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Hyperlipoproteinaemia(a) in patients with spondyloarthritis: results of the Cardiovascular in Rheumatology (CARMA) project

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Abstract

Objective

Cardiovascular (CV) disease is one of the main causes of morbi-mortality in spondyloarthritis (SpA), partially explained by traditional CV risk factors. Information on lipoprotein(a) [Lp(a)], a non-conventional risk factor, in SpA is scarce. In this study we assessed the prevalence of hyperlipoproteinaemia(a) in SpA patients and analysed the possible related factors.

Methods

A baseline analysis was made of ankylosing spondylitis (AS) and psoriatic arthritis (PsA) patients and controls included in the CARMA project (CARdiovascular in RheuMAtology), a 10-year prospective study evaluating the risk of CV events in chronic inflammatory rheumatic diseases. A multivariate logistic regression model was performed using hyperlipoproteinaemia(a) (Lp(a) >50 mg/dl) as a dependent variable and adjusting for confounding factors.

Results

19.2% (95% CI: 16.80-22.05) of the SpA patients [20.7% (95% CI: 16.91-24.82) of those with AS and 17.7% (95% CI: 14.15-21.75) of those with PsA] and 16.7% (95% CI: 13.23-20.86) of the controls had hyperlipoproteinaemia(a) (p=0.326). Adjusting for age and sex, SpA patients were more likely to have hyperlipoproteinaemia(a) than controls (OR: 1.43, 95%CI: 1.00-2.04; p=0.05), especially those with AS (OR: 1.81, 95%CI: 1.18-2.77; p=0.007). In the adjusted model, apolipoprotein B in all patients, non-steroidal anti-inflammatory drugs in AS, and female sex in PsA, were associated with hyperlipoproteinaemia(a). No disease-specific factors associated with hyperlipoproteinaemia(a) were identified.

Conclusion

SpA patients show a moderately increased risk of hyperlipoproteinaemia(a) compared to controls, especially those with AS. Lp(a) determination may be of interest to improve the CV risk assessment in SpA patients.

Key words

spondyloarthritis, ankylosing spondylitis, psoriatic arthritis, cardiovascular disease, lipoprotein(a), lipids

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Introduction

The Spondyloarthritis (SpA) are a group of chronic inflammatory rheumatic diseases (CIRD) affecting the axial and/or peripheral skeleton, with different forms of clinical manifestations (1). They mainly encompass patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Regardless of the potential cardiovascular (CV) complications observed in patients with AS, such as aortic regurgitation, conduction disorders or cardiomyopathy (2, 3), recent evidence indicates that cardiovascular disease (CVD), mainly acute coronary syndrome and stroke, is one of the main causes of the increased mortality and morbidity observed in patients with SpA (4-6). In this regard, CVD impairs the quality of life and reduces the life expectancy of patients with SpA (7).

As observed in rheumatoid arthritis (RA), SpA patients also present accelerated atherosclerosis (8-11), partially explained by a higher prevalence of traditional CV risk factors (CVRF) (12). Although several studies have described alterations in the lipid profile and insulin sensitivity in SpA patients, chronic inflammation seems to be a key, being also implicated in the process of endothelial dysfunction and atherosclerosis observed in these patients (8, 13).

With regard to the lipid metabolism, it is known that disease activity is associated with a decrease in the lipid levels, mainly due to a reduction of high-density lipoprotein cholesterol (HDL-c) levels, resulting in a proatherogenic lipid profile (14, 15). It is also known that lipid levels increase following the initiation of the anti-rheumatic therapy (16). Nevertheless, unlike in RA (17), this aspect has not been extensively documented in patients with SpA. With respect to this, the qualitative alterations in the lipid metabolism (18), probably related to chronic systemic inflammation (19, 20), may be implicated in the increased CV risk reported in SpA. In this context, lipoprotein(a) [Lp(a)], a non-conventional lipid risk factor may also play a pathogenic role, as it appears to act as an acute-phase reactant (21). This lipoprotein, which has atherogenic and thrombogenic properties, is considered as an independent CVRF (22). Indeed, Lp(a) is a lipoprotein structurally similar to the low-density lipoprotein cholesterol (LDL-c) molecule, whose main protein is the apolipoprotein(a) [apo(a)], besides the apolipoprotein B 100. Apo(a) gives Lp a) more atherogenic properties, based mostly on its size, which is under tight genetic regulation (23), and with an inverse relationship between the isoform size and the plasma concentration of Lp(a). Given the large impact of genetic factors on Lp(a) levels, their plasma concentrations remain fairly stable throughout life. However, besides the strong genetic component, other factors influence the plasma Lp(a) levels. In this regard, they increase with kidney failure, nephrotic syndrome and are higher in black individuals. In contrast, thyroid hormone, estrogen and anabolic steroids decrease plasma Lp(a) levels. Inflammation is another mechanism that modulates plasma Lp(a) levels, and as observed in patients with RA (24), they are higher during acute and chronic inflammation (23). Nonetheless, unlike the well-described relationship between inflammation and conventional lipid profile (25), little is known about how inflammation affects lipoprotein(a) regulation.

Strong evidence supports the association between high Lp(a) levels and increased CVD. According to the consensus manuscript of the European Atherosclerosis Society (26), Lp(a) less than 50 mg/dL is the desirable and recommended cut off level for clinical use and decision-making. Nevertheless, to the best of our knowledge, Lp(a) has been poorly studied in SpA, a well-characterised chronic inflammatory disease.

Taking all of these considerations into account, the purpose of the present study was to assess the prevalence of hyperlipoproteinaemia(a) in Spanish individuals with AS and PsA who were followed-up in Rheumatology Units and identify potential factors associated with hyperlipoproteinaemia(a) in this population. For this purpose, we took advantage of the data from the patients enrolled in the CARdiovascular in rheuMAtology (CARMA) project, a 10-year prospective cohort study designed to determine the CV mortality risk in patients with CIRD, including those with SpA.

Material and methods

Study design

This is a cross-sectional analysis from the baseline visit of a 10-year prospective follow-up study (CARMA Project). A cohort of patients with AS and PsA were included in the study. The prevalence of hyperliproteinaemia(a) was compared with that of a control group.

Patient recruitment

Patients diagnosed with AS and PsA at sixty-seven Rheumatology Units, selected from the Spanish National Health System hospitals, participated in the study. The participant Rheumatology Units were randomly selected after a probabilistic cluster sampling from the database of the Spanish Society of Rheumatology (SER). Inclusion criteria for the recruitment period (between July 2010 and January 2012) were as follows: patients diagnosed with AS according to the modified New York criteria (27) and with PsA according to the Moll and Wright criteria (28), and aged 18 years or older.

Individuals included in the study as controls were eligible if they did not present any inflammatory arthritis or chronic inflammatory diseases. According to that, patients attending rheumatology outpatient clinics because of osteoarthritis, osteoporosis or any soft tissue rheumatism were eligible as controls. However, those with erosive osteoarthritis of hands or with gout were excluded. Recruitment of individuals included in the control group, as well as that of patients with inflammatory arthritis, was performed consecutively at each centre without considering the severity or duration of the disease. To confirm that there was not selection bias, information was also collected from the patients who did not agree to enter the study. They did not exhibit epidemiological differences when compared with those who agreed to participate in the study (data not shown). All participants included in the study signed the informed consent. The information regarding the sample size and the baseline characteristics of the project participants, patients and controls was described by Castañeda *et al*. (29). This study protocol was performed according to the principles of Helsinki Declaration and was approved by the Ethics Committee for Clinical Research of Galicia (Spain) (protocol no. 2009/077), and subsequently also in each participant hospital.

Variables and operative definitions

The cohort with AS and PsA was evaluated according to standardised definitions and the Spanish validated versions of the questionnaires currently used, following international protocols. A systematically and continuously online evaluation was done in all patients included in this study. Data monitoring was performed *in situ* in 15% of randomly selected patients, to verify the quality of the information (29).

Hyperlipoproteinaemia(a) was considered as the main variable, being defined as plasma concentration of Lp(a) equal to or greater than 50 mg/dL (30). All biochemistry determinations were made after an overnight fast and they were analysed according to the methodology and reproducibility level of each participant institution. In most cases lipoprotein(a) was quantified by immunoassay methods.

Other secondary variables analysed were: 1) variables related to the characteristics of each disease and disease duration; 2) educational level (primary, secondary and higher); 3) obesity [body mass index (BMI) ≥30 kg/m^2]; 4) physical activity (considering some physical activity such as walking, practicing some sport, gymnastics); 5) traditional CVRF (hypertension, dyslipidaemia, smoking, diabetes and family history of CV event); 6) personal history of CV event; 7) rheumatic therapy [non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and synthetic or biological disease-modifying anti-rheumatic drugs (DMARDs)]; 8) parameters of inflammation, disease activity and function: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score including 28-joint count and ESR (DAS28-ESR), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, Health Assessment Questionnaire (HAQ) with a range from 0 to 3 (where 0 represents no functional impairment and 3 total disability) and Bath Ankylosing Spondylitis Functional Index (BASFI); 9) lipid and lipoprotein profiles: total cholesterol (TC), triglycerides (TG), LDL-c, HDL-c, apolipoprotein AI (apo AI), apolipoprotein B (apo B) and Lp(a); and 10) potential confounding factors such as comorbidities and other therapies (statins and others). Atherogenic index (AI) was also calculated (TC/HDL-c).

Statistical analysis

Statistical analysis was performed for both AS and PsA patients separately. Continuous variables were described by mean and standard deviation (SD), or median and interquartile range (IQR) for non-symmetric variables, and categorical variables by frequencies and percentages. The contrast of equality for patients with or without hyperlipoproteinaemia(a) was obtained by *t*-test or K-Wallis tests for continuous variables, and Chi-squared for categorical variables. To reduce variability in the methods of measurement of Lp(a) across the participating hospitals, mixed multivariate regression models were constructed with robust variance estimators using the hospital as a cluster for variable estimation. The association of each independent variable with hyperlipoproteinaemia(a) was estimated by odds ratio (OR), calculated by logistic regression. Also, OR adjusted by age and gender were calculated for AS and PsA as well as for controls. Two different multivariate logistic models for AS and PsA were calculated. The selection of adjusted variables in the multivariate model was based on clinical judgment and those with a p-value <0.20 in the bivariate analysis. Multicollinearity among independent variables was also explored to build the model. Data management and statistical analysis were centralised at the Research Unit of the SER. All analyses were performed using Stata 13.1 package Copyright 1985-2013 StataCorp LP (4905 Lakeway Drive College Station, Texas 77845 USA).

Results

General clinical characteristics of the cohort

One thousand four hundred and fifty-

nine patients with SpA (738 AS patients and 721 PsA patients) and 677 controls of the CARMA study project were assessed. Information on Lp(a) levels was available in 426 (57.7%) patients from the AS group, 412 (57.1%) from the PsA group and 393 (58%) from the control group (p=0.941). The percentage of women in the group of AS patients was 27%, while among PsA patients and in controls it was significantly higher (44% and 62% respectively), p<0.001. AS were younger (mean age 48.3±SD: 11.9 years) than those with PsA (51.4±12.0 years) and controls (53.5±12.1 years) (p<0.001).

The median value of plasma concentrations of Lp(a) in the whole group of patients with SpA was 16.05 mg/dL (IQR: 6.7–37). The median Lp(a) levels in the subgroups of PsA and AS patients were similar [16.20 mg /dL (6.03–35.7) in PsA *versus* 16.00 mg/dL (7–38.9) in AS patients (p=0.491)]. Also, 19.2% (95% CI: 16.80–22.05) of the SpA patients [20.7% (95% CI: 16.91–24.82) of those with AS and 17.7% (95% CI: 14.15–21.75) of those with PsA] had hyperlipoproteinaemia(a), as they had Lp(a) levels ≥50 mg/dL. No statistically significant differences between the whole group of SpA patients and controls [16.70 mg/dL (95%CI: 13.23–20.86); p=0.326] were observed. However, after adjusting for age and sex (Fig. 1), patients with SpA were more likely to have hyperlipoproteinaemia(a) than controls (OR: 1.43, 95% CI: 1.00–2.04, p=0.05). It was mainly due to patients with AS (OR: 1.81, 95% CI: 1.18–2.77, p=0.007), since differences between PsA patients and controls in the adjusted model for age and sex did not achieve statistical significance (OR: 1.26, 95% CI: 0.86–1.85, p=0.24).

Most patients from this study were Caucasians (97% in AS and 98.5% in PsA). The main demographic, clinical and laboratory features of the CARMA SpA cohort patients are summarised in Tables I and II. Serum lipids, lipoprotein and apolipoprotein values are shown in Table III.

Differences between AS patients with and without hyperlipoproteinaemia(a)

A bivariate analysis disclosed that patients with AS and hyperlipoproteinaemia(a) had a significantly higher percentage of personal history of previous CV events than those without hyperlipoproteinaemia(a) (p=0.002). Also, AS patients with hyperlipo-proteinaemia(a) displayed marginally significant differences with a higher percentage of hypercholesterolaemia (p=0.07), higher values of ESR (p=0.05) and higher physician visual analogue scale (VAS) scores (p=0.08). No statistically significant differences were observed in the rest of the variables evaluated, which included disease assessment parameters and therapies (Tables I and II).

AS patients with hyperlipoproteinaemia(a) exhibited a statistically significant worse atherogenic lipid profile than those without hyperlipoproteinaemia(a) (p=0.01), with significantly higher plasma concentrations of LDL-c and apo B (p=0.01), and lower plasmatic concentrations of HDL-c (p=0.03) and apo AI (p=0.01) (Table III).

Table IV shows the results of the multivariate analysis in AS after adjusting for confounding factors. This analysis disclosed that a higher value of apo B as well as NSAIDs therapy were associated with the presence of hyperlipoproteinaemia(a) in these patients, and that raised values of apo AI were associated with a lower probability of presenting hyperlipoproteinaemia(a).

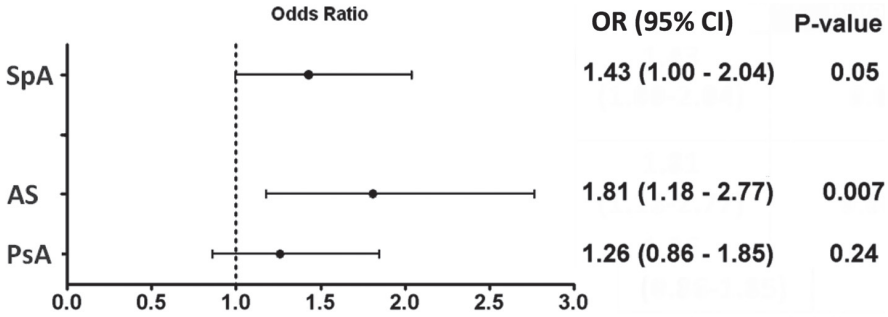

Fig. 1. Hyperlipoproteinaemia(a) in SpA *vs*. controls adjusted for age and sex.
SpA: spondyloarthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; OR: odds ratio.

Differences between PsA patients with and without hyperlipoproteinaemia(a)

The bivariate analysis in the subgroup of patients with PsA showed that hyperlipoproteinaemia(a) was more common in women (54.8% *vs*. 41.6%; p=0.01), older patients (54.8 *vs*. 50.8 years; p=0.01) (Table I) and in those with later onset of symptoms (44.9 *vs*. 38.6 years; p=0.01). As observed in patients with AS, those with PsA and hyperlipoproteinaemia(a) had more commonly history of CV events than those without hyperlipoproteinaemia(a) (p=0.00) and thyroid disease (p=0.05). Also, the subgroup of PsA patients with hyperlipoproteinaemia had higher DAS28-ESR score (3.3 *vs*. 2.9; p=0.01), lower disease duration (9.3 *vs*. 11.6 years; p=0.05), and higher exposure to methotrexate (71.2% *vs*. 58.4%; p=0.04) (Tables I and II). Moreover, PsA patients with hyperlipoproteinaemia(a) displayed marginally significant differences with higher scores in the VAS of the physician (p=0.06) and slightly higher plasma creatinine values (p=0.07) than those without hyper-lipoproteinaemia(a) (Table I). PsA patients with hyperlipoproteinaemia (a) showed a significantly worse atherogenic lipid profile than those without hyperlipoproteinaemia(a) with significantly higher plasma concentrations of LDL-c (p=0.03) and apo B (p=0.01), as shown in Table III.

Table V shows the results of the multivariate analysis in PsA after adjusting for confounding factors. It showed that sex (women), higher age at study entry and elevated values of apo B were associated with the presence of hyperlipoproteinaemia(a) in these patients. A shorter disease duration was also associated with higher risk of hyperlipoproteinaemia(a).

Discussion

The present study encompasses the largest series of SpA patients in whom the presence hyperlipoproteinaemia(a) was specifically assessed. Our results indicate that SpA patients exhibit

Table I. Characteristics of patients with ankylosing spondylitis and psoriatic arthritis stratified according to the presence or not of hyperliproteinaemia(a).

Variables	Ankylosing spondylitis				Psoriatic arthritis			
	Total	Hyperlp(a) Yes (n=88)	Hyperlp(a) No (n=338)	*p*-value	Total	Hyperlp(a) Yes (n=73)	Hyperlp(a) No (n=339)	*p*-value
Sociodemographic								
Sex (women), n (%)	115 (27.0)	20 (22.7)	95 (28.1)	0.31	181 (43.9)	40 (54.8)	141 (41.6)	0.01
Age of onset of symptoms, mean (SD)	29.9 (12.2)	31.3 (12.0)	29.6 (12.3)	0.26	39.7 (12.9)	44.9 (13.3)	38.6 (12.3)	0.01
Study entry age, mean (SD)	48.3 (11.9)	50.2 (10.8)	47.8 (12.1)	0.10	51.4 (12.0)	54.8 (10.9)	50.8 (12.1)	0.01
Level of studies, n (%)								
Less than primary	20 (4.7)	5 (5.7)	15 (4.5)	0.45	25 (6.2)	9 (12.7)	16 (4.8)	0.21
Primary	183 (43.4)	40 (46.0)	143 (42.7)		177 (43.6)	29 (40.9)	148 (44.2)	
Secondary	119 (28.2)	27 (31.0)	92 (27.5)		110 (27.1)	15 (21.1)	95 (28.4)	
Superior	100 (23.7)	15 (17.2)	85 (25.4)		94 (23.2)	18 (23.4)	76 (22.7)	
Cardiovascular risk factors								
Leisure activity, n (%)	286 (67.9)	58 (67.4)	228 (68.1)	0.91	253 (62.2)	41 (58.6)	212 (62.9)	0.50
Smoking status, n (%)								
Current smoker	156 (36.6)	35 (39.8)	121 (35.8)	0.51	94 (22.8)	15 (20.6)	79 (23.3)	0.80
Ex-smoker (> 1 year)	128 (30.1)	22 (25.0)	106 (31.4)		129 (31.3)	25 (34.3)	104 (30.7)	
Never smoker	142 (33.3)	31 (35.2)	111 (32.8)		189 (45.9)	33 (45.2)	156 (46.0)	
History of CV events, n (%)	31 (7.3)	13 (14.8)	18 (5.3)	0.002	28 (6.8)	11 (15.1)	17 (5.0)	0.00
Family history of IHD, n (%)	56 (13.2)	16 (18.2)	40 (11..9)	0.12	39 (9.6)	10 (13.7)	29 (8.7)	0.19
Hypertension, n (%)	110 (25.8)	24 (27.3)	86 (25.4)	0.73	134 (32.5)	27 (37.0)	107 (31.6)	0.37
Hypercholesterolaemia, n (%)	117 (27.5)	31 (35.2)	86 (25.4)	0.07	149 (36.2)	30 (41.1)	119 (35.1)	0.33
Diabetes mellitus, n (%)	34 (8.0)	10 (10)	24 (7.1)	0.19	39 (9.5)	9 (12.3)	30 (8.9)	0.36
Abdominal perimeter, mean (SD)	96.1 (12.87)	96.6 (13.07)	96.0 (12.8)	0.73	98.8 (13.3)	98.7 (13.4)	98.8 (13.3)	0.90
BMI, mean (SD)	28.3 (15.8)	27.1 (4.8)	28.6 (17.4)	0.48	28.6 (4.9)	28.2 (5.2)	28.7 (4.8)	0.45
Comorbidities								
Kidney disease, n (%)	6 (1.41)	2 (2.3)	4 (1.2)	0.44	5 (1.2)	2 (2.7)	3 (0.9)	0.19
Intestinal disease, n (%)	25 (5.87)	7 (8)	18 (5.3)	0.35	6 (1.5)	0 (0.0)	6 (1.8)	0.25
Thyroid disease, n (%)	8 (1.9)	1 (1.1)	7 (2.1)	0.57	21 (5.1)	7 (9.6)	14 (4.1)	0.05
Activity and severity of the disease								
BASDAI, mean (SD)	3.5 (2.2)	3.5 (2.2)	3.5 (2.2)	0.91	--	--	--	--
BASFI, mean (SD)	3.3 (2.4)	3.3 (2.5)	3.3 (2.6)	0.93	--	--	--	--
PASI, median [p25-p75]	--	--	--	--	0.6 [0.0-2.1]	0.9 [0.0-2.5]	0.6 [0.0-2.1]	0.74
HAQ, median [p25-p75]	--	--	--	--	0.4 [0.0-1.0]	0.5 [0.1-0.9]	0.3 [0.0-1.0]	0.19
DAS28, mean (SD)	--	--	--	--	3.0 (1.4)	3.3 (1.4)	2.9 (1.3)	0.01
ASDAS-CRP, mean (SD)	2.0 (1.0)	2.0 (0.9)	2.0 (1.0)	0.90	--	--	--	--
Peripheral arthritis, n (%)	92 (21.6)	18 (20.5)	74 (21.9)	0.77	--	--	--	--
HLA-B27 positive, n (%)	347 (81.5)	71 (80.7)	276 (81.7)	0.83	--	--	--	--
Enthesitis, n (%)	123 (29.1)	29 (33.0)	94 (28.1)	0.37	100 (25.1)	23 (32.4)	77 (23.6)	0.12
Dactylitis, n (%)	--	--	--	--	162 (39.3)	25 (34.2)	137 (40.4)	0.33
VAS of the physician, median [p25-p75]	2 [1-4]	3 [2-4]	2 [1-4]	0.08	2.0 [1.0-3.0]	3.0 [1.0-4.0]	2.0 [1.0-3.0]	0.06
Time evolution (years), mean (SD)	17.9 (12.2)	18.2 (11.8)	17.8 (12.3)	0.78	11.2 (8.9)	9.3 (7.9)	11.6 (9.1)	0.05
ESR (mm/1st hour), mean (SD)	10 [6.0-18.0]	13.0 [6.0-26.0]	10.0 [6.0-19.0]	0.05	11 [6-20]	15.5 [6-27.5]	11 [6-19]	0.10
CRP (mg/L), mean (SD)	3.95 [1.4-9.3]	5.4 [1.7-9.2]	3.4 [1.3-9.0]	0.27	2.9 [1.2-6.8]	2.4 [1.5-7.2]	2.9 [1.2-6.8]	0.38
Laboratory parameters								
Glycaemia (mg/dl), mean (SD)	97.1 (19.0)	99.1 (22.3)	96.6 (18.1)	0.27	100.28 (25.75)	98.77 (17.90)	100.60 (27.14)	0.58
Serum creatinine (mg/dl), mean (SD)	0.9 (0.2)	0.9 (0.3)	0.9 (0.2)	0.24	0.84 (0.23)	0.89 (0.31)	0.84 (0.21)	0.07

Hyperlp: hyperlipoproteinaemia; SD: standard deviation; CV: cardiovascular; IHD: ischaemic heart disease; BMI: body mass index PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

some differences in the frequency of hyperlipoproteinaemia(a) when compared to controls. These differences became evident when the results were adjusted for age and gender, showing a moderately higher risk of presenting hyperlipoproteinaemia(a) in the whole SpA group compared to the control group, especially in those with AS.

Lp(a) has an independent positive association with CVD in different in epidemiological studies and new therapies have shown to effectively reduce Lp(a) levels (31). Recently, it has been proposed the value of ≥50 mg/dL, corresponding to values >80th percentile in the Danish population, as the cut-off value to determine a higher CV risk (26). In this cohort, 20% of the population, both men and women, had Lp(a) values ≥50 mg/dL, similar results to those found in our series of SpA.

As expected, SpA patients with hyperlipoproteinaemia(a) displayed a worse lipid profile, including higher plasma LDL-c levels. This may be explained because the cholesterol content of Lp(a)

Table II. Treatments of patients with ankylosing spondylitis and psoriatic arthritis stratified according to the presence or not of hyperliproteinaemia(a).

Variables	Ankylosing spondylitis				Psoriatic arthritis			
	Total	Hyperlp(a) Yes (n=88)	Hyperlp(a) No (n=338)	*p*-value	Total	Hyperlp(a) Yes (n=73)	Hyperlp(a) No (n=339)	*p*-value
NSAIDs, n (%)	247 (58.0)	57 (64.8)	190 (56.2)	0.15	181 (43.9)	35 (48.0)	146 (43.1)	0.45
Statins, n (%)	70 (16.4)	19 (21.6)	150 (15.1)	0.14	85 (20.6)	15 (20.6)	70 (20.7)	0.96
Glucocorticoids, n (%)	37 (8.7)	11 (12.5)	26 (7.7)	0.16	91 (22.1)	20 (27.4)	71 (20.9)	0.23
Beta blockers, n (%)	28 (6.6)	7 (8.0)	21 (6.2)	0.56	26 (6.3)	6 (8.2)	20 (5.9)	0.46
Calcium antagonists, n (%)	19 (4.5)	3 (3.4)	16 (4.7)	0.59	22 (5.3)	3 (4.1)	19 (5.6)	0.61
Non-biological DMARDs, n (%)	135 (31.7)	25 (28.4)	110 (32.5)	0.46	302 (73.3)	56 (76.7)	246 (75.6)	0.47
Methotrexate, n (%)	77 (18.1)	15 (17)	62 (18.3)	0.78	250 (60.7)	52 (71.2)	198 (58.4)	0.04
Leflunomide, n (%)	6 (1.4)	2 (2.3)	4 (1.2)	0.44	59 (14.3)	11 (15.1)	48 (14.2)	0.84
Cyclosporine A, n (%)	--	--	--		6 (1.5)	1 (1.4)	5 (1.5)	0.95
Salazopyrin, n (%)	63 (14.8)	9 (10.2)	54 (16)	0.18	31 (7.5)	4 (5.5)	27 (8.0)	0.47
Biological DMARDs, n (%)	207 (48.6)	39 (44.3)	168 (49.7)	0.37	177 (43.0)	26 (35.6)	151 (44.5)	0.16
Infliximab, n (%)	85 (20.0)	18 (20.5)	67 (19.8)	0.89	40 (9.7)	5 (6.8)	35 (10.3)	0.36
Etanercept, n (%)	52 (12.2)	8 (9.1)	44 (13)	0.32	62 (15.0)	7 (9.6)	55 (16.2)	0.15
Adalimumab, n (%)	69 (16.2)	13 (14.8)	56 (16.6)	0.68	70 (17.0)	14 (19.2)	56 (16.5)	0.59
Rituximab, n (%)	1 (0.2)	0 (0)	1 (0.3)	0.61	1 (0.2)	0 (0.0)	1 (0.3)	0.64

Hyperlp: hyperlipoproteinaemia; NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease modifying anti-rheumatic drugs.

Table III. Lipid profile in patients with ankylosing spondylitis and in psoriatic arthritis according to the presence or not of hyperliproteinaemia(a).

Variables	Ankylosing spondylitis				Psoriatic arthritis			
	Total	Hyperlp(a) Yes (n=88)	Hyperlp(a) No (n=338)	*p*-value	Total	Hyperlp(a) Yes (n=73)	Hyperlp(a) No (n=339)	*p*-value
Atherogenic Index, mean (SD)	3.9 (1.2)	4.2 (1.2)	3.9 (1.2)	0.01	3.9 (1.1)	4.0 (1.2)	3.9 (1.1)	0.34
Total cholesterol (mg/dl), mean (SD)	196.2 (36.5)	202.1 (37.7)	194.7 (36.1)	0.09	202.8 (36.6)	207.9 (34.0)	201.7 (37.0)	0.19
Apolipoprotein B*, mean (SD)	9.5 (2.4)	10.2 (2.4)	9.3 (2.4)	0.01	9.8 (2.5)	10.4 (2.2)	9.6 (2.5)	0.01
Apolipoprotein A*, mean (SD)	15.2 (3.1)	14.5 (2.5)	15.4 (3.2)	0.01	15.6 (3.1)	15.3 (2.8)	15.7 (3.2)	0.10
LDL-c (mg/dl), mean (SD)	122.5 (31.4)	129.9 (33.4)	120.4 (30.6)	0.01	123.5 (32.1)	131.1 (26.4)	121.9 (33.0)	0.03
HDL-c (mg/dl), mean (SD)	53.0 (14.8)	50.0 (12.9)	53.8 (15.2)	0.03	54.8 (15.4)	54.5 (14.0)	54.9 (15.7)	0.84
Triglycerides (mg/dl), mean (SD)	114.3 (78.7)	122.9 (96.3)	112.0 (73.4)	0.25	125.1 (79.5)	117.1 (75.4)	126.9 (80.3)	0.34

Hyperlp: hyperlipoproteinaemia; SD: standard deviation; LDL-c: low density lipoprotein-cholesterol; HDL-c: high density lipoprotein-cholesterol. *10 mg/dl.

is also included in the calculation of the serum LDL-C by the Friedewald formula, and cholesterol constitutes 25 to 35% of each Lp(a) molecule (32-33). Furthermore, they had higher values of apo B, given that Lp(a) contains one molecule of this apolipoprotein per particle, and lower HDL-c and apo AI levels, probably as the result of the inverse relationship with inflammation.

PsA patients with hyperlipoproteinaemia had higher disease activity (DAS28-ESR) and higher methotrexate exposure. Also, NSAID intake was associated with the presence of hyperlipoproteinaemia(a) in patients with AS. These results might suggest a potential role of disease activity in the risk of hyperlipoproteinaemia(a) in patients with SpA. However, most indicators of disease activity were

Table IV. Multivariate model to determine the factors associated with the presence of hyperliproteinaemia(a) in patients with ankylosing spondylitis.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value
Age at entry into the study, years	1.02 (1.00-1.04)	1.00 (0.98-1.03)	0.83
Sex (reference, man)	0.75 (0.43-1.31)	0.98 (0.49-1.93)	0.95
Studies (reference, Primary)			
Less than Primary	1.19 (0.41-3.48)	1.08 (0.31-3.75)	0.91
Secondary	1.05 (0.60-1.83)	1.10 (0.60-2.04)	0.75
Superior	0.63 (0.33-1.21)	0.79 (0.38-1.63)	0.52
Diabetes Mellitus (reference, no)	1.68 (0.77-3.65)	1.81 (0.76-4.34)	0.18
NSAIDs (reference, no)	1.43 (0.88-2.33)	1.78 (1.04-3.05)	0.04
Statins (reference, no)	1.55 (0.86-2.79)	1.24 (0.59-2.6)	0.57
Glucocorticoids (reference, no)	1.71 (0.81-3.62)	1.94 (0.85-4.41)	0.11
Salazopyrin (reference, no)	0.60 (0.28-1.27)	0.51 (0.23-1.15)	0.10
Family history of IHD (reference, no)	1.65 (0.87-3.11)	1.60 (0.77-3.31)	0.21
History of CV events (reference, no)	3.08 (1.45-6.57)	2.47 (0.95-6.41)	0.06
ESR (mm/1st hour)	1.02 (1.00-1.03)	1.01 (0.99-1.03)	0.37
Apolipoprotein A*	0.90 (0.82-0.98)	0.90 (0.81-0.99)	0.05
Apolipoprotein B*	1.17 (1.06-1.29)	1.19 (1.07-1.33)	0.01

OR: odds ratio; CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; IHD: ischaemic heart disease; CV: cardiovascular; ESR: erythrocyte sedimentation rate. OR adjusted for all variables included in the multivariate model. *OR for 10 mg/dl.

Table V. Multivariate model to determine the factors associated with the presence of hyperliproteinaemia(a) in patients with psoriatic arthritis.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value
Age at entry into the study, years	1.03 (1.01-1.05)	1.03 (1.00-1.06)	0.04
Sex (reference, man)	1.70 (1.02-2.83)	2.26 (1.03-4.93)	0.04
Studies (reference, Primary)			
Less than Primary	2.87 (1.16-7.12)	1.96 (0.65-5.96)	0.24
Secondary	0.81 (0.41-1.58)	1.05 (0.48-2.30)	0.89
Superior	1.21 (0.63-2.32)	1.68 (0.76-3.71)	0.20
Enthesitis. (reference, no)	1.56 (0.89-2.72)	1.59 (0.76-3.35)	0.22
DAS28	1.19 (0.98.1.43)	0.90 (0.70-1.16)	0.43
Time of evolution, years	0.97 (0.94-1.00)	0.96 (0.93-1.00)	0.03
Biological DMARDs, (reference, no)	0.69 (0.41-1.16)	0.78 (0.40-1.50)	0.45
Family history of IHD, (reference, no)	1.66 (0.77-3.59)	1.24 (0.47-3.30)	0.66
History of CV events, (reference, no)	3.36 (1.50-7.52)	1.08 (0.27-4.33)	0.91
Serum creatinine (mg/dl)	2.54 (0.92-7.04)	3.11 (0.66-14.70)	0.15
Apolipoprotein A*	0.96 (0.88-1.05)	0.92 (0.83-1.03)	0.14
Apolipoprotein B*	1.14 (1.04-1.26)	1.17 (1.04-1.32)	0.01
Kidney disease, (reference, no)	3.15 (0.52-19.23)	7.80 (0.90-67.94)	0.06
Thyroid disease, (reference, no)	2.46 (0.96-6.34)	1.64 (0.54-4.98)	0.40

OR: odds ratio; CI: confidence interval; DAS: disease activity score; DMARDs: disease-modifying anti-rheumatic drugs; IHD: ischaemic heart disease; CV: cardiovascular. OR adjusted for all variables included in the multivariate model. *OR for 10 mg/dl.

not associated with the presence of hyperlipoproteinaemia(a) in the multivariate analysis. With respect to this, patients from the present study were periodically followed-up at Rheumatology Units and had a low-grade of disease activity according to ESR, s-CRP and ASDAS in AS, and ESR and DAS8-ESR in PsA, at the time of assessment. This fact may explain the absence of strong differences between the cohort of SpA and controls. On the other hand, it is known that Lp(a) levels depend mainly on the polymorphisms of apo(a) and the relationship with interleukin (IL)-6, since this cytokine plays an important role in its genetic transcription (34). However, IL-6 does not have a relevant role in the pathogenesis in SpA, and therapies inhibiting IL-6 are not effective in SpA.

Lp(a) appears to be more resistant to lifestyle interventions and drugs than any other lipoprotein (35). In this sense, there is a paucity of information concerning the effect of anti-rheumatic therapies on Lp(a) levels in patients with SpA. As previously discussed, PsA patients from our cohort taking methotrexate had more commonly hyperlipoproteinaemia(a), which may be due to higher disease activity. In fact, they had higher DAS-28 scores.

A study that evaluated the effect of targeting the TNF-α pathway in patients with PsA disclosed significantly decreased Lp(a) concentrations in anti-TNF-treated patients (36). However, we could not observe statistically significant differences in our series between patients undergoing or not anti-TNF therapies at the time of recruitment in the CARMA project. Possibly, the cross-sectional nature of our study may explain the absence of differences.

In our study, a model adjusted for potential confounding factors showed that elevated values of apo AI were associated with a lower probability of presenting hyperlipoproteinaemia(a) in AS. In contrast, elevated values of apo B were associated with a higher probability of presenting hyperlipoproteinaemia(a), given that Lp(a) contains one molecule of apo B. These results may account for the inverse relationship between hyperlipoproteinaemia(a) and inflammation discussed before.

The model adjusted for potential confounding factors for PsA patients showed that women, higher age at entry into the study and elevated values of apo B were associated with a higher probability of presenting hyperlipoproteinaemia(a). However, to our surprise, shorter disease duration was associated with a higher probability of presenting hyperlipoproteinaemia(a). Higher disease activity in individuals with a more recent diagnosis may be a potential explanation for these findings.

Recommendations to measure Lp(a) in the general population are focused on individuals with intermediate or high risk of CVD/coronary heart disease (CHD) who experience premature CVD, familial hypercholesterolaemia, a family history of premature CVD and/or elevated Lp(a), recurrent CVD despite statin treatment, a 10-year risk of fatal CVD ≥3% according to the European guidelines, and a 10-year risk of fatal and/or non-fatal CHD ≥10% according to the US guidelines (26). Repeat measurements are not necessary, except for evaluating therapeutic response if treatment for high Lp(a) levels is initiated. Nonetheless, due to the factors that influence the variability of Lp(a) values, such as race, age and sex, Lp(a) is considered a predictor of greater power in young and middle-age people than in the elderly. In this regard, the majority of patients with SpA in our series were young, especially those affected by AS. In conclusion, the results of the CARMA project show a modest higher risk to present hyperlipoproteinaemia(a) in SpA patients compared to controls, especially in those with AS. Although our study constituted a cross-sectional analysis, which did not allow establishing causality, Lp(a) determination may be of potential interest to improve the assessment of the CV risk in patients with SpA. Nevertheless, further studies are required to fully establish the relevance of Lp(a) in the assessment of CV risk in these patients.

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