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Tip 2 diyabet ile monosit-yüksek dansitelilipoprotein kolesterol oranı ve karotisintimamedia kalınlığı arasındaki ilişki

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Abstract

Aim: Diyabetes mellitus (DM) is a majör risk factor for atheroscleros. Circulating monocyte count plays an important role for new atherosclerotic plaque development. Also, there is a strong inverse relationship between high density lipoprotein cholesterol (HDL) and atherosclerosis. Monocyte count/HDL ratio (MHR) is a novel inflammatory marker for atherosclerosis. Carotid intima-media thickness (CIMT) can predict the presence or absence of coronary artery disease (CAD). I aimed to investigate relationship between CIMT, MHR and type 2 DM

Methods: A total of 120 patients were divided into two groups (with type2 DM group = 60, control group: 60). Baseline characteristics, laboratory parameters, MHR and CIMT were recorded and compared between groups.

Results: The Diabetes group had considerable higher CIMT, MHR levels compared to the control ($p<0.001$,$p<0,001$ respectively). Also, CIMT levels showed significant correlation with blood glucose level ($r=0.474$, $p<0.001$). On the contrary, HDL levels were higher in the control group ($p=0.010$).

Conclusion: In conclusion, I found significantly higher MHR and CIMT in the diabetic group and thus I think MHR, which is an easily calculated index, can be used in the daily clinical practice as an indicator of atherosclerosis in Type 2 DM patients.

Keywords: Monocyte; monocyte to high density lipoprotein cholesterol rate; carotid intima-media thickness.

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ÖZET

Amaç: Diyabet ateroskleroziçin majör bir risk faktörüdür. Dolaşımdaki monosit miktarı yeni aterosklerotik plak gelişiminde önemli bir rol oynar. Ayrıca yüksek dansiteli lipoprotein (HDL) kolesterol ve ateroskleroz arasında güçlü bir ters ilişki olduğu gösterilmiştir. Monosit ile HDL kolesterol oranı ateroskleroz için yeni bir inflamasyon belirtecidir. Karotis intimamedia kalınlığı (KİMK) koroner arter hastalığının olduğunu veya olmadığını gösterebilir.

Gereç ve yöntemler: 60 diyabet hastası ve 60 kontrol grubu olarak toplam 120 hasta iki gruba ayrıldı. Karakteristik özellikler, labaratuvar parametreleri, KİMK ve monosit ile HDL kolesterol oranları kaydedildi ve iki grup arasında karşılaştırıldı.

Bulgular: Diyabetik grupta KİMK ve monosit ile HDL oranı anlamlı derecede yüksek izlendi ($p<0.001$,$p<0,001$ sırasıyla). Ayrıca KİMK kan glukoz düzeyleri ile anlamlı derecede korelasyon gösterdi ($r=0.474$, $p<0.001$). Buna karşın, HDL oranı kontrol grubunda daha yüksekti ($p=0,010$).

Sonuç: Sonuç olarak, çalışmamda diyabetik grupta anlamlı olarak daha yüksek MHR ve CIMT düzeyleri tespit ettim ve böylece kolayca hesaplanan bir indeks olan MHR'nin, Tip 2 DM hastalarında aterosklerozun bir göstergesi olarak günlük klinik uygulamada kullanılabileceğini düşünüyorum.

Anahtar sözcükler: Monosit; monosit ile yüksek dansiteli lipoprotein oranı; yüksek dansiteli lipoprotein; karotis intima-media kalınlığı.

INTRODUCTION

Atherosclerosis and CAD are among the leading causes of mortality in the world. Diabetes mellitus is a major risk factor for atherosclerosis (1). Often, atherosclerosis is detected at its advanced stages, and interventions are generally palliative or focused on secondary prevention (2). Atherosclerosis manifests with subclinical signs long before it is clinically overt. Early detection and treatment of atherosclerosis in patients with DM prevent development of much pathology.

The most important changes that occur at the early stages of atherosclerotic disease include endothelial dysfunction and increased intima-media thickness. In many studies, detection of increased carotid intima-media thickness (CIMT) via non-invasive methods may predict the presence or absence of CAD (2,3).

Recently many studies have been conducted to understand the relationship between inflammation and atherosclerosis. These studies show significant relationships between atherosclerosis and are easily detectable by peripheral blood count parameters including platelet/lymphocyte ratio, neutrophil-lymphocyte ratio, and red blood cell distribution width (4,5,6). In addition, monocytes and macrophages are known to play an essential role in the progression of atherosclerosis. One study demonstrated that monocyte count had predictive value in atherosclerotic plaque development (7). Increased levels of serum (HDL), however, shows anti-atherogenic effects. High density lipoprotein inhibits the cytokine-induced expression of inflammatory adhesion molecules in endothelial cells. Monocyte count/HDL ratio is a novel inflammatory marker for atheroscleros. A recent study showed that MHR was negatively correlated with cardiovascular mortality in patients with chronic kidney disease (8).

In this study, I examined the relationship between CIMT, which is an established indicator of subclinical atherosclerosis in patients with type 2 DM, and a novel index monocyte/HDL ratio

METHODS

Study population

This prospective study was conducted with 60 patients previously diagnosed with type 2 DM that were admitted to the cardiology clinic, and 60 healthy volunteers. All cases provided anamnesis and underwent general physical examination. Exclusion criteria included acute or chronic infection, malignancy, hematological disease, cerebrovascular accident, coronary artery disease, renal failure, connective tissue disease, acute coronary syndrome, decompensated heart failure, blood transfusion within a few months, and the use of anti-lipidemic drugs such as statin and niacin. The local ethics committee approved the study, and all patients included in the study provided proper written informed consent.

Study design

In all patients echocardiography was performed. Ejection fraction was calculated via M-mode technique. Carotid artery imaging was performed with the patient in the supine position and neck angled 20 degrees to the counter side. The measurements were made at 3 distinct points: right and left carotid artery, bifurcation, and the first 2 cm of internal carotid artery. CIMT measurements were made by evaluating the posterior (far) wall only. Carotid intima-media thickness measurements were performed with B-mode examination in the long axis of the distance defined between vessel lumen echogenicity and media/adventitia echogenicity. Mean CIMT was calculated as the mean of the 3 measurements from both carotid arteries. Age, gender, body mass index (BMI), fasting blood glucose, creatinine, lipid profile, and systolic and diastolic blood pressures of the cases were evaluated. Additionally, hemoglobin A1c (HbA1c) levels were measured. Blood samples were obtained following a 12 hour fast. The monocyte/HDL ratio was calculated by dividing the monocyte count, measured via a complete blood count device, to the serum HDL level.

Statistical Analysis

All statistical calculations were performed using SPSS for Windows (ver. 21.0; SPSS, Chicago, IL, USA). Categorical variables were expressed as count and ratio. Continuous variables were expressed as mean ± standard deviation. Normality of the data distribution was analyzed with Kolmogorov-Smirnov test. The significance of the difference between the groups regarding mean values was analyzed with Student t-test. Comparison of categorical variables between the groups was made with chi-square test. Continuous non-parametric variables were compared between the groups with Mann-Whitney U test. Correlation analysis

was made using Pearson's or Spearman's test. Logistic regression analysis was used to investigate the independent determinants of Type 2 Diabetes. In the logistic regression analysis, most deterministic factors in discriminating the groups were confirmed. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

Sixty patients diagnosed with Type 2 DM (mean age 60.8±8.2 years, 75.0% male), and 60 healthy individuals as the control group (mean age 61.3±7.4 years, 76.6% male) were included in the study. There were no differences between the groups regarding mean age, ejection fraction, clinical systolic or diastolic pressures, creatinine level, white blood cell count, or hemoglobin level ($p>0.05$). The Diabetes group had markedly higher body mass index (BMI), CIMT, MHR, fasting blood glucose, HbA1c, and low density lipoprotein (LDL) levels compared to the control ($p<0.001$ for all). Additionally, total cholesterol (TC) and triglyceride (TG) levels were significantly higher in the Diabetes group ($p=0.002$ and $p=0.008$, respectively). On the contrary, HDL levels were higher in the control group ($p=0.010$) (**Table 1**).

CIMT, BMI, HbA1c, TC, TG, and LDL levels showed significant correlation with blood glucose level ($r=0.474$, $p<0.001$; $r=0.492$, $p<0.001$; $r=0.910$, $p<0.001$; $r=0.251$, $p=0.002$; $r=0.228$, $p=0.008$; and $r=0.392$, $p<0.001$ respectively). On the other hand, HDL showed a negative correlation with blood glucose level ($r=-0.202$, $p=0.010$). Multivariate logistic regression analysis showed that CIMT, BMI, HbA1c and LDL levels were independent determinants of type 2 DM (Odds ratios (ORs)=1.967, 95% CI, 1.574–2.459, $p < 0.001$; OR=1.564, 95% CI, 1.402–2.102, $p < 0.001$; OR=1.102, 95% CI, 1.034–1.366, $p = 0.012$; OR= 1.017, 95% CI, 1.002–1.023, $p=0.014$, respectively) (Table 2).

Table 1. Thedistribution of demographicandlaboratoryfindingsin studypopulation

Baselinevariables	Controls (n = 60)	Diabetes (n = 60)	P value
Gender, male, n, (%)	45 (56.3)	46 (57.5)	0.873
Age, (years)	60.8±8.2	61.3±7.4	0.569
BMI (kg/m²)	27.9±1.2	29.2±1.5	< **0.001**
CIMT (mm)	0.71±0.48	1.18±0.16	< **0.001**
Ejectionfraction (%)	55.8±2.3	55.1±3.4	0.456
Clinicsystolic BP (mmHg)	107.3±11.2	108.5±10.1	0.724
Clinicdiastolic BP (mmHg)	71.1±6.4	71.7±5.5	0.872
Fastingplasmaglucose (mg/dL)	98.6±7.2	128.1±9.3	< **0.001**
HbA1c (%)	4.8±0.3	6.8±1.3	< **0.001**
Cre (mg/dL)	0.89±0.12	0.87±0.28	0.656
TC (mg/dl)	177.9±31.6	194.3±31.5	**0.002**
TG (mg/dl)	165.1±24.3	182.2±32.8	**0.008**
HDL (mg/dl)	37.6±8.4	32.8±6.3	**0.010**
LDL (mg/dl)	103.7±24.6	127.7±18.6	< **0.001**
WBC ($10^3 \times \mu L$)	10.1±3.3	10.1±3.2	0.937
Hgb (g/dl)	13.8±1.2	14.0±1.3	0.856
MHR	5.3±1.7	8.7±0.5	< **0.001**
Monocyte (µl)	332.7±102	465.4±87	< **0.001**

BMI, body massindex; BP, bloodpressure; CIMT, carotidintimamediathickness; Cre, creatinine; HbA1c, glycolized hemoglobin; HDL, highdensitylipoprotein; Hgb, haemoglobin; LDL, lowdensitylipoprotein; MHR, monocyte/HDL ratio; TC, total cholesterol; TG, triglyceride; WBC, whitebloodcell

Table 2. Factorsassociatedwithdiabetes

	Univariateanalysis		Multivariateanalysis		
Variables	**Correlationcoefficient(r)**	**P value**	**Oddsratio**	**95% CI**	**P value**
Age, (years)	0.091	0.306	1.056	0.987-1.044	0.304
LV-EF (%)	-0.089	0.501	1.002	0.917-1.043	0.500
CIMT (mm)	0.474	< **0.001**	1.967	1.574-2.459	< **0.001**
BMI (kg/m²)	0.492	< **0.001**	1.564	1.402-2.102	< **0.001**
HbA1c (%)	0.910	< **0.001**	1.102	1.034-1.366	**0.012**
MHR	0.482	< **0.001**	1.956	1.426-2.202	< **0.001**
TC (mg/dl)	0.251	**0.002**	1.008	1.004-1.021	**0.003**
TG (mg/dl)	0.228	**0.008**	1.013	1.002-1.019	**0.010**
LDL (mg/dl)	0.392	< **0.001**	1.017	1.002-1.023	**0.014**
HDL (mg/dl)	-0.202	**0.010**	0.972	0.922-0.991	**0.011**

BMI, body massindex; CIMT, carotidintimamediathickness; HbA1c, glycolizedhaemoglobin; HDL, highdensitylipoprotein; LV-EF, leftventricularejectionfraction; LDL, lowdensitylipoprotein; MHR, monocyte/HDL ratio; TC, total cholesterol; TG, triglyceride

DISCUSSION

Patients with Type 1 or Type 2 DM are well known to have increased risk of atherosclerosis (9). The most important change occurring at the early stage of atherosclerotic disease is increased intima-media thickness in the whole arterial bed. As early atherosclerotic changes occur in the vascular bed, intima-media thickening has been proposed to indicate endothelial dysfunction or concurrent involvement of both layers. Thus, in addition to clinical evaluation, the two powerful markers of subclinical vessel disease, coronary artery calcium scan and CIMT can be used discriminate low- and high-risk groups of Diabetic patients (10). Moreover, CIMT has been generally associated with cardiovascular risk factors and extent of symptomatic CAD (11). Additionally, various studies have documented the relationship between insulin resistance, hyperlipidemia, DM duration hyperglycemia and CIMT (12). In this study, I also found significant correlation with blood glucose level and CIMT. Recently, there have been many studies investigating the association between inflammation and atherosclerosis. Circulating monocytes migrate to the intima and sub-intima regions of the vessels and transform into macrophages. These macrophages then internalize LDL cholesterol and other lipids via many scavenger receptors. These lipids accumulate inside macrophages and later give rise to formation of the so-called “foam cells”. Foam cells create fatty streaks in the intima at the early stage of the process (13,14). Monocyte groups involve endothelial and monocytic adhesion molecule expression. The adhesive interaction of monocytes and 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. Çakmakoğlu et al. Reported an association between glucose and monocyte in the form of chemotaxis in diabetic patients with CAD. In this study, similarly, I found significantly higher monocyte ratio in the Diabetic group. Plasma HDL cholesterol level is associated with reduced cardiovascular mortality and morbidity, and the main mechanism underlying this protective effect is reverse cholesterol transport. High density lipoprotein concentration is often inversely associated with the plasma levels of pro-inflammatory agents, such as cytokines and CRP, in atherosclerotic cardiovascular diseases. This highlights the importance of the balance between anti-inflammatory and pro-inflammatory potentials in the pathogenesis of these diseases. Besides many anti-atherosclerotic effects, HDL has been suggested to be an inhibiting molecule against

monocyte activation (16). A recent study by Kanbay et al. found that b MHR was an independent predictive factor for composite and fatal cardiovascular events in 340 patients with chronic kidney disease (8). Many studies have shown that MHR has predictive value in acute coronary syndromes, that it indicates high thrombus load, and is closely associated with stent thrombosis in patients undergoing coronary stent implantation with primary percutaneous intervention (17,18). Kızıltunç et al. found an association with MHR and the extent of atherosclerosis as indicated by Gensini score among patients with stable angina pectoris (19). Another study by Canpolat et al. reported that high baseline MHR was associated with recurrent atrial fibrillation development in patients that underwent cryoablation due to atrial fibrillation (20). In this study, I also found a significantly higher MHR in patients with Type 2 DM.

In conclusion, I found significantly higher MHR and CIMT in the diabetic group and I think MHR, which is an easily calculated index, can be used in the daily clinical practice as an indicator of atherosclerosis in Type 2 DM patients.

REFERENCES

1. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation 2009; 119: 1728–1735.

2. Kupfer R, Larrubia MR, Bussade I, et al. Predictors of subclinical atherosclerosis evaluated by carotid intima-media thickness in asymptomatic young women with type 1 diabetes mellitus. Arch EndocrinolMetab. 2017;61(2):115-21.

3. Tetik SS, Tanrıverdi B. The pathophysiology and risk factors of Atherosclerosis Marmara Pharmaceutical Journal. 2017;21(1):1-9.

4. Akyel A, Çelik IE, Öksüz F et al: Red Blood Cell Distribution Width in Saphenous Vein Graft Disease. Canadian Journal of Cardiology 2013;29:448–451.

5. Yayla Ç, Canpolat U, Akyel A et al: Association Between Platelet to Lymphocyte Ratio and Saphenous Vein Graft Disease. Angiology 2016;67(2):133-138.

6. Tasoglu I, Turak O, Nazli Y et al: Preoperative Neutrophil-Lymphocyte Ratio and Saphenous Vein Graft Patency After Coronary Artery Bypass Grafting. ClinApplThrombHemost 2014;20(8):819-824.

7. Woollard KJ, Geissmann F: Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol 2010;7(2):77–86.

8. Kanbay M, Solak Y, Unal HU et al: Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. IntUrolNephrol 2014;46(8):1619-1625.

9. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.Lancet. 2010;375(9733):221522.

10. Malik S, Budoff MJ, Katz R, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the multi-ethnic study of atherosclerosis. Diabetes Care. 2011;34(10):2285-90.

11. Polak JF, Pencina MJ, Pencina KM, et al. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011;365(3):213-21.

12. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014;37(10):2843-63.

13. Greaves D. r. & Gordon S: The macrophage scavenger receptor at 30 years of age: current knowledge and future challenges. J. Lipid Res 2009;50(Suppl.):282–286.

14. Galkina, E. and Ley K: Immune and inflammatory mechanisms of atherosclerosis. Annu. Rev. Immunol 2009;27:165-197.

15. Çakmakoğlu B, Çınçın ZB, Daşdemır S, et al. The evaluation gene polimorphisms of monocyte chemotactic protein(MCP-1) a-2518G and CCR2 receptors G190A in coronary artery diseases in diabetic populatios: Deneysel Tıp AraştırmaEnstitüsüDergisi. 2011;1(2):9-13.

16. Andrew J. Murphy, Kevin J. Woollard, Anh Hoang et al: High-Density Lipoprotein Reduces the Human Monocyte Inflammatory Response. ArterioscIerThrombVascBiol 2008;28:2071-2077.

17. Tok D, Turak O, Yayla C, et al. Monocyte to HDL ratio in prediction of BMS restenosis in subjects with stable and unstable angina pectoris. Biomarkers in medicine. 2016;10(8):853-60.

18. Cetin EHO, Cetin MS, Canpolat U, et al. Monocyte/HDL-cholesterol ratio predicts the definite stent thrombosis after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Biomarkers. 2015;9(10):967-77.

19. Kızıltunç E, Alsancak Y, Sezenöz B, et al. Relationship between monocyte/high-density lipoprotein cholesterol ratio and angiographic severity and extent of coronary artery disease Koşuyolu Heart J 2017;20(1):30-5.

20. Canpolat U, Aytemir K, YorgunH , et al. The role of preprocedural monocyte-to-high-density lipoprotein ratio in prediction of atrial fibrillation recurrence after cryoballoon-based catheter ablation. EP Europace. 2015;17(12):1807-15.