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The LDL/HDL ratio and atherosclerosis in ankylosing spondylitis

Introduction

Ankylosing spondylitis (AS) is a prototype of spondyloarthropathies characterized by chronic inflammatory arthritis with spinal and sacroiliac joint involvement. It may cause structural and functional damage to the skeletal system. In addition, several systems may be affected, such as the eyes, skin, gastrointestinal system, heart and vascular structures [1]. There may be anatomical and functional changes when both cardiac and vascular involvement are present. Cardiac and vascular involvement include cardiomyopathy (systolic and/or diastolic dysfunction), valvular diseases (aortic valve insufficiency, regurgitation) and conduction disorders. Furthermore, there may be an increased risk of atherosclerosis and coronary artery disease [2, 3].

Atherosclerosis is one of the most important causes of mortality and morbidity in cardiovascular system (CVS) diseases. Increased carotid intima–media thickness (CIMT) is a convenient, noninvasive marker that can be used to monitor atherosclerosis in general, as well as the progression of cardiovascular diseases [4]. Dyslipidaemia is the most important risk factor for atherosclerosis. Low-density lipoprotein (LDL) easily infiltrates the endothelium and renders the tissue sensitive to oxidative changes, while high-density lipoprotein (HDL) has anti-atherogenic properties and provides a protective effect against cardiovascular disease [5, 6].

Systemic inflammation is thought to be involved in lipid profile changes in patients with AS [7]. The presence of systemic inflammation causes the release of free oxygen radicals via immune-mediated mechanisms, which have been suggested to contribute to the pathogenesis of inflammatory disorders. Systemic inflammation, endothelial inflammation and increased oxidative stress are important for the development and progression of atherosclerosis [8]. Ischemic modified albumin (IMA) is formed as a result of changes in the metal ion-binding properties of the N-terminal domain of human serum albumin. IMA has only recently been introduced but has rapidly become a marker of both ischemia and oxidative stress [9].

Our study is the first to investigate the relationship between CIMT and the LDL/HDL ratio and also to assess the IMA levels. The aim of the study is to investigate CIMT, the LDL/HDL ratio and the oxidative stress markers IMA and total oxidant status (TOS), to determine their relationships among patients with AS and also to evaluate their use in atherosclerosis assessment.

Materials and methods

Our study was conducted from June 2013 to June 2014 at the Rheumatology Clinic of the University Faculty of Medicine. Sixty AS patients diagnosed using the Modified New York Criteria and 54 age- and gender-matched controls were included [10]. The Ethics Committee for Clinical Research of our University Faculty of Medicine approved the present study. Basic laboratory values and demographics, as well as the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI) were used to evaluate disease activity and were recorded for both the patients and the control group. Participants with any immune deficiency, hypertension, diabetes, acute and/or chronic infection, coronary artery disease, chronic obstructive pulmonary disease, a history of malignancy or suspected malignancy and a history of smoking were excluded from the study.

Biochemical analyses

Coagulated blood samples were collected from the patients and the controls following a 12-h fast. After suitable centrifugation, the samples were stored at −80 °C until testing. Clinical data and blood samples were collected over a time period of 6 months. The serum IMA concentrations were analysed by measuring the complex composed of dithiothreitol (DTT) and cobalt chloride ($CoCl_{26}H_2O$) unbound from albumin by the colorimetric method as described by Bar-Or et al. [11]. Colour development with DTT was measured spectrophotometrically at 470 nm and compared with

Tab. 1 Demonstrative and laboratory data of the patient and the control groups

	AS ($n = 60$)	Controls ($n = 54$)	*P*-value
Age (years)	41.68 ± 10.98	41.80 ± 9.56	0.953
Gender, m/f (%)	45 (75)/15 (25)	32 (59.3)/22 (40.7)	0.174
BMI (kg/m^2)	27.09 ± 4.68	28.24 ± 3.77	0.148
Hb (g/dL)	14.38 ± 1.80	14.33 ± 1.39	0.852
WBC (×10^9/L)	8.12 ± 2.53	6.85 ± 1.35	0.001
ESR (mm/h)	13.31 ± 13.51	6.55 ± 4.87	0.001
CRP (mg/dL)	11.53 ± 22.23	3.33 ± 2.41	0.006
Creatinine (mg/dL)	0.75 ± 0.11	0.82 ± 0.48	0.291
ALT (IU/L)	22.41 ± 11.26	23.61 ± 7.84	0.503
TG (mg/dL)	143.85 ± 66.68	133.81 ± 87.81	0.517
TC (mg/dL)	189.91 ± 37.83	183.25 ± 35.77	0.357
HDL (mg/dL)	43.21 ± 10.04	46.79 ± 12.49	0.114
LDL (mg/dL)	117.92 ± 34.39	109.69 ± 33.58	0.219
LDL/HDL ratio	2.85 ± 1.00	2.47 ± 0.90	0.047
TOS (μmol H_2O_2 equivalent/L)	212.57 ± 149.44	116.70 ± 122.98	0.005
IMA ABSU	0.44 ± 0.17	0.32 ± 0.13	< 0.0001
CIMT (mm)	0.99 ± 0.27	0.76 ± 0.25	< 0.0001

AS ankylosing spondylitis, *BMI* body mass index, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high--density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Hb* haemoglobin, WBC white blood cells, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ALT* alanine aminotransferase, *LDL/HDL ratio* low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, *TOS* total oxidative status, *IMA* ischemic modified albumin, *CIMT* carotid intima–media thickness, *AS* ankylosing spondylitis, *m* male, *f* female, *BMI* body mass index, *Hb* hemoglobin, *WBC* white blood cells, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ALT* alanine aminotransferase, *TG* triglyceride, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LDL/HDL* ratio low-density lipoprotein/high-density lipoprotein ratio, *TOS* total oxidative status, *IMA* ischemic modified albumin, *ABSU* absorbance units, *CIMT* carotid intima–media thickness
[a]Mean ± SD

Tab. 2 Age, family history, BASFI and BASDAI scores and drug use rates of the patients with AS

	AS ($n = 60$)
Age at diagnosis[a], (years)	33.51 ± 9.16
Family history, *n* (%)	11 (18.3)
BASFI[a]	2.72 ± 2.16
BASDAI[a]	4.01 ± 2.14
SLZ, *n* (%)	24 (40)
ETA, *n* (%)	8 (13.3)
ADA, *n* (%)	8 (13.3)
IFX, *n* (%)	7 (11.7)

AS ankylosing spondylitis, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *SLZ* sulfasalazine, *ADA* adalimumab, *IFX* infliximab, *ETA* etanercept
[a]Mean ± SD

a serum cobalt blank without DTT. The results were reported in absorbance units (ABSU). TOS levels were measured using commercially available kits (Rel Assay, Gaziantep,Turkey). Serum TOS levels were expressed as μmol H_2O_2 equivalent/l [12]. Total cholesterol (TC), triglycerides (TG) and HDL were measured using a Synchron LX20 system (Beckman Coulter, Brea, CA, USA) and Beckman reagents. HDL levels were assessed using a direct enzymatic method instead of precipitation. LDL levels were calculated using the Friedewald formula when TG levels were lower than 400 mg/dl. If the TG levels were higher than 400 mg/dl, the LDL levels were directly measured.

Carotid intima–media measurements

In all cases, imaging was conducted using a high-resolution ultrasound machine (Logiq S6; General Electric, Milwaukee, WI, USA) with a 12-MHz mechanical sector transducer. The intima media thickness of both the right and left arteria carotis communis (CCA) was measured at three points on the far walls in each CCA 2 cm proximal to the CCA bifurcation. The three locations were then averaged to obtain the mean IMT for each side. The average of the two-sided measurements was considered as the patient's overall mean CIMT.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 14.0 (SPSS Inc, Chicago, IL, USA), was used for our statistical analyses. Continuous variables were presented as mean ± standard deviation, while categorical variables were indicated as a number (n) that was expressed as a percent (%). Variables meeting the parametric assumptions were assessed using the *t*-test and one-way analysis of variance (ANOVA) in independent groups and Tukey's HSD test in the intergroup posthoc evaluation, while categorical variables were assessed by chi-square test. Pearson's correlation analysis was carried out to test the correlation of the data. Any *p*-values that were less than 0.05 were considered statistically significant.

Results

The general clinical characteristics and demographics of patients with AS are summarized in **Tab. 1**. There was no significant difference between AS patients and the control group regarding their age, gender and body mass index (BMI; **Tab. 1**). The clinical characteristics and the medical treatment of AS patients are displayed in **Tab. 2**.

IMA was higher in AS patients compared to the control group (0.44 ± 0.17 ABSU and 0.32 ± 0.13 ABSU, respectively; $p < 0.0001$). A higher TOS was seen in AS patients than it was in the control group (212.57 ± 149.44 μmol H_2O_2 equivalent/l and 116.70 ± 122.98 μmol

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The LDL/HDL ratio and atherosclerosis in ankylosing spondylitis

Abstract

Objectives. In ankylosing spondylitis (AS) patients, cardiac and vascular involvement may manifest as atherosclerosis and coronary artery disease. Systemic inflammation, oxidative stress, increased low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol constitute a significant risk for atherosclerosis. This study investigated the relationship between carotid intima–media thickness (CIMT), LDL/HDL ratio, total oxidant status (TOS; an indicator of oxidative stress) and ischemic modified albumin (IMA; an ischemic marker in AS patients).

Patients and methods. Sixty AS patients were diagnosed using the Modified New York Criteria; 54 age- and gender-matched participants were included as controls. CIMT, LDL/HDL ratio, TOS and IMA were measured using the most appropriate methods.

Results. IMA was higher in AS patients compared to controls ($p < 0.0001$). TOS was also increased in AS patients ($p = 0.005$); as was CIMT ($p < 0.0001$). The LDL/HDL ratio was also greater in AS patients compared to controls ($p = 0.047$). A positive correlation was found between CIMT and LDL/HDL ratio among AS patients.

Conclusion. Elevated CIMT, IMA and TOS levels suggest an increased risk of atherosclerotic heart disease in AS patients. The LDL/HDL ratio was higher in AS patients compared to controls, and there was a correlation between LDL/HDL ratio and CIMT, albeit statistically weak. Therefore, the LDL/HDL ratio is not a reliable marker to predict atherosclerotic heart disease in AS patients.

Keywords

Dyslipidemias · Atherosclerosis · Ankylosing spondylitis · Ischemia-modified albumin · Oxidative Stress

Das Verhältnis von LDL zu HDL und Atherosklerose bei ankylosierender Spondylitis

Zusammenfassung

Ziel. Bei Patienten mit Spondylitis ankylosans (AS) kann sich eine kardiale und vaskuläre Beteiligung als Atherosklerose und koronare Herzkrankheit (KHK) manifestieren. Systemische Entzündung, oxidativer Stress, erhöhtes Low-Density-Lipoprotein(LDL)-Cholesterin und vermindertes High-Density-Lipoprotein(HDL)-Cholesterin stellen ein signifikantes Risiko für Atherosklerose dar. In der vorliegenden Studie wird die Beziehung zwischen Karotis-Intima-Media-Dicke (CIMT), LDL-HDL-Quotient, totalem oxidativem Status (TOS, Indikator für oxidativen Stress) und ischämiemodifiziertem Albumin (IMA, Ischämiemarker bei AS-Patienten) untersucht.

Patienten und Methoden. Anhand der Modified New York Criteria erfolgte die Diagnosestellung bei 60 AS-Patienten; Kontrollen waren 54 in Alter und Geschlecht entsprechende Personen. CIMT, LDL/HDL-Quotient, TOS und IMA wurden mit den am besten geeigneten Methoden ermittelt.

Ergebnisse. IMA war bei AS-Patienten höher als bei den Kontrollen ($p < 0{,}0001$). Auch TOS war bei AS-Patienten erhöht ($p = 0{,}005$) sowie CIMT ($p < 0{,}0001$). Der LDL/HDL-Quotient war bei AS-Patienten ebenfalls größer als bei den Kontrollen ($p = 0{,}047$). Es fand sich eine positive Korrelation zwischen CIMT und LDL/HDL-Quotient bei AS-Patienten.

Schlussfolgerung. Erhöhte Werte für CIMT, IMA und TOS sprechen für ein erhöhtes Risiko einer KHK bei AS-Patienten. Der LDL/HDL-Quotient war bei AS-Patienten höher als bei den Kontrollen, und es bestand eine – allerdings schwache – Korrelation zwischen dem LDL/HDL-Quotienten und CIMT. Folglich ist der LDL/HDL-Quotient kein reliabler Marker zur Vorhersage einer KHK bei AS-Patienten.

Schlüsselwörter

Dysliplidämie · Atherosklerose · Spondylitis ankylosans · Ischämiemodifiziertes Albumin · Oxidativer Stress

H_2O_2 equivalent/l, respectively; $p = 0.005$). CIMT was higher in AS patients compared to the control group (0.99 ± 0.27 mm and 0.76 ± 0.25 mm, respectively; $p < 0.0001$; **Fig. 1**). A higher LDL/HDL ratio was seen in AS patients than in the control group (2.85 ± 1.00 and 2.47 ± 0.90, respectively; $p = 0.047$; **Fig. 2**). A positive correlation was observed between CIMT and age, BMI and the LDL/HDL ratio among the patients (**Tab. 3**, **Fig. 3**).

There was no correlation between IMA, TOS and BMI, CIMT, or the LDL/HDL ratio, erythrocyte sedimentation rate, C-reactive protein or the leukocyte count. No difference was seen in CIMT, IMA, TOS or the LDL/HDL ratio across the treatment options (between when the patients received anti-tumour necrosis factor alpha treatment and sulfasalazine).

Discussion

AS is a systemic inflammatory disorder that may involve multiple systems and organs, mainly in the cardiovascular system. Systemic inflammation is involved in the development of atherosclerosis due to its direct effects on the vascular structures and also its influence on the lipid profile [7, 13]. Increased LDL and decreased HDL levels pose an important risk for atherosclerosis [14]. CIMT is a reliable and inexpensive marker that has become a predictor of atherosclerosis and can be used to predict cardiovascular events [4]. Our results showed a higher IMA, TOS, CIMT and LDL/HDL ratio in AS patients compared to the healthy control group. We also found a positive correlation between the CIMT and LDL/HDL ratios. However, the correlation between the LDL/HDL ratio and CIMT was statistically weak.

Although the underlying reasons for increased atherosclerosis in chronic inflammatory disorders are not fully understood, systemic inflammation exerts important effects on the process. CIMT is used to assess early-stage atherosclerosis and is known to have a strong association with coronary artery disease [15]. Gupta

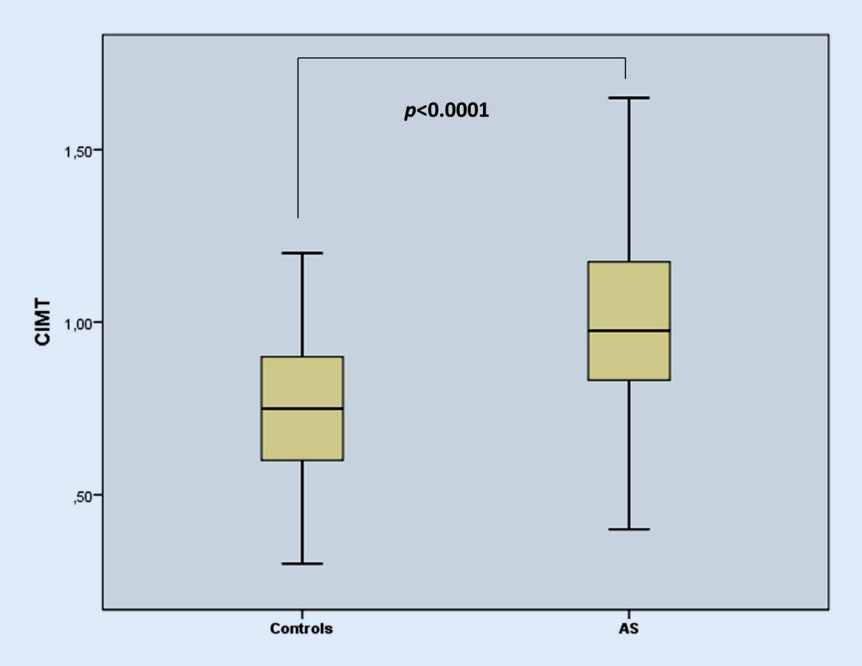

Fig. 1 ▲ Carotid intima–media thickness (*CIMT*) among ankylosing spondylitis (*AS*) and control groups

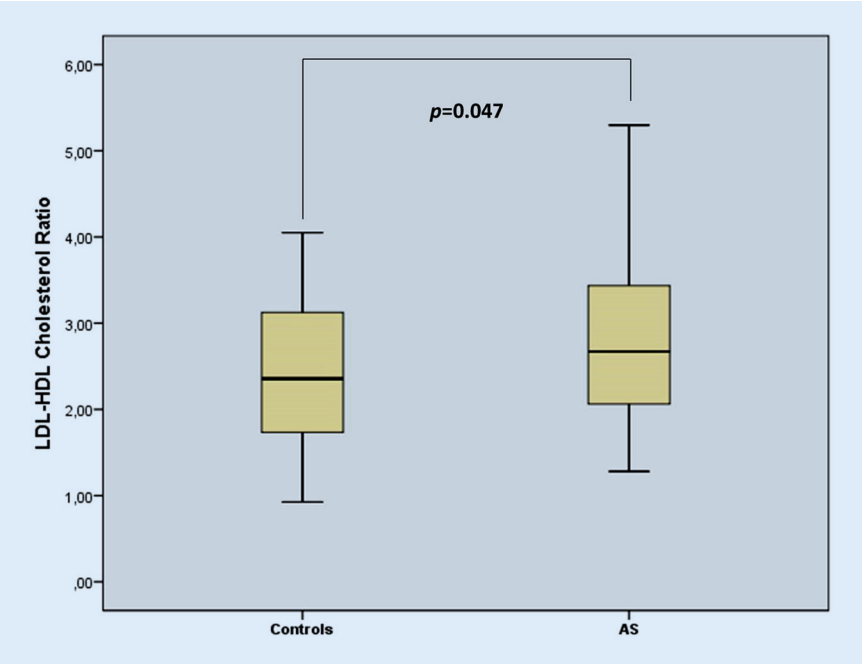

Fig. 2 ▲ Low-density lipoprotein (*LDL*)/high-density lipoprotein (*HDL*) cholesterol ratio among ankylosing spondylitis (*AS*) and control groups

et al. [16] showed an increased prevalence of CIMT in AS patients compared to their control group. Additionally, Gonzalez-Juanatey et al. [17] demonstrated higher CIMT values in AS patients than in the control group. In another study, Mathieu et al. [18] reported increased CIMT in patients with AS compared to the control group.

AS patients are known to be at an increased risk for atherosclerosis, which is influenced by changes in their lipid profile. During systemic inflammation, structural changes in endothelial cells and lipid molecules accelerate the development of atherosclerosis. LDL transfers cholesterol from the liver to the peripheral tissues, and immune system elements are involved in its placement on the vascular wall. In contrast, HDL carries cholesterol to the liver and prevents its adhesion to endothelial cells [19]. Any rise in LDL levels and decreases in HDL levels are important factors in the diagnosis of atherosclerosis. Divecha et al. [20] reported lower HDL levels in AS patients compared to the control group in their study. Mathieu et al. [21] found lower HDL levels in patients with AS than in their control group. Considering the effects of LDL and HDL on atherogenesis, the predictive value of the LDL/HDL ratio regarding the atherosclerotic changes on the vascular wall is even higher. Sathiya et al. [22] observed a greater LDL/HDL ratio in patients with coronary artery disease compared to the control group in their study. Yang et al. [5] demonstrated a relationship between the LDL/HDL ratio and CIMT and carotid plaques. Recently, the ratio of LDL and HDL has become a representative marker of regression and progression in coronary atherosclerosis [14].

The systemic inflammation commonly seen in patients with AS causes increased oxidative stress and impaired endothelial functions. Normally, the antioxidant system and its mechanisms balance the effects of oxidative radicals. Any inconsistency between these systems leads to oxidative stress. TOS is a recently introduced and commonly used marker that can assess these oxidative stress products [23, 24]. In their study, Karakoc et al. [25] found higher TOS levels in AS patients compared to the control group. Endothelial dysfunction is the first sign in the development process of atherosclerosis. The endothelial dysfunction resulting from oxidative stress plays a major role in cardiovascular disease pathogenesis [26, 27].

Changes in IMA levels are thought to be associated with acute and/or chronic hypoxia and oxidative stress. IMA is formed as a result of decreased metal ion-binding capacity due to the effects of free oxygen radicals on albumin [28]. IMA is a considerably sensitive marker, and it can

Tab. 3 Correlation between serum CIMT and age, body mass index and LDL/HDL ratio

CIMT	Age (years)	BMI	LDL/HDL ratio
R	0.737	0.315	0.395
P	< 0.0001	0.014	0.002

CIMT carotid intima–media thickness, *BMI* body mass index, *LDL/HDL ratio* low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio

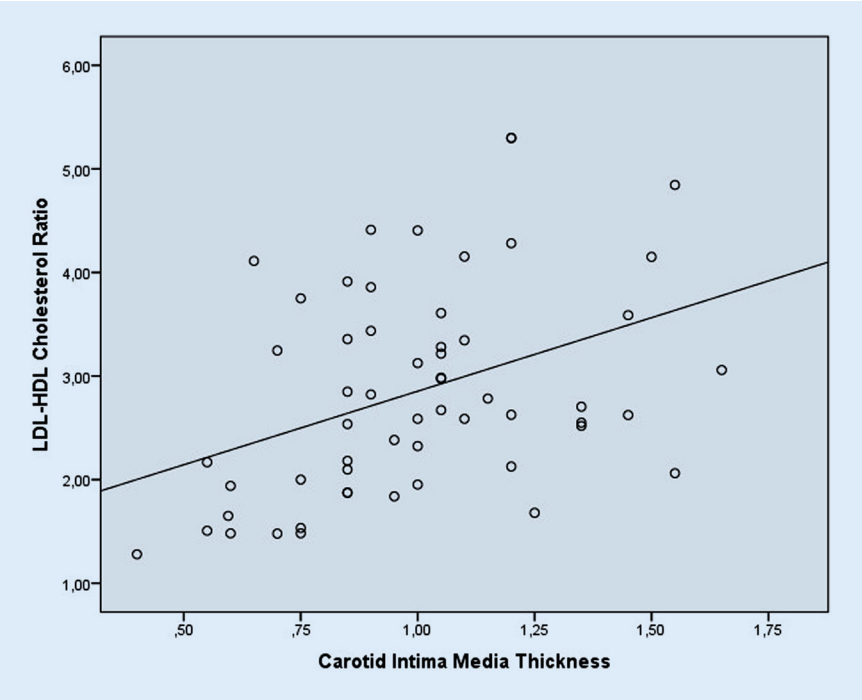

Fig. 3 ▲ The relationship between cholesterol ratio and carotid intima-media thickness (*CIMT*) among ankylosing spondylitis (*AS*) patients

be used as an early indicator of cardiac ischemia [9, 28]. Although there have been no studies on IMA in AS patients, investigations into autoimmune disorders have reported an increased frequency of atherosclerotic heart disease and systemic inflammation, such as rheumatoid arthritis (RA) and systemic sclerosis (SSc). Leitemperguer et al. [29] demonstrated higher IMA values in RA patients compared to the control group, while Montagnana et al. [30] reported increased IMA values in patients with SSc compared to the controls.

The cause of 20–40 % of the mortality seen in AS patients is cardiovascular disease, and cardiovascular mortality is increased by approximately two- to three-fold in these patients compared to the general population [17, 18]. Atherosclerotic coronary heart diseases account for an important portion of cardiovascular mortality. There are several factors in AS that may lead to atherosclerotic heart disease, including metabolic syndrome, medications, changes in lipid profiles (low HDL levels) and inflammatory processes [31]. The presence of a chronic inflammatory process, increased oxidative stress and the interaction between the two contribute to all stages, including the formation and progression of atherosclerotic plaque and thrombus formation [32, 33].

In our study, the higher CIMT, IMA and TOS values in AS patients compared with the control group may suggest an increased risk of atherosclerotic heart disease in patients with AS. The LDL/HDL ratio was higher in AS patients than it was in the control group, and there was a correlation between the LDL/HDL ratio and CIMT. However, this correlation was statistically weak. In reality, a normal or increased LDL level is not a reliable marker for the risk of atherosclerosis, since LDL is composed of various subtypes; small, dense LDL and oxide subfractions, which are two of these subtypes, are more atherogenic [34, 35]. Thus, LDL subgroup analysis is a more reliable marker used to diagnose atherosclerotic heart disease. On the other hand, development of atherosclerotic heart disease is not all the time prevented by the increment in the HDL [36]. HDL can be easily dysfunctional and even it can gain a pro-inflammatory feature by undergoing oxidation and modification by various oxidant materials [37]. HDL may not show an antioxidant effect as a result of the polymorphism of the paraoxonase enzyme, which is responsible for the antioxidant effect of HDL [38]. Increased HDL leads to a higher amount of lipid transport in the liver; thus, it can show adverse effects [36, 39]. Therefore, even though the LDL/HDL ratio of a patient with normal LDL and high HDL levels is low, there can be high risk of atherosclerotic heart disease. Similarly, the LDL/HDL ratio will be disproportionately high in a patient with high LDL and low atherogenic LDL subtypes. Shah et al. reported that the LDL/HDL ratio was not associated with CIMT, and it did not provide any additional information about atherosclerotic heart disease [40]. In our opinion, the LDL/HDL ratio is not a reliable or good marker to determine the risk of atherosclerotic heart disease. However, it may be beneficial to assess the LDH/HDL ratio together with other markers to determine the risks of atherosclerotic heart disease.

Our study has a few limitations. These include the small number of patients, the prospective cross-sectional nature of the study, and the fact that the differences between the patients with mild and severe disease activity as per the BASDAI scoring system were not taken into account.

In conclusion, the high levels of CIMT, IMA and TOS that were observed in AS patients in the present study suggest an increased risk of atherosclerotic heart disease. The LDL/HDL ratio was higher in AS patients than it was the control group, and the correlation between the

LDL/HDL ratio and CIMT was statistically weak. The LDL/HDL ratio is therefore not a promising or reliable marker to detect the risk for atherosclerotic heart disease. However, it can be useful to evaluate the LDH/HDL ratio along with other markers to determine the risk for atherosclerotic heart disease.

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Compliance with ethical guidelines

Conflict of interest. A. Kucuk, A. Ugur Uslu, A. Icli, E. Cure, S. Arslan, K. Turkmen, A. Toker and M. Kayrak state that there are no conflicts of interest.

The Ethics Committee for Clinical Research of Necmettin Erbakan University Faculty of Medicine approved the present study.

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