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Original Article

Monocyte count to high-density lipoprotein cholesterol ratio may be a predictor in ascending aortic aneurysm

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Abstract

Aim: The predictive value of the monocytes count and HDL-cholesterol ratio (MHR) has been demonstrated in several cardiovascular diseases. Ascending aortic aneurysm (AAA) is an important cause of mortality in adults. The aim of our study was to investigate the relationship between MHR and AAA in patients with hypertension.

Material and Methods: 240 consecutive patients with AAA and 240 consecutive patients with normal ascending aortic diameter were recruited into the study by comprehensive transthoracic echocardiography. All data and MHR was compered between two groups.

Results: MHR levels were significantly higher in AAA group compared to normal ascending aortic diameter group ($p<0.001$). Higher levels of MHR was found significantly and independently associated with the AAA ($p<0.001$). Also there was significant positive correlation between the diameter of the ascending aorta and the MHR ($p<0.017$).

Conclusion: MHR as a marker of chronic low-grade inflammation may play a role in the pathogenesis of aneurysm of the ascending aorta.

Keywords: Ascending aortic aneurysm; inflammation; monocyte/HDL ratio

INTRODUCTION

Out of one hundred thousand people randomly selected, 5 or 10 may have ascending aortic aneurysms (AAA) (1,2). Etiologically, AAAs have remained idiopathic, and it is risky to diagnose this disease based on atherosclerosis (3), rather than descending and abdominal aortic aneurysms. Ascending aorta dilation may potentially occur when the extracellular matrix is deformed and destructed, and in long periods, the aortic wall is exposed to hemodynamic force, for instance, led by high blood pressure (4,5). In the pathophysiological aspect, although which mechanisms may cause AAAs has been now better understood by means of recent studies, there are limited biomarkers for risk assessment of aneurysms.

Typically, in controlling the cholesterol attack from tissues and modulating inflammation and oxidative stress, normal HDL is an effective anti-inflammatory molecule and antioxidant (6). For human monocytes, its major protein component, apolipoprotein A-I (apo A-I), inhibits CD11b from activating (7). These monocytes help a variety of cytokines and molecules be produced and on the other hand, their interaction with platelets or endothelial cells during circulation allows proteases to destroy the extracellular matrix, and hence smooth muscle cells may differentiate (apoptosis), oxidative stress may progress, or neovascularization or calcification may occur (8). In cardiovascular science, there is an innovative precursor for chronic kidney patients in these days: the ratio of monocyte count to high-density lipoprotein cholesterol or MHR (9). It has been reported that MHR may slow coronary flow (10) and cause stent thrombosis (10), stent thrombosis (11), coronary artery ectasia (12), acute coronary syndrome (13) and loss of aortic elasticity among hypertension patients (14).

According to the literature review, the pathogenesis of degenerative AAA could be caused by monocytes or HDL-cholesterol and accordingly, its diagnosis and management should advance (15) With this, the aim this of study is to determine whether the maximum diameter of ascending aorta observed in admission of each asymptomatic patients are associated with the MHR calculated.

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MATERIAL and METHODS

For the objective of the study, newly diagnosed AAA patients were screened in a sequence from June 2014 to February 2018. Out of the 386 patients in total, those with arrhythmias (n= 12), Marfan syndrome (n =3), cardiomyopathies (n =13), acute and chronic hepatitis (n= 6), renal dysfunction (creatinine > 1.5 mg/dl) (n= 9), chronic inflammatory disease (n =2), active infectious disease (n= 1), malignancy (n= 21), chronic obstructive pulmonary disease (n =35), severe aortic regurgitation (n=4), and dilation only in the aortic root (n=31) were excluded from our study. Then, the remaining AAA patients (n=240) were studied. For this purpose, the control group consisted of patients having normal aortic dimensions to the study group of newly diagnosed AAA patients with hypertension, following age and gender matching. Our application for approval was granted by the Ethics Committee of the Hospital.

Involved in this study, 480 in total patients all went through a complete transthoracic echocardiographic examination, and for each, the size of aorta was obtained. AAA was diagnosed when the diameter dimension of the individual ascending aorta was equal to or greater than 40 mm. Prior to physical examination, patient histories were profoundly reviewed on an individual basis, and medical judgment was made using 12-channel ECG. Based on the blood pressure levels physically measured by a Riester mercury sphygmomanometer (Nova Presameter, Riester, Germany) in accordance with the guidelines, when the mean value of three records (in two or three visits) for a systolic or a diastolic blood pressure was not less than 140 and/or 90 mmHg, respectively (16) this measurement and or usage of any antihypertensive agent was clinically determined as hypertension. A fasting glucose level of 126 mg/dl or higher, ongoing antidiabetic treatment, or following a diabetic diet was considered as diabetes mellitus and as diabetic tendency when it extended to 100 mg/dl. Identification of active smokers was based on the time of diagnosis, irrespective of the number of cigarettes consumed. Hyperlipidaemia was diagnosed for patients whose total cholesterol and/or triglyceride level was higher than 200 and/or 150 mg/dl, respectively. The BMI formula that was used in the study was [weight (kg)/height (m2)].

For the baseline, blood samples were taken in the morning to measure the 12h-fasting plasma glucose, total serum cholesterol (TC), triglycerides (TGs), HDL-cholesterol and low-density lipoprotein cholesterol in each patient's first visit. A Beckman Coulter LH 780 hematology analyzer (Beckman Coulter, FL, USA) was used for complete blood count (CBC) analysis for the samples in EDTA-anticoagulated tubes. The differential analysis also determined monocyte count to calculate the monocyte/HDL ratio individually. The hospital considered 2-10% as the reference value for MHR. The formula of Chronic Kidney Disease Epidemiology Collaboration was used to estimate the glomerular filtration rate. The nephelometric method provided the high-sensitivity C-reactive protein (hsCRP) levels accepted as baseline, using a Beckman Coulter AU 680 Analyzer, by Beckman Coulter.

For all the patients, complete transthoracic examination was conducted based on the aortic dimensions measured via a 2.5–3.5 MHz transducer, GE-Vingmed Vivid S5 (GEV Vingmed Ultrasound AS, Horten, Norway). Available on the electronic patient record system, the echocardiography sheets displayed at least three consecutive beats, and all the blinded image analyses were performed by an experienced cardiologist. The intra-observer correlation To describe left ventricular ejection fraction the modified Simpson method offered an apical four-chamber view. Left ventricular mass (LVM) was calculated using Devereux's adjusted formula: LVM= 0.8× 1.04 × [(left ventricular diastolic diameter + left ventricle posterior wall thickness + interventricular septum diameter)3 – left ventricular diastolic diameter3]+ 0.6 g. An index was established by dividing LVM by body surface area (LVM/BSA, g/m2) or height^2 (17).

Morphological examination of the aortic valve was thoroughly made in the long-axis and short-axis views. The annulus diameter of the aortic valve was estimated. The aortic diameter was measured at both the sinus of the valsalva level and the sinotubular junction. The guidelines of the American Society for Echocardiography were referred to for measurement of the diameter of the proximal ascending aorta based on M-mode echocardiography in the parasternal long-axis view in which the largest aortic diameter can be observed through the leading-edge technique in a perpendicular plane to the long axis of the aorta (18).

Statistical analysis

The results were statistically analyzed using SPSS 21.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test offered the pattern of distribution. The mean ± standard deviation, medians and interquartile range, or proportions described the raw data. Inter-group comparison was performed using Student's t-test for normally distributed or parametric data and Mann–Whitney U test for non-parametric data. As for the categorical variables Chi-square test was used. The linearity of two continuous variables was explained based on the Pearson's or Spearman's correlation coefficients when applicable. Univariate and stepwise multivariate linear regression analyses determined the association between AAA diameter and other potential risk factors. The prerequisite for the multivariate linear regression model was $p < 0.10$. The significance level was defined as $p < 0.05$ for the statistical analyses.

RESULTS

A summary of the demographic data and clinical findings are presented in Table 1. There were no significant differences between two groups, except for hypertension ($P < 0.001$).

Table 1. Clinical and demographic characteristics of the study population

Variables	Control group (n=240)	Case group (n=240)	p value
Age,years	58.81 ±14.82	57.45 ±15.04	0.312
Female, n(%)	76 (31.7%)	61 (25.4%)	0.130
Body mass index, kg/m^2	28.95±2.31	28.12±2.78	0.534
Diabetes Mellitus, n(%)	42 (17.5%)	49 (20.4%)	0.415
Hypertension, n(%)	92 (38.3%)	119 (49.6%)	**0.013**
Hyperlipidemia, n(%)	53 (22.1%)	63 (26.3%)	0.286
Smoking, n(%)	91 (37.9%)	97 (40.4%)	0.575
Coronary artery disease, n(%)	32 (13.3%)	31 (12.9%)	0.892
Peripheral vascular disease, n(%)	24 (10.0%)	32 (13.3%)	0.255
Beta Blocker usage, n(%)	21 (8.8%)	32 (13.8%)	0.086

Table 2. Echocardiographic characteristics of the study population

Variables	Control group (n=240)	Case group (n=240)	p value
LVEF (%)	63.1 ± 2.1	60.8 ± 2.2	0.412
ARVC (mm)	2.4 ± 1.0	2.4 ± 1.0	**<0.001**
Aortic annulus diameter (mm)	2.15 ± 0.21	2.36 ± 0.30	**0.036**
Sinus valsalva diameter (mm)	3.42 ± 0.71	4.04 ± 0.77	**<0.001**
Ascending aorta diameter (mm)	4.51 ± 1.41	3.27 ± 0.24	**<0.001**
Arcus aorta diameter (mm)	2.49 ± 0.21	3.29 ± 0.71	**<0.001**
Bicuspid aortic valve, n(%)	7 (2.9%)	45 (18.8%)	**<0.001**

ARVC, vena contracta width of aortic regurgitation; LVEF, left ventricular ejection fraction

Table 3. Blood parameters of the study population

Variables	Control group (n=240)	Case group (n=240)	p value
Glucose, mg/dL	112.6 ± 42.3	110.6 ± 35.9	0.507
Creatinine, mg/dL	1.06 ± 0.28	1.08 ± 0.31	0.676
Uric Acid, mg/dl	5.57 ± 2.42	6.58 ± 2.52	**0.038**
Hemoglobin, g/dL	13.7 ± 1.5	14.0 ± 1.7	0.290
WBC,10^3/mm^3	7.7 ± 2.3	8.0 ± 2.4	0.303
Neutrophil,10^3/mm^3	5.0 ± 2.0	5.2 ± 3.2	0.485
Lymphocyte,10^3/mm^3	1.9 ± 0.8	2.0 ± 1.0	0.195
Monocyte,10^3/mm^3	0.6 ± 0.2	0.7 ± 0.3	**<0.001**
Platelet, 10^3/mm^3	255.8 ± 78.6	259.2 ± 83.7	0.731
Hs-CRP,mg/L	4.6 ± 2.5	8.3 ± 3.7	**<0.001**
Total cholesterol, mg/dL	189.3 ± 43.0	184.3 ± 45.1	0.155
LDL-C, mg/dL	117.8 ± 33.6	112.3 ± 45.1	0.272
HDL-C, mg/dL	47.3 ± 10.7	47.3 ± 12.7	0.975
Triglyceride, mg/dL	143.1 ± 84.8	148.8± 73.0	0.460
MHR	0.013 ± 0.006	0.016 ± 0.006	**<0.001**

WBC, white blood cell; Hs-CRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MHR, Monocyte – high-density lipoprotein ratio

Table 2 briefly presents the echocardiographic characteristics of the patients. AAA significantly enlarged the diameters of the vena contracta of aortic regurgitation, the sinus of valsalva, aortic annulus diameter (p=0.036), sinotubular junction, arcus aorta and ascending aorta (p <0.001). Left-ventricular ejection fraction was not significantly different between the hypertensive patients with and without AAA.

The AAA patients had significantly higher levels of Monocyte, high-sensitivity C-reactive protein, MHR (for all p <0.001), and Uric Acid (p=0.036), as shown in Table 3.

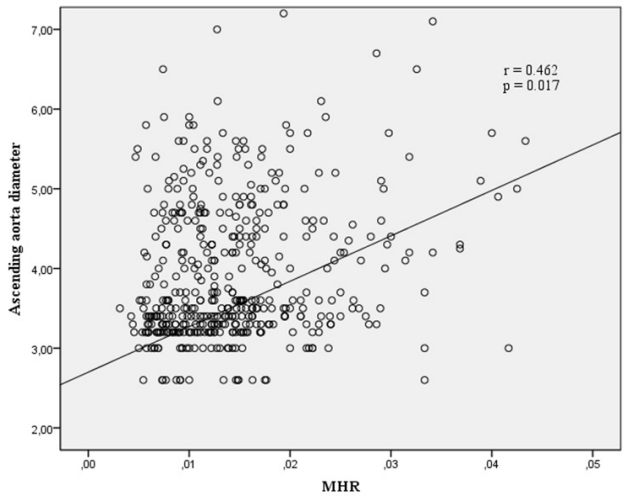
In the multiple logistic regression model the dependent variable was set as ascending aortic diameter and the explanatory parameters were determined from the analysis, including higher high-sensitivity C-reactive protein and MHR levels (for both p <0.001) (see Table 4).

Furthermore, MHR was significantly correlated positively with the diameter of the ascending aorta (p=0.017, r=0.462) (Figure 1).

Table 4. Multivariate linear regression analysis showing the predictors for the Ascending aortic dilatation

Variables	Univariable Beta (95% CI)	P value	Multivariable Beta (95% CI)	P value
Hypertension	1.582 (1.101-2.274)	**0.013**	1.477 (0.998-2.187)	0.057
Uric Acid	1.041 (0.997-1.087)	0.070		
Monocyte count	7.092 (3.196-15.738)	**0.030**	4.483 (0.906-8.159)	0.066
Hs-CRP,	1.040 (1.024-1.060)	**<0.001**	1.032 (1.013-1.052)	**0.001**
MHR	1.025 (1.011-1.039)	**<0.001**	1.013 (1.005-1.023)	**0.001**

Hs-CRP, high-sensitivity C-reactive protein; MHR, Monocyte – high-density lipoprotein ratio



MHR, monocyte count-to-high-density lipoprotein cholesterol ratio

Figure 1. The correlation between monocyte count-to-high-density lipoprotein cholesterol ratio and ascending aorta diameter

DISCUSSION

This study assumes that increased MHR is independently associated with the maximum diameter of the ascending aorta in asymptomatic AAA patients.

Unlike the descending and abdominal aorta, the ascending and thoracic aorta may or may not have aneurysm and even its etiology was mostly uncertain as an idiopathic disease (19). It was reported that one of the precursors for any cardiovascular mortality is the ascending aorta width, as well as incident congestive heart failure, stroke and so on (20).

However, the pathogenesis of aneurysmal disease may be associated with the impaired wall of the ascending aorta due to deformation of structural proteins including elastin and collagen (21). Replacement by an amorphous material or cystic medial degeneration leads to a dysfunction in the medial aortic layer, other than fragmentation of elastic fibers, and smooth muscle dropout, which in turn contributes to higher stiffness and weakness of the aortic wall and the ascending aorta is eventually dilated (21).

Moreover, aortopathy could possibly be related to inflammation (22, 23) and one of the major biomarkers for inflammation is the neutrophil lymphocyte ratio in association with a higher ascending aorta diameter (24). A type of leukocytes is monocytes with a great part in this process. There are overexpressed proinflammatory cytokines or adhesion molecules, such as monocyte chemotactic protein 1 ligand, vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, due to the interaction of activated monocytes with damaged or activated endothelium (25). The foamy cells appear as threatening as the oxidized LDL cholesterol is ingested by macrophages transformed from monocytes (26, 27). Then, outflow of cholesterol increases by means of HDL molecules eliminating the influence of their influx. In recent times, there has been evidence for function of HDL in limiting monocyte activation, adhesiveness, and inflammation (28) and debilitating the multiplication of progenitor cells in favour of monocytes (29). In addition

to their anti-inflammatory and antioxidative effects, vasorelaxation is enhanced by HDL molecules as endothelial nitric oxide synthase expression increases (30). Thus, HDL-C acts as a reversal factor during those processes while monocytes exert an influence of proinflammation and prooxidation (21)

One of the important underlying mechanisms in pathophysiology of ascending aorta dilation is oxidative stress (31). Matrix metalloproteinases play a major role in the cystic medial degeneration and reshaping of the aortic wall (32). In vitro studies have shown that the rate of matrix metalloproteinases increases during conditions such as increased oxidative stress (33, 34). Reactive oxygen species scavengers, which are known as antioxidants, have been shown to decrease MMP-9 expression in macrophage foam cells in aortic plaques (35). Therefore, in addition to increased oxidative stress, decreased antioxidant activity may play a role in the development of aneurysms. Moreover, the local environment, which is generated by the inflammatory cells and smooth muscle cells within the aortic wall structure, various growth factors released from these cells, and lipid intermediates, has been shown to lead to the production of reactive oxygen species (ROS), especially through the NADPH pathway (31, 36). HDL has been demonstrated to possess significant antioxidant activity that is primarily mediated via the inhibition of the oxidation of LDL with a subsequent reduction of the cellular uptake by the monocyte macrophage system (37). The mechanism by which HDL performs antioxidant activity is complex and multifactorial. Transition metals have played a role in oxidative stress and HDL has been demonstrated to exhibit chelation properties due to be presence of proteins such as ceruloplasmin on the surface of the lipoprotein, although the clinical relevance is controversial (38). Lipid peroxidation products are derived from oxidized LDL and have been demonstrated to be cytotoxic and predispose to atherosclerosis. HDL has been demonstrated to accept hydroperoxides from oxidized membranes in vitro studies, which would potentially provide a pathway for excretion or detoxification (39). For this reasons, the balance between monocyte amount and HDL may explain the effect of oxidative stress in ascending aorta dilation.

Our study has some limitations. This study is a cross-sectional retrospective study with a relatively small sample size. We do not have followup MACE data. So, our results should be verified by future multi-center prospective longitudinal studies with larger sample sizes.

CONCLUSION

MHR is valuable in practice as it is not only simple to use and easy to find but also inexpensive to afford, and clinicians may decide on AAA for their patients under the life-threatening condition of aneurysm rupture or dissection. In this study, it is concluded that this ratio should not be neglected for its contribution in grading the pathogenic risk of AAA.

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