Does Monocyte/High-Density Lipoprotein Cholesterol Ratio Predict Saphenous Vein Graft Patency in Patients with Stable Angina Pectoris?

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ABSTRACT

Introduction: Circulating monocyte count is a predictive factor of new atherosclerotic plaque development. In addition, there is a strong inverse relationship between high-density lipoprotein (HDL) cholesterol and atherosclerosis. It has been shown that the monocyte/HDL cholesterol ratio (MHR) is a novel inflammatory marker. We aimed to investigate the relationship between MHR and saphenous vein graft disease (SVGD).

Patients and Methods: A total of 3 69 patients were divided into 3 groups (positive SVGD group= 150, negative SVGD group= 89, normal coronary artery group= 130). Baseline characteristics and laboratory parameters were recorded and compared among the groups.

Results: There were no significant differences between the positive and negative SVGD groups, except for age of SVG and left ventricular ejection fraction, according to baseline characteristics. C-reactive protein (CRP) levels, fasting blood glucose levels and mean platelet volume were higher in the positive SVGD group than in the negative SVGD group (p= 0.008, 0.048 and 0.042, respectively). MHR was not significantly different between the positive and negative SVGD groups (p= 0.169) and normal coronary artery group (p= 0.364). CRP was found to be an independent predictor factor of SVGD.

Conclusion: There was no association between MHR and coronary atherosclerosis. MHR was not a predictive factor of SVGD.

Key Words: Monocyte count; high-density lipoprotein cholesterol; atherosclerosis; saphenous vein graft disease

Monosit/ Yüksek Dansiteli Lipoprotein Kolesterol Oranı Stabil Anjina Pektorisi Olan Hastalarda Safen Ven Greft Açıklığını Öngördürebilir mi?

ÖZET

Giriş: Dolaşımdaki monosit sayısı yeni aterosklerotik plak gelişimi için öngördürücü bir faktördür. Ayrıca, yüksek dansiteli lipoprotein kolesterol (HDL) ile ateroskleroz arasında güçlü bir ters ilişki vardır. Monosit sayısı/HDL oranının (MHR) yeni bir inflamatuvar belirteç olduğu gösterilmiştir. Biz MHR ile safen ven greft hastalığı (SVGD) arasındaki ilişkiyi araştırmayı amaçladık.

Hastalar ve Yöntem: Toplam 369 hasta 3 gruba bölündü (SVGD olan grup= 150, SVGD olmayan grup= 89, normal koroner arter grubu= 130). Bazal karakteristikler ve laboratuvar parametreleri kayıt edildi ve gruplar arasında karşılaştırıldı.

Bulgular: Bazal karakteristiklere göre SVGD olan ve olmayan gruplarda, SVG yaşı ve sol ventrikül ejeksiyon fraksiyonu haricinde istatistiksel farklılık yoktu. C-reaktif protein, açlık kan şekeri ve ortalama platelet hacmi SVGD olan grupta SVGD olmayan gruba göre daha yüksekti (sırasıyla p değerleri= 0.008, 0.048 ve 0.042). MHR değeri SVGD olan, SVGD olmayan (p= 0.169) ve normal koroner arter grupları (p= 0.364) arasında istatistiksel farklılık göstermedi. CRP, SVGD için bağımsız öngördürücü faktör olarak bulundu.

Sonuç: MHR ve koroner ateroskleroz arasında ilişki yoktu. MHR, SVGD için bir öngördürücü faktör değildi.

Anahtar Kelimeler: Monosit sayısı; yüksek dansiteli lipoprotein kolesterol; ateroskleroz; safen ven greft hastalığı

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Submitted: 02.03.2016
Accepted: 05.04.2016

INTRODUCTION

Atherosclerotic cardiovascular disease is still one of the most common causes of death worldwide. In recent years, surgical and non-surgical interventions have led to a significant improvement in the mortality and morbidity associated with atherosclerotic or non-atherosclerotic cardiovascular disease. Coronary artery bypass graft (CABG) surgery is a procedure used to treat blocked coronary arteries for many years. Blood vessels or grafts used for the bypass procedure may be pieces of a vein taken from the legs (saphenous vein) or an artery (radial artery or left or right internal mammary artery). Saphenous vein grafts (SVGs) have a relatively high rate of degeneration and stenosis compared with arterial grafts, and this is one of the most important problems in both early and late stages after CABG surgery[1].

Previous studies have demonstrated that the patency rate of SVGs is only 32%-71% at the end of the first 10 postoperative years[2,3]. Many mechanisms may be responsible for SVG disease (SVGD). Thrombosis, neointimal hyperplasia and atherosclerosis are the best-defined pathological reasons over long periods of time[4]. The main mechanism underlying SVGD is graft thrombosis during the first month after surgery, whereas intimal hyperplasia accounts account for the development of the disease in the subacute period (1-12 months). Atherosclerosis is the main cause of SVGD and total occlusion after 1 year, even though it plays a role in every stage of the disease[4].

In recent years, many studies have been designed to recognise the inflammatory effect in atherosclerosis. According to these studies, there are significant relationships between atherosclerosis and the platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), red blood cell distribution width (RDW) and platelet distribution width (PDW) parameters, which are easily detectable by peripheral blood tests[5-7]. In addition, it is known that monocytes and macrophages play an essential role in the progression of atherosclerosis[8]. Further, a study has suggested that the monocyte count is a predictive factor of atherosclerotic plaque formation[9]. On the other hand, increased serum high-density lipoprotein (HDL) cholesterol levels are associated with an anti-atherogenic effect. Previous studies have demonstrated that HDLs inhibit the cytokine-induced expression of inflammatory adhesion molecules in endothelial cells[10]. A recent study has shown that the monocyte/HDL cholesterol ratio (MHR) is negatively correlated with cardiovascular mortality in patients with chronic kidney disease[11]. In the present study, we aimed to investigate the relationship between MHRD and SVGD.

PATIENTS and METHODS

This study included patients with a > 1-year-old history of CABG surgery who underwent coronary angiography because of indications of the procedure (positive treadmill stress test, myocardial perfusion scintigraphy and others) and patients with normal epicardial coronary artery results after coronary angiography between 2010 and 2015. The local ethics committee approved the study, and all the patients included in the study provided proper written informed consent. The study population was divided into 3 groups: positive SVGD group, negative SVGD group and normal coronary artery group. SVGD was defined as at least 50% occlusion of SVG, as described previously[5,6].

The exclusion criteria were active infection, chronic inflammatory disease or connective tissue disease, chronic kidney disease, acute coronary syndrome, decompensated heart failure, blood transfusion within a few months and haematological diseases (including anaemia). Hypertension was defined as systolic pressure above 140 mmHg and diastolic pressure above 90 mmHg or provision of treatment for hypertension. Patients with fasting blood glucose levels above 126 mg/dL or those using anti-diabetic drugs were described as diabetics. Haematological and biochemical tests were performed after 12 h of fasting and before the coronary angiography procedure. Complete blood count was performed using A Coulter Counter LH Series (Beckman coulter Inc, Hialeah, Florida). Other biochemical tests (including lipid panel) were performed using standard techniques. C-reactive protein (CRP) levels were measured using the nephelometry method. The left ventricular ejection fraction was measured using biplane Simpson's method. Coronary angiography was performed for imaging the saphenous graft veins with at least 2 angulations using the Seldinger technique with standard Judkings catheters. Coronary angiography images were assessed by at least 2 experienced cardiologists. In addition, aortic root angiography was performed in most patients to show the implanted grafts.

Statistical Analysis

The SPSS 16.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois) was used for statistical analysis. Continuous variables were presented as the median (range) or mean ± standard deviation, and categorical variables were presented as percentages. The Kolmogorov-Smirnov test was used to test the normality of distribution. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Student's t-test or Mann-Whitney U test. Logistic regression analysis was used to determine the independent predictors of SVGD. A p value of < 0.05 indicated statistical significance.

RESULTS

Baseline clinical and demographic characteristics of the study population are shown in Table 1. There were 150 (40.6%) patients with SVGD (mean age, 67.10 ± 8.0 years, 30% females), 89 (24.1%) patients with patent SVG (mean age, 65.7 ± 7.50 years, 25.8% females) and 175 (35.2%) patients with normal coronary arteries (mean age, 55.6 ± 11.8 years, 61.5% females). Age, diabetes mellitus, hypertension and smoking

rates were lower in the normal coronary artery group than in the CABG surgery history group, as expected. There were no significant differences between the positive and negative SVGD groups after excluding the normal coronary artery group, except for age of SVG and left ventricular ejection fraction, according to baseline characteristics. Laboratory parameters of the population are demonstrated in Table 2. There were no significant significance differences between the positive and negative SVGD groups, except for CRP levels, fasting blood glucose levels and MPV. These parameters were higher in the positive SVGD group than in the negative SVGD group (p= 0.008, 0.048 and 0.042, respectively). In addition, MHR was not significantly different between the positive and negative SVGD groups (p= 0.169). Interestingly, there were no differences among the 3 groups according to MHR (p= 0.364) (Figure 1). The significantly different parameters between the positive and negative SVGD groups are shown in Table 3. Although CRP levels were higher in the positive SVGD group, there was no positive or negative correlation between MHR and CRP levels (p= 0.843, Spearman's rho= 0.019). Finally, in multivariate logistic regression analysis, we found that only CRP was an independent predictor of SVGD (Table 4).

DISCUSSION

The results of this study failed to demonstrate a positive association between SVGD and MHR by peripheral blood tests. In addition, the results showed that MHR is not increased in patients with a CABG surgery history compared with patients with angiographically normal coronary arteries. Therefore, the available data are inadequate to accept that MHR may be a novel predictive marker of atherosclerotic cardiovascular diseases or SVGD. To the best of our knowledge, this is the first study to investigate the relationship between MHR and SVGD.

CABG is a surgical procedure used to treat coronary artery disease to relieve patients' symptoms and confer survival benefit. During this procedure, patients generally receive a left internal mammary artery (LIMA) graft to the left anterior descending coronary artery, and other additional bypasses are constructed using reversed SVGs with aortic anastomoses[12]. The patency of LIMA and other arterial grafts is better than that of saphenous grafts[12]. During the first month after CABG surgery, 3.4% of saphenous graft veins are occluded because of thrombosis, and this is known as early graft vein disease. Mechanical damage to the graft vessel wall during graft resection is accepted as the main mechanism underlying the pathogenesis in this period[13-15]. Thrombocyte activation, leukocyte migration through the vessel wall, pro-inflammatory cytokine discharge, activation of the coagulation cascade and rise in intimal smooth muscle cells are the most important factors associated with the progress of SVGD following 1 to 12 months of surgery[16]. Patients with a > 1 year of surgery were included in the study because atherosclerosis is the principal cause of SGVD pathogenesis after the first year of surgery[4].

Table 1. Baseline clinical characteristics of study population and comparison of groups

Variables	Normal coronary arteries (n= 130)	Negative saphenous vein graft disease (n= 89)	Positive saphenous vein graft disease (n= 150)	Total (n= 369)	p
Age (years, mean ± SD)	55.6 ± 11.8	65.7 ± 7.5	67.1 ± 8.0	62.7 ± 10.8	< 0.001
Gender (male, n, %)	50 (38.5)	66 (74.2)	105 (70.0)	221 (59.9)	< 0.001
Hypertension (n, %)	74 (56.9)	63 (70.8)	117 (78.0)	254 (68.8)	< 0.001
Diabetes mellitus (n, %)	37 (28.5)	32 (36.0)	73 (48.7)	142 (38.5)	< 0.002
Smoking (n, %)	41 (31.5)	56 (62.9)	82 (57.7)	179 (48.5)	< 0.001
Family history (n, %)	30 (23.0)	20 (22.4)	40 (26.6)	90 (24.4)	0.180
Age of SVG, (years, median, IQR)	-	6 (5-10)	9 (5-13)	4 (0-9)	< 0.001
Number of SVGs (1,2,3,4 grafts, median, IQR)	-	2 (1-2)	2 (1-2)	1 (0-2)	0.670
LVEF, %, (median, IQR)	65 (60-68)	50 (45-60)	48 (40-55)	55 (45-65)	< 0.001
medical therapy (%)					
Acetylsalicylic acid, n (%)	-	88 (99.9)	144 (98)	232 (62.9)	0.294
Beta-blocker, n (%)	-	74 (84.1)	129 (87.8)	203 (55)	0.438
RAS blocker, n (%)	-	73 (83.0)	126 (85.7)	199 (53.9)	0.570
Statin, n (%)	-	80 (90.9)	138 (93.9)	218 (59.1)	0.395
Trimetazidine (n, %)	-	29 (33.0)	61 (41.5)	90 (24.4)	0.192
Oral nitrates (n, %)	-	22 (25.0)	61 (41.5)	83 (22.5)	< 0.010
Ivabradine (n, %)	-	1 (1.1)	1 (0.7)	2 (0.5)	1.0

*IQR: Interquartile range, LVEF: Left ventricular ejection fraction, RAS: Renin-angiotensin system, SD: Standard deviation, SVG: Saphenous vein graft.

Table 2. Laboratory parameters of study population and comparison of groups

Variables	Normal coronary arteries	Negative saphenous vein graft disease	Positive saphenous vein graft disease	Total	p
Hb, g/dL (median, IQR)	13.7 ± 1.7	13.6 ± 1.7	13.4 ± 2.0	13.6 ± 1.8	0.391
WBC count/μL, mean ± SD	7.5 (6.3-9.1)	7.6 (6.5-9.1)	7.8 (6.5-9.6)	7.7 (6.5-9.3)	0.206
Platelet count, $\times 10^3$/μL (median, IQR)	241 (214-292)	210 (176-251)	228 (192-257)	228 (192-268)	< 0.001
Neutrophil count/μL, mean ± SD	4.5 (3.3-5.6)	4.6 (3.4-5.7)	4.6 (3.9-5.9)	4.6 (3.8-5.8)	0.189
Lymphocyte count/μL, mean ± SD	2.02 ± 0.71	2.03 ± 0.72	2.13 ± 0.77	2.1 ± 0.7	0.328
Monocyte count/μL (median, IQR)	0.57 (0.49-0.72)	0.61(0.46-0.73)	0.60 (0.48-0.79)	0.59 (0.48-0.75)	0.501
MHR	13.1 (9.3-17.9)	15.2 (11.8-18.3)	14.9 (11.4-26)	14.5 (10.8-19.4)	0.364
Fasting blood glucose, mg/Dl	97 (90-112)	100 (88-130)	115 (97-178)	101 (90-135)	< 0.001
Total cholesterol, mg/dL (median, IQR)	190.8 ± 40.9	169.8 ± 41.1	178.3 ± 48.3	181.4 ± 44.4	< 0.001
LDL, mg/dL, mean ± SD	118 (95-141)	92 (79-110)	100.5 (78.9-127.6)	104.0 (85.1-130.0)	< 0.001
HDL, mg/dL, mean ± SD	43 (38-51)	39 (34-44)	39 (35-46)	41 (36-48)	< 0.001
Triglyceride, mg/dL	122 (95-178)	124 (91-171)	140 (97-197)	132 (95-180)	0.257
CRP, mg/dL (median, IQR)	3 (2-4)	12 (8.5-19.5)	18 (12-23)	11 (4-19)	< 0.001
RDW, % (median, IQR)	13.6 (13.0-14.1)	13.7 (13.0-14.5)	13.7 (13.1-14.8)	13.7 (13.1-14.7)	0.548
MPV, fL (median, IQR)	8.8 (8.0-9.6)	10.4 (9.8-11.1)	10.9 (9.9-11.5)	10.1 (8.9-11.0)	< 0.001
Creatinine, mg/dL (median, IQR)	0.74 (0.62-0.86)	0.89 (0.74-1.06)	0.91 (0.78-1.17)	0.85 (0.69-1.0)	< 0.001

CRP: C-reactive protein, Hb: Haemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MHR: Monocyte-HDL ratio, MPV: Mean platelet volume, RDW: Red blood cell distribution width, WBC: White blood cell.

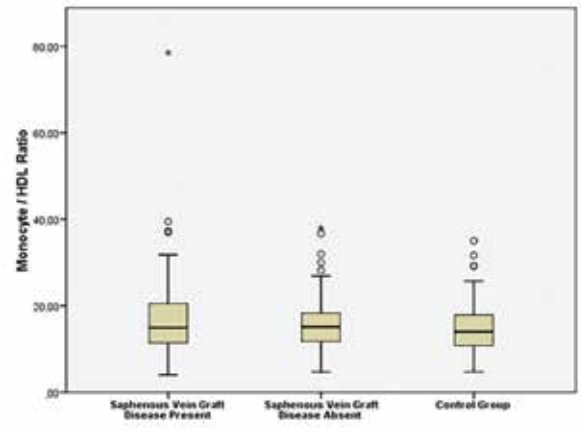

Figure 1. General situation of monocyte/HDL cholesterol ratio in 3 groups.

Table 3. Positive and negative saphenous vein graft disease and significant baseline variables, excluding normal coronary artery group

Variables	Negative saphenous vein graft disease	Positive saphenous vein graft disease	p
CRP, mg/dL (mean ± SD)	14.1 ± 8.3	19.6 ± 11.6	0.008
Age of SVG (years, median, IQR)	6 (5-10)	9 (5-13)	0.005
LVEF, % (median, IQR)	50 (45-60)	48 (40-55)	0.010
MPV, fL (median, IQR)	10.4 (9.8-11.1)	10.9 (9.9-11.5)	0.042
Fasting blood glucose, mg/dL	100 (88-130)	115 (97-178)	0.048

CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, MPV: Mean platelet volume.

Table 4. Logictic regression analysis demonstrating independent predictors of saphenous vein graft disease

			95% Confidence interval	
	p	β	Lower	Upper
CRP	0.049	0.944	0.891	1.000
Age of SVG, years	0.143	0.900	0.782	1.036
LVEF	0.154	1.041	0.985	1.099
Fasting blood glucose	0.303	0.996	0.989	1.004
MPV	0.305	0.807	0.537	1.215
Constant	0.430	10.772	-	-

CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, MPV: Mean platelet volume.

The long-term patency of SVG is strongly associated with grafting to the left anterior descending coronary artery and grafting to the vessel with a large diameter. Other predictive risk factors of SVGD are older age, diabetes mellitus, high serum cholesterol levels, smoking and hypertension[12]. In this context, previous studies have suggested that inflammatory markers such as CRP, homocysteine, low-density lipoprotein cholesterol, NLR, PLR and RDW are associated with atherosclerosis and SVGD[5-7,17,18]. It also well known that monocytes are part of this inflammation and play a key role during this process[8].

Blood monocytes enter the intima and subintima of vessels, and after becoming macrophages, they internalise oxide LDL and other lipids by their several scavenger receptors. These lipids accumulate in macrophages, which are then called foam

cells. Foam cells create fatty streaks in the intima at the early stage of the process[19,20]. Monocyte groups involve endothelial and monocytic adhesion molecule expression. The adhesive interaction of monocytes and the endothelium initially occurs by selectins expressed on endothelial cells. Firm adhesion of monocytes to endothelium occurs via interactions of the vascular cell adhesion melocule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) to monocyte adhesion molecules such as CD11b/CD18[21,22]. Thus, blood monocyte count is a predictive factor of new atherosclerotic plaque formation[9]. On the other hand, plasma HDL levels are associated with decreased cardiovascular morbidity and mortality[23]. The main mechanism underlying this protection is reverse cholesterol transport. Other cardioprotective mechanisms underlie the anti-oxidative properties and ability to enhance the bioavailability of nitric oxide (NO)[24,25]. Some previous studies have shown that HDLs inhibit the cytokine-induced expression of inflammatory adhesion molecules in endothelial cells[26]. Indeed, epidemiological and clinical studies have demonstrated that the HDL concentration is often inversely correlated with plasma levels of pro-inflammatory agents such as cytokines and CRP in atherosclerotic cardiovascular diseases, revealing the importance of the balance between anti-inflammatory and pro-inflammatory potentials in the pathogenesis of these diseases[27,28]. Besides its several anti-atherosclerotic effects, HDL is suggested to inhibit monocyte activation[29].

A recent study by Kanbay et al. found that MHR is an independent predictive factor of composite and fatal cardiovascular events in 340 patients with chronic kidney disease[11]. Another study showed a relation between coronary slow flow and MHR and a positive correlation between high-sensitive CRP levels and MHR. These results demonstrated that MHR is associated with systemic inflammation[30]. However, our results do not support the hypothesis that there is a positive correlation between CRP levels and MHR. This situation may be explained with our small study population or it may be a coincidence in the previous study. We also found that CRP is an independent predictor of SVGD, as previously accepted, but there was no positive correlation between MHR and CRP levels[18]. We need further studies with other inflammatory markers (such as interleukins and cytokines) to demonstrate a relationship between MHR and inflammation. A study on 1170 patients undergoing primary percutaneous coronary intervention because of ST elevation myocardial infarction indicated a positive correlation between stent thrombosis and MHR after a 37.2-month follow-up period. In the same study, it was emphasised that there is an association between increased MHR and inflammation[31].

CONCLUSION

According to our results, there is no association between MHR and SVGD or atherosclerosis. We need more prospective studies and molecular investigations with a large homogeneous patient population.

STUDY LIMITATIONS

Although we met our study objectives, there were some unavoidable limitations. First, study had a retrospective design with a small patient population. Second, similar to a previous study, cardiovascular endpoints were not considered. On the other hand, the blood monocyte count may be variable. Only a single measurement of blood monocyte counts may not reflect the true levels of blood monocytes, and several measurement and their average results may be required to reflect the actual blood monocyte levels. Further, the study design may involve the use of blood monocyte subtypes and HDL cholesterol subtypes. Finally, anti-hyperlipidaemic drugs, diet and exercise result in decreased serum HDL levels, and this can decrease MHR.

CONFLICT of INTEREST

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: YA, SS

Analysis/Interpretation: YA, SA

Data Acquisition: HB, HS

Writting: SS, YA

Critical Revision: AY, MB

Final Approval: All of authors

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