Relationship Between Monocyte/High-Density Lipoprotein Cholesterol Ratio and Angiographic Severity and Extent of Coronary Artery Disease

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ABSTRACT

Introduction: Circulating monocyte count is predictive of new atherosclerotic plaque development. In addition, there is a strong inverse relationship between high-density lipoprotein (HDL) cholesterol and atherosclerosis. We aimed to investigate the relationship between the monocyte/HDL cholesterol ratio and severity of coronary artery disease.

Patients and Methods: A total of 760 patients who underwent coronary angiography were included in the study. The severity of coronary atherosclerosis was calculated by the Gensini score, and the patients were grouped as having low (< 20) and high (> 20) Gensini scores. Baseline characteristics and laboratory parameters were recorded and compared between patients with low and high Gensini scores.

Results: Hypertension, diabetes mellitus, hyperlipidaemia, advanced age and smoking were more common in patients with a high Gensini score. Fasting blood glucose levels, creatinine levels and monocyte/HDL cholesterol ratio were significantly lower in patients with a low Gensini score than in those with a high Gensini score. Logistic regression analysis revealed that older age, fasting blood glucose levels, hyperlipidaemia, family history of coronary artery disease and male gender were independent predictors of a high Gensini score. We observed a correlation between the monocyte/HDL cholesterol ratio and Gensini score ($p< 0.001$). However, this correlation was weak (Spearman's rho = 0.159).

Conclusion: We observed a positive but weak correlation between the monocyte/HDL cholesterol; ratio and increased coronary atherosclerotic burden, as calculated by Gensini scoring. Further studies are required to demonstrate the relationship between the monocyte/HDL cholesterol ratio and atherosclerotic cardiovascular disease.

Key Words: Monocyte count; high-density lipoprotein cholesterol; atherosclerosis; coronary artery disease; Gensini score

Monosit Sayısı/HDL Oranı ile Koroner Arter Hastalığının Ciddiyeti ve Yaygınlığı Arasındaki İlişki

ÖZET

Giriş: Kan dolaşımında bulunan monosit sayısı yeni aterosklerotik plak oluşumunda öngörücüdür. Bununla birlikte yüksek dansiteli lipoprotein kolesterol (HDL) düzeyleri ile ateroskleroz arasında güçlü bir negatif ilişki vardır. Bu çalışmada, monosit sayısı/HDL oranıyla koroner arter hastalığı ciddiyeti arasındaki ilişkiyi değerlendirmeyi amaçladık.

Hastalar ve Yöntem: Koroner anjiyografi yapılan toplam 760 hasta çalışmaya dahil edildi. Koroner ateroskleroz ciddiyeti Gensini skorlama sistemi kullanılarak değerlendirildi ve hastalar Gensini skorlarına göre yüksek (> 20) ve düşük (< 20) olarak iki gruba ayrıldı. Bazal karakteristik özellikler ve laboratuvar parametreleri kaydedilerek yüksek ve düşük Gensini skoru olan hastalar arasında karşılaştırıldı.

Bulgular: Hipertansiyon, diabetes mellitus, hiperlipidemi, ileri yaş ve sigara içiciliği yüksek Gensini skoru olan hastalarda daha fazlaydı. Açlık kan şekeri, kreatinin düzeyleri ve monosit/HDL oranı düşük Gensini skoru olan hastalarda yüksek Gensini skoru olanlara kıyasla daha düşüktü. Lojistik regresyon analizinde ileri yaş, açlık kan şekeri, hiperlipidemi, aile öyküsü ve erkek cinsiyetin yüksek Gensini skoru için bağımsız parametreler olduğu gözlendi. Monosit/HDL oranının, Gensini skoruyla korele olduğu ($p< 0.001$) ancak bu korelasyonun çok zayıf olduğu tespit edildi (Spearman's Rho: 0.159).

Sonuç: Monosit/HDL oranı ile Gensini skoruyla elde edilen ateroskleroz yaygınlığı arasında zayıf da olsa bir ilişki izlenmiştir. Ancak Monosit/HDL oranı ve aterosklerotik kalp hastalığı arasındaki ilişkiyi belirlemek için daha fazla klinik çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Monosit sayısı; yüksek dansiteli lipoprotein kolesterol; ateroskleroz, koroner arter hastalığı; Gensini skoru

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INTRODUCTION

Atherosclerotic cardiovascular diseases (CVDs) are still the leading cause of mortality worldwide. Atherosclerosis, a progressive inflammatory process, is characterised by the formation and build-up of atherosclerotic plaques that consist of a well-defined structure of lipids, necrotic cores, calcified regions, inflamed smooth muscle cells, endothelial cells, immune cells and foam cells[1]. It has been shown that monocytes and tissue macrophages play a pivotal role in atherosclerotic plaque formation[2,3]. In addition, this knowledge has been supported by studies showing that the circulating monocyte count is a predictor of atherosclerotic plaque formation in the carotid arteries[4,5].

There is a strong inverse association between high-density lipoprotein (HDL) cholesterol and atherosclerosis. One of the protective mechanisms of HDL is the inhibition of cytokine-induced expression of inflammatory adhesion molecules in endothelial cells, thereby preventing monocyte and endothelium interaction[6,7]. Recently, the monocyte/HDL cholesterol ratio (MHR) has been presented as a marker of inflammation and a predictor of cardiovascular risk[8,9]. However, there are limited data about the association between MHR and the severity of coronary atherosclerosis.

Because MHR is suggested as a new marker of inflammation and a predictor of cardiovascular disease, we investigated the association between MHR and the severity of atherosclerosis in the coronary arteries.

PATIENTS and METHODS

A total of 760 patients who underwent elective (positive cardiac stress test, ischaemia in myocardial perfusion scintigraphy, recently detected left ventricular wall motion abnormalities, stable angina pectoris and others) or emergency (acute coronary syndromes) coronary angiographies in our hospital between 1 October 2012 and 30 June 2013 were included in this retrospective cross-sectional study. Patients who had acute or chronic inflammatory disease (e.g. rheumatoid arthritis), active malignancy or acute or chronic infections were excluded from the study. In addition, patients who were receiving lipid-lowering therapy were not included. Patients whose fasting plasma glucose level was ≥ 126 mg/dL or who were using oral antidiabetic drugs and insulin were accepted as diabetic; patients whose blood pressure was ≥ 140/90 mmHg or who were using antihypertensive medications were accepted as hypertensive.

The local ethics committee approved the study, and all the patients in this study provided proper written consent.

Coronary Angiography

Coronary angiography was performed using a Toshiba Digital Radiography System Model DFP-8000D (Toshiba American Medical Systems, Tustin, USA). A 6 F sheath was inserted into the femoral artery using the Seldinger method, and coronary angiography was performed using Judkins catheters. Coronary angiography results were evaluated by at least 2 cardiologists blinded to the patients. The Gensini scoring system was used for assessing the severity and extensiveness of coronary artery disease (CAD); in this system, the narrowing of the lumen of the coronary arteries is graded as follows: 1 for 1%-25% narrowing, 2 for 26%-50% narrowing, 4 for 51%-75% narrowing, 8 for 76%-90% narrowing, 16 for 91%-99% narrowing and 32 for a totally occluded artery. This score was then multiplied by a factor that accounts for the importance of the lesion's position in the coronary arterial anatomy[10,11]. A Gensini score of ≥ 20 was accepted as severe CAD[12]. Patients with a low Gensini score (< 20) were considered as Group 1 and those with a high Gensini score (> 20) were considered as Group 2.

Routine Laboratory Examinations

Routine haematological and biochemical tests were performed before coronary angiography. Serum lipid levels were measured after a 12-h fasting period. Fasting plasma glucose, lipid, creatinine, uric acid, calcium and albumin levels were calculated using standard methods. The C-reactive protein (CRP) level was examined using the nephelometric method. The monocyte count was determined using the Pentra 120 Retic haematology analyser (ABX, Montpellier, France), as part of the routine haemogram. The reference value for monocytes in our laboratory is between 2% and 10%. Serum MHR is calculated by dividing the monocyte count by the HDL cholesterol level.

Statistical Analysis

Research data were evaluated using the SPSS 15.0 statistical package program (SPSS Inc., Chicago, IL, USA). Descriptive statistics were shown as mean ± standard deviation or median (interquartile range) for continuous variables and as the number of cases (n) and percentages (%) for nominal variables. Normality distribution was evaluated using the Kolmogorov-Smirnov test. Baseline characteristics were compared using the independent-sample t-test, Mann-Whitney U test, chi-square test or Fisher's exact test, where appropriate. Spearman's correlation test was used for assessing the correlation between MHR and the Gensini score. Logistic regression analysis was used to determine the independent predictors of a high Gensini score. A p value < 0.05 was considered as statistically significant.

RESULTS

The demographic features and laboratory parameters of the study population are shown in Table 1.

A total of 760 patients were aged 60.5 ± 11.7 years in the study population, and 460 (60.5 %) were males. Of these, 441 patients (mean age 58.2 ± 11.5 years, 53.5% males) were enrolled in Group 1 and 319 patients (mean age 63.8 ± 11.2 years, 70.2% males) were enrolled in Group 2 ($p< 0.001$). Hypertension, diabetes mellitus, hyperlipidaemia, advanced age and smoking were more common in patients with high Gensini scores, as expected ($p< 0.05$). Fasting blood glucose levels, blood urea nitrogen (BUN) levels, creatinine levels,

Table 1. Demographic characteristics of the study population

	Overall (n= 760)	Low Gensini score (n= 441)	Low Gensini score (n= 319)	p
Age (years)	60.5 ± 11.7	58.2 ± 11.5	63.8 ± 11.2	< 0.001
Gender (male), n (%)	460 (60.5)	236 (53.5)	224 (70.2)	< 0.001
Hypertension, n (%)	479 (63.0)	258 (58.5)	221 (69.2)	0.002
Diabetes, n (%)	248 (32.6)	117 (26.5)	131 (41.1)	< 0.001
Hyperlipidaemia, n (%)	307 (40.4)	150 (34.0)	157 (49.2)	0.001
Smoking, n (%)	302 (39.7)	162 (36.7)	140 (43.8)	0.047
Family history, n (%)	129 (16.9)	59 (13.3)	70 (21.9)	0.003
Diagnosis, n (%)				
STEMI	63 (8.3)	12 (2.7)	51 (15.9)	
NSTE-ACS	131 (17.2)	55 (12.4)	76 (23.8)	< 0.001
Stabil angina	566 (75.4)	374 (84.8)	192 (60.2)	
Fasting blood glucose (mg/dL) (median, IQR)	99.0 (90.0-127.5)	96.0 (89.0-113.5)	104.5 (93.0-153.2)	< 0.001
BUN (mg/dL) (median, IQR)	15.8 (12.7-19.1)	15.0 (12.0-18.6)	16.5 (13.4-20.0)	0.001
Creatinine (mg/dL) (median, IQR)	0.8 (0.6-0.9)	0.8 (0.7-0.9)	0.8 (0.7-1.0)	< 0.001
HbA1c (%) (median, IQR)	6.6 (5.8-8.0)	6.2 (5.8–7.5)	7.0 (6.0-8.6)	0.001
Total cholesterol (mg/dL) (mean ± SD)	191.9 ± 51.1	194.2 ± 46.2	188.9 ± 56.7	0.184
HDL (mg/dL) (median, IQR)	41.0 (35.0-48.0)	42.0 (36.2-49.0)	39.0 (34.0-46.0)	0.001
LDL (mg/dL) (median, IQR)	117.0 (90.0-143.0)	119.0 (93.0-144.2)	112.0 (85.0-142.0)	0.093
TG (mg/dL) (median, IQR)	131.0 (94.0-193.7)	129.0 (95.0-193.0)	131.5 (91.0-198.0)	0.609
Total bilirubin (mg/dL) (median, IQR)	0.6 (0.4-0.7)	0.6 (0.4-0.8)	0.6 (0.4-0.7)	0.852
Direct bilirubin (mg/dL) (median, IQR)	0.13 (0.09-0.20)	0.14 (0.09-0.21)	0.12 (0.09-0.20)	0.461
AST (U/L) (median, IQR)	22.0 (18.0-27.0)	21.0 (18.0-26.0)	22.0 (18.0-29.0)	0.089
ALT (U/L) (median, IQR)	20.0 (15.0-28.0)	20.0 (15.0-28.0)	20.0 (15.0-28.0)	0.883
ALP (U/L) (median, IQR)	81.0 (66.0-97.5)	82.0 (66.0-98.0)	79.0 (66.0-96.5)	0.210
Albumin (g/dL) (median, IQR)	4.2 (4.0-4.4)	4.2 (4.0-4.5)	4.1 (3.9-4.4)	0.010
Uric acid (mg/dL) (median, IQR)	5.4 (4.4-6.4)	5.4 (4.3-6.3)	5.5 (4.6-6.5)	0.232
CRP (mg/L) (median, IQR)	5.4 (3.0-9.3)	5.1 (2.6-9.4)	5.8 (3.5-8.8)	0.388
Haemoglobin (g/dL) (mean ± SD)	13.9 ± 1.7	13.9 ± 1.6	13.9 ± 1.8	0.998
Platelet × 1000 K/uL (median, IQR)	234.9 (197.0-277.4)	239.9 (201.0-285.5)	226.0 (192.5-271.0)	0.013
MPV (fL) (median, IQR)	8.9 (8.2-9.8)	8.8 (8.1-9.6)	9.0 (8.2-9.9)	0.026
Monocyte/HDL ratio (K/uL: mg/dL) (median, IQR)	14.5 (10.7-19.1)	13.7 (10.3-18.1)	15.3 (11.2-20.1)	0.004
Ejection fraction (%) (median, IQR)	62.0 (50.0-66.0)	64.0 (60.0-67.0)	55.0 (45.0-63.0)	< 0.001
Gensini score (median, IQR)	12.0 (1.5-42.4)	2.5 (0-7.0)	50.5 (30.5-80.0)	< 0.001

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CA: Coronary artery, CRP: C-reactive protein, HbA1c: Haemoglobin A1C, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MPV: Mean platelet volume, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, TG: Triglyceride.

mean platelet volume (MPV), HBA1C levels and MHR were significantly lower in patients with a low Gensini score than in those with a high Gensini score. The median MHR was 14.5 (10.7-19.1 IQR) in the overall population. It was 13.7 (10.3-18.1 IQR) in patients with a low Gensini score and 15.3 (11.2–20.1 IQR) in those with a high Gensini score (p< 0.004). Ejection fraction, HDL levels and platelet count were significantly higher in patients with a low Gensini score than in those with a high Gensini score. The median Gensini score was 12.0 (1.5-42.4 IQR) in the study population. It was 2.5 (0-7 IQR) in patients with a low Gensini score and 50.5 (30.5-80 IQR) in those with a high Gensini score (p< 0.001). In binary logistic regression analysis, we found that only older age, fasting blood glucose levels, hyperlipidaemia, family history of CAD and male gender were associated with a high Gensini score [MHR 95% confidence interval (CI)= 0.983-1.052; p value = 0.336;

Table 2. Logistic regression analysis to determine high Gensini score

				95% Confidence interval	
	B	p	Odds ratio	Lower	Upper
Age	0.057	**< 0.001**	1.059	1.038	1.081
Male gender	0.672	**0.007**	1.959	1.206	3.180
Hypertension	0.082	0.730	1.085	0.682	1.726
Diabetes	-0.125	0.645	0.883	0.519	1.501
Monocyte/HDL cholesterol ratio	0.017	0.336	1.017	0.983	1.052
Family history	0.659	0.016	1.933	1.130	3.308
Hyperlipidaemia	0.751	**0.001**	2.119	1.388	3.236
Smoking	0.167	0.462	1.182	0.757	1.845
Albumin	0.002	0.968	1.002	0.930	1.078
Platelet	0.000	0.829	1.000	0.997	1.003
Creatinine	-0.028	0.716	0.972	0.834	1.133
Fasting blood glucose	0.008	**0.001**	1.008	1.003	1.013
HDL	-0.010	0.435	0.990	0.966	1.015
LDL	0.001	0.660	1.001	0.997	1.005

odds ratio (OR)= 1.017] (Table 2). We observed a significant but weak correlation between MHR and the Gensini score (p< 0.001) (Spearman's rho= 0.159) (Figure 1).

DISCUSSION

In this study, we demonstrated a positive but weak correlation between MHR and increased coronary atherosclerotic burden, as calculated by Gensini scoring. We found an increased MHR in Mann-Whitney U test in patients with a high Gensini score. However, multivariate logistic regression model revealed that MHR is not an independent predictor of a high Gensini score. According to logistic regression analysis, fasting blood glucose levels, history of hyperlipidaemia, family history of CAD and male gender were associated with a high Gensini score rather than MHR. There was a significant correlation between MHR and the Gensini score. However, this correlation should be considered as incidental or weak.

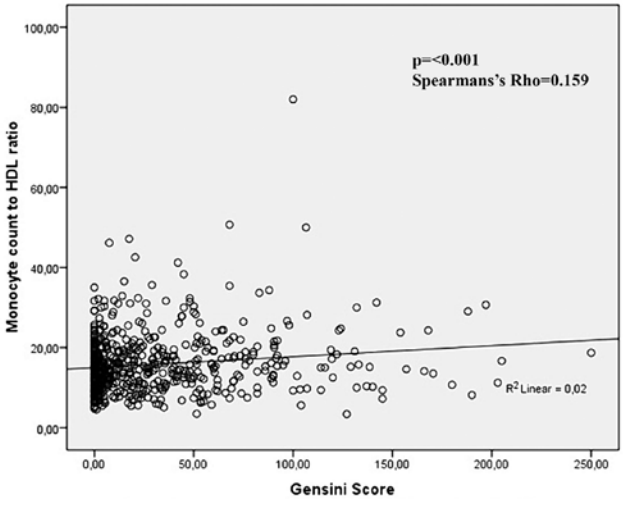

Figure 1. Correlation between monocyte to HDL cholesterol ratio and Gensini score.

Chronic inflammation is the main characteristic of atherosclerotic cardiovascular disease. Macrophages, transformed from circulating monocytes, are among the key cell types responsible for atherosclerotic plaque formation; therefore, attention has been paid to circulating monocyte counts to clarify atherosclerosis pathogenesis. The circulating monocyte count, as the source of tissue macrophages and foam cells, has been found to be a predictor of new plaque development[4]. In addition, Nazowa et al. have demonstrated the association between the circulating monocyte count and coronary plaque progression after acute coronary syndrome[13]. Another study by Olivares et al. has reported a high monocyte count to be a predictor of coronary events during nearly 7 years of follow-up[14].

Besides many antiatherosclerotic effects, HDL is suggested to inhibit monocyte activation. Murphy et al. have demonstrated that activated monocytes may be inhibited by HDL[15]. They have also shown that HDL decreases CD11b expression dose-dependently and increases the activation of primary human monocytes in an in vitro environment[15]. In addition, previous studies have indicated that monocyte spreading and transmigration may control the inhibition of cytokine-induced expression of adhesion molecules on endothelial cells that interact with integrins to mediate the adhesion of monocytes to the endothelium by HDL or synthetic apo AI/phospholipid vesicles[6,16,17].

As discussed above, circulating monocytes may be associated with atherosclerosis and HDL may affect monocyte function; this knowledge supports the hypothesis that an increased MHR is a predictor of atherosclerosis development, atherosclerosis progression and cardiovascular events. Kanbay et al. have reported MHR to be an independent predictor of fatal and composite cardiovascular events in chronic kidney disease patients in their study[8]. In a recently published study by Kundi et al., a positive association has been demonstrated between the severity of coronary atherosclerosis and MHR. Differently, they used the SYNTAX score to investigate this association in a smaller study population (n= 428)[18]. They also demonstrated that CRP levels and MHR are significantly higher in patients with a higher SYNTAX score.

In this study, we expected to find an association between MHR and CAD severity using the Gensini scoring system. We found a statistically significant but weak correlation between the Gensini score and MHR; therefore, our data cause a suspicion about the usage of a simple MHR to assess the severity and extensiveness of coronary atherosclerosis. Our findings do not support our initial hypothesis and raise 2 questions about the usage of MHR in clinical practice. The first question is about the monocyte type studied. We know that circulating monocytes are functionally heterogeneous. Distinct monocyte subtypes have different inflammatory potentials; therefore, a simple monocyte count does not truly reflect the activation status of monocytes [19]. The second question is about the HDL subclasses. The antiatherogenic properties of HDL subclasses are thought to be different from each other and there is no firm evidence about whether one of the subclasses is definitely predominant[20]. In this study, we used a simple MHR and did not evaluate HDL subclasses or monocyte subtypes because new published studies suggest the usage of a simple MHR as a marker of inflammation and cardiovascular risk. However, our findings did not support the hypothesis that an increased MHR may be independently associated with CAD severity and extensiveness. Lack of data about monocyte subtypes and HDL subclasses are an important limitation of this study, and our hypothesis should be reinvestigated using other data, including those of HDL subclasses and monocyte subtypes.

CONCLUSION

In this study, we demonstrated a positive but poor relationship between MHR and increased coronary atherosclerotic burden, as calculated by Gensini scoring, unlike previously published studies.

LIMITATIONS

This was a cross-sectional study and we did not evaluate cardiovascular endpoints; we evaluated monocyte counts and HDL levels, which are simply measured in peripheral blood counts and are easily available in daily practice. However, the monocyte count does not fully demonstrate activated monocytes and the HDL level does not guarantee that the HDL molecules of our study population are protective with regard to atherosclerosis development. A study that collects data on the activated monocyte burden and HDL subfractions or evaluates the association between these parameters would be more valuable. In this study, we chose to use the Gensini scoring system to evaluate the severity and extensiveness of atherosclerosis, but compared with other systems (SYNTAX, CASS or Duke CAD Severity Index and others), it may be more effective to investigate the relationship between MHR and atherosclerosis. Finally, inclusion of patients with acute coronary syndromes is a major limitation of our study. Acute coronary syndromes are accepted as an inflammatory process; therefore, this situation may have affected our results.

CONFLICT of INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EK, YA

Analysis/Interpretation: YA, BS, SÖ

Data Acquisition: SS, AA

Writting: EK, YA, SS

Critical Revision: GT, SÖ

Final Approval: All of authors

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