulant and samples were tested within 4–30 hours. An elevated mean platelet volume was defined as more than 11.5 fl with a low value less than 7.5fl adjusting for the platelet count (Siemens Advia 2120). Day to day variability was previously assessed in 52 subjects that had platelet determinations on 2 consecutive days without significant change in platelet count. The intraclass correlation coefficient to be 0.94 (95% CI: 0.91, 0.96).

Risk factor classification

Clinical examination was used to generate data for body mass index (BMI) and blood pressure (BP). Anthropometric measurements of height and weight were performed according to the Third National Health and Examination Survey (NHANES III) procedures.²⁵ BMI was calculated based on measured weight and height and was classified as underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30.0 kg/m²). Hypertension was defined as either measured systolic BP>140 mm Hg, or diastolic BP>90 mm Hg, or a self-reported diagnosis of hypertension with use of antihypertensive medications.

The WIHS semiannual visits include medical history and health behavior questionnaires, assessments of medication use, standardized clinical and laboratory measurements, and phlebotomy. Race/ethnicity was self-reported at baseline. Information regarding cigarette smoking, the occurrence of an AIDS-defining illness, and highly active antiretroviral therapy (HAART) is collected routinely at each study visit via self-report. History of an AIDS-defining illness (ADI) was defined as a prior report of conditions consistent with the 1993 Centers for Disease Control and Prevention surveillance definition. HIV status, RNA viral load and CD4⁺ lymphocyte counts were determined at the time of the WIHS visit. HAART was defined as self-reported therapy being taken at the time of data collection.

Statistical methods

Continuous variables are reported as mean±standard deviation (SD). Student's t tests were used to test differences in means. Pearson's chi square test statistic was used to assess differences in proportions for dichotomous and categorical variables; if the expected

frequencies within a cell were small (i.e., $n < 5$) then Fisher's exact test was used. Spearman's correlation coefficient was used to assess univariate relationships between scored variables. Simple and multiple linear regression models were used to predict MPV from clinical risk factors, HIV status, race, BMI category, smoking, hypertension, diabetes, platelet count and low density lipoprotein cholesterol levels. In HIV-infected women further linear regression models were used to predict MPV from HIV-specific variables, nadir CD4 count, history of AIDS Defining Illness (defined as a prior report of conditions consistent with the 1993 Centers for Disease Control and Prevention surveillance definition), and current use of HAART in addition to clinical risk factors, race, BMI category, smoking, hypertension, diabetes, platelet count and low density lipoprotein cholesterol levels. MPV values were square-root-transformed to correct mild skew of distribution. Loess plots were used to examine univariate relationship of continuous predictors platelet count, low density lipoprotein, viral load, CD4 nadir with the transformed dependent variable. Viral load was positively skewed and was $\log_{10}$ -transformed. Both platelet and CD4 nadir count as predictors of MPV appear to exhibit a change of slope near counts of 350, so piecewise linear response surfaces for platelet and nadir CD4 count were constructed, to allow slopes to change at 350. Inspection of model residuals was conducted to detect skew and outliers. A p-value < 0.05 was used to guide interpretation. All analyses were performed using IBM SPSS version 20 (Armonk, NY).

Results

A total of 368 women with records of MPV values were enrolled in the study, of which 234 were HIV infected and 134 were uninfected. No patient was known to have Idiopathic or Thrombotic Thrombocytopenic Purpura. HIV-infected women were older, more likely to have diabetes, and had higher triglyceride levels than HIV-uninfected women (Table 1). The mean platelet count was lower in HIV infected than uninfected women ($249/\mu\text{l}$ 95% CI 238, 259 vs. $276/\mu\text{l}$ 95% CI 265, 287, $p < 0.01$). The bivariate relationship between platelet count and MPV is shown in Figure 1. In multiple regression analysis in addition to lower platelet counts ($\beta = -0.54$ for < 350 per μl $p < 0.01$), adjusted mean MPV was lower in the HIV-infected than in the uninfected group (adjusted means 8.66 fl 95% CI $8.52, 8.79$ vs. 9.05 fl 95% CI $8.87, 9.24$ $\beta = -0.17$ $p < 0.01$ $R^2 = 0.20$ $p < 0.01$ for model). An association between being underweight and having higher MPV did not reach statistical significance ($p = 0.07$). The same multivariate analysis was repeated after exclusion of subjects with thrombocytopenia (< 150) and the results remained unchanged.

In multiple regression analysis confined to HIV infected women, history of AIDS defining illness (adjusted means 8.59 fl 95% CI $8.39, 8.78$ vs. 8.93 fl 95% CI $8.71, 9.15$ $p = 0.03$) were associated with significantly lower MPV, whereas smoking ($p = 0.01$) and being underweight ($p = 0.03$) were associated with higher MPV values ($R^2 = 0.28$, $p < 0.01$ for model). There were no significant relationships between MPV and HAART use, CD4 nadir count or viral load (Table 2). Since there exists a controversial association between abacavir and platelet function the potential relation between abacavir use and MPV was further assessed. Among HIV infected subjects, 45 were taking abacavir and 189 were not. Square root value values of MPV were similar between the 2 groups (2.96 SD 0.20 vs 2.94 SD 0.17 , $p = 0.53$). Inclusion of abacavir ($\beta = -0.014$, $p = 0.64$) into the multivariate model did not significantly change the model.

Discussion

Concern regarding cardiovascular disease in HIV-infected individuals has led to multiple studies examining the associations of HIV infection with atherosclerosis.²¹ Recently, the measurement of MPV, which is routinely included in a complete blood count report and is

used clinically to aid in the evaluation of thrombocytopenia, has been shown to provide prognostic information in patients with acute and chronic coronary artery disease syndromes.²⁶ Since HIV infected patients have been reported to have lower platelet counts and higher cardiovascular event rates, we sought to determine the relation between MPV and HIV infection.

Few prior studies have assessed MPV values in HIV-infected populations.^{26–28} The present study findings are consistent with those of Koenig who studied 34 HIV infected subjects and found two thirds to have thrombocytopenia, of which 92% had inappropriately low platelet volume.²⁶ However this study was limited with the number of subjects in contrast to our cohort which has a larger sample size and is more focused on women. They remarked that the platelet number volume relationship was similar to that seen in myelosuppressive bone marrow disorders and confirmed 90% of thrombocytopenic patients to have normal or decreased megakaryocytes on bone marrow examination. Cole studied 6 HIV infected patients and observed similar MPV values (10.5fl vs. 9.5fl) despite markedly reduced numbers of platelets.²⁷ In contrast, larger not smaller MPV was recently reported among HIV-infected treatment-naïve patients by Mena, who also noted MPV to increase significantly during the untreated course of asymptomatic HIV infection in 103 subjects (83% male).²⁸ Although an exact explanation for the latter study findings is lacking, HIV related thrombocytopenia is likely multifactorial with direct invasion of megakaryocyte by HIV causing apoptosis, dysmegakaryopoiesis, either abnormal or dysfunctional production of megakaryocytes and immune related peripheral platelet destruction proposed as mechanisms for lowered platelet counts.²⁹ Therefore different mechanisms of thrombocytopenia are likely to account for the disparate findings between the prior and present studies. In our cohort of HIV infected women, higher MPV values were significantly associated with underweight status. This finding is a new one as prior studies have shown higher MPV values associated with obesity in the general population.³⁰ Of note, MPV was unrelated to use of HAART or viral count.

The major finding in our study is that HIV infection is associated with lower MPV among women. Of note, gender has not been found to influence MPV in uninfected patients. Importantly, the significant relation between HIV status and mean platelet volume persisted after adjusting for platelet count, which was also lower in the infected group. More advanced HIV disease as defined by history of AIDS defining illness was associated with further lowering of MPV.

Limitations

Although, to our knowledge this is the largest evaluation of MPV in HIV-infected individuals published to date, it is subject to the limitations of a cross-sectional design including difficulty in attributing causality between the investigated factors and MPV. Only 16% of HIV infected subjects were untreated, which limits the assessment of anti-retroviral therapy on MPV. Only 17% of all subjects had thrombocytopenia (<150). We evaluated single values and did not evaluate temporal changes in MPV in this initial study. Left ventricular function and atherosclerosis are known to be associated with MPV values; although they were not investigated in this study, the cohort has performed sophisticated assessment of cardiac and vascular disease. In addition given the age of the cohort attempting to link MPV to cardiovascular clinical events at this juncture could be premature. Although the women in the WHS reflect the demographics of the HIV epidemic among women in the United States, the results may not be generalized to HIV-infected men. Moreover, women in this study had relatively well-controlled HIV infection, and had been enrolled in a prospective study for many years at the time of MPV assessment. All subjects (infected and uninfected) had MPV measured by the Siemens Advia counter, which has been shown to yield lower MPV values than other devices.³¹ Although antiplatelet

medications were not considered, aspirin has been shown to alter platelet size.³² Although EDTA was used as an anticoagulant, the samples were tested within 4–30 hours making it unlikely that this affected MPV measurement. Despite these limitations, we conclude that MPV, which has been proposed as a risk marker for cardiovascular events is lower and not higher in the setting of HIV infection in women. This suggests impaired platelet production rather than increased peripheral destruction. Therefore, higher than expected cardiovascular event rates probably should not be attributed to greater platelet reactivity as measured by MPV. Given that thrombocytopenia has been found to be associated with increased morbidity and mortality, low CD4 counts and a rapid progression to full blown AIDS, the prognostic value of MPV determination in the setting of HIV infection has not been established.²⁹ Therefore, the broader significance of this simple and inexpensive laboratory aid in the setting of HIV infection merits further study.

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Figure 1.
The relationship of mean platelet volume and platelet count in the Women's Interagency HIV Study (WIHS).

Table 1

Characteristics of HIV-Infected and -Uninfected Participants, the Women's Interagency HIV Study (WIHS)

Characteristics ^a	HIV-infected women (N=234)	HIV-uninfected women (N=134)	<i>p</i> -value ^b
Mean age (years)	41.0±8.6	36.1±10.6	<0.01
Race/ethnicity			0.18
African American	175 (74.8%)	108 (80.6%)	
Hispanic	36 (15.4%)	20 (14.9%)	
White/Other	23 (9.8%)	6 (4.5%)	
BMI ^c			0.20
Underweight	8 (3.4%)	3 (2.2%)	
Normal BMI	84 (35.9%)	36 (26.9%)	
Overweight	68 (29.1%)	40 (29.9%)	
Obese	74 (31.6%)	55 (41%)	
Current smoker	108 (46.2%)	52 (38.8%)	0.17
Mean systolic BP ^d (mmHg)	119±17	118±17	0.68
Hypertension	57 (24.4%)	31 (23.1%)	0.79
Diabetes	33 (14.1%)	30 (22.4%)	0.04
Total cholesterol (mg/dl)	174±38	176±40	0.65
HDL cholesterol (mg/dl)	50±62	84±41	0.46
Triglycerides (mg/dl)	127±71	84±41	<0.01
LDL cholesterol (mg/dl)	103±35	105±34	0.56
CD4 count			
500cells/μl	109 (46.6%)	—	
200–499cells/μl	84 (35.9%)	—	
<200cells/μl	41 (17.5%)	—	
History of ADI ^e	128 (54.7%)	—	
Current HAART	197 (84.2%)	—	
Platelet count (/μl)	249 ± 80	276 ± 66	<0.01
Mean platelet volume (fl) ^f	8.66 (95% CI 8.52, 8.79)	9.05 (95% CI 8.87, 9.24)	<0.01

^a Means are presented±standard deviation^b *p*-values for differences in means were calculated using *t* test statistics. *p*-values for differences in proportions were calculated using Pearson's Chi square test statistic unless the cells have *n*<5; then Fisher's exact test was used^c BMI, body mass index; underweight is <18.5, normal is 18.5–24.9, overweight is 25.0–29.9, and obese is ≥30.0.^d BP, blood pressure.^e AIDS defining illness is a prior report of conditions consistent with the 1993 CDC surveillance definition^f Expressed as an adjusted mean value

Table 2

Results of Multiple Linear Regression with Mean Platelet Volume as the Dependent Variable.

	Beta	p value	Beta (HIV infected)	p value (HIV infected)
Platelet count	−0.54	<0.01	−0.54	<0.01
HIV	−0.17	<0.01	-	-
BMI ^a				
Underweight	0.09	0.07	0.14	0.03
Overweight	0.02	0.76	−0.03	0.69
Obese	−0.01	0.90	−0.01	0.96
Current Smoker	0.07	0.14	0.17	0.01
Hypertension	0.05	0.30	0.05	0.46
Diabetes	−0.03	0.60	0.02	0.81
LDL cholesterol	0.01	0.94	0.03	0.59
ADI ^b	-	-	−0.15	0.03
Viral Load ^c	-	-	0.06	0.48
CD4 count	-	-	−0.10	0.73
HAART	-	-	0.01	0.88

^aBMI, body mass index; underweight is <18.5, normal is 18.5–24.9, overweight is 25.0–29.9, and obese is ≥30.0.

^bAIDS defining illness is a prior report of conditions consistent with the 1993 CDC surveillance definition.

^cViral Load entered after log₁₀ transformation to correct for skewed distribution.