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ORIGINAL RESEARCH

Primary Sjögren's syndrome independently promotes premature subclinical atherosclerosis

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ABSTRACT

Objectives Cardiovascular comorbidities are common in patients with autoimmune diseases. This study investigates the extent of subclinical atherosclerosis in patients with primary Sjögren's syndrome (pSS). Correlations with clinical factors such as organ involvement (OI) or disease activity were analysed and oxLDL antibodies (oxLDL ab) were measured as potential biomarkers of vascular damage.

Methods Patients with pSS were consecutively included from the rheumatology outpatient clinic. Age- and sex-matched controls were recruited (2:1 ratio). Data collection was performed by a standardised questionnaire and Doppler ultrasound to evaluate the plaque extent and carotid intima-media thickness (cIMT). Propensity score matching included all cardiovascular risk (CVR) factors and corresponding laboratory markers.

Results Data were available for 299 participants (199 pSS/100 controls), aged 59.4 years (50.6–65.0), 19.1% male. After matching, the pSS cohort had greater cIMT ($p<0.001$) and plaque extent (OR=1.82; 95% CI 1.14 to 2.95). Subgroup analyses of patients with pSS revealed that OI was associated with increased cIMT ($p=0.025$) and increased plaque occurrence compared with patients without OI (OR=1.74; 95% CI 1.02 to 3.01). OxLDL ab tended to be lower in patients with plaque ($p=0.052$). Correlations of higher Oxidized Low Density Lipoprotein (oxLDL) ab with EULAR Sjögren's Syndrome Disease Activity Index ($p<0.001$) and anti–Sjögren's-syndrome-related antigen A autoantibodies (SSA/Ro antibodies) ($p=0.026$) were observed.

Conclusions Subclinical atherosclerosis occurs earlier and more severely in patients with pSS. The difference in cIMT between pSS and controls seems mainly driven by patients with OI, suggesting that this subgroup is particularly at risk. OxLDL ab might protect against atherosclerotic progression in patients with pSS. CVR stratification and preventive medications such as Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors should be discussed and further longitudinal studies are needed.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ Inflammatory diseases such as systemic lupus erythematosus or rheumatoid arthritis are known to increase the development of subclinical atherosclerosis, but for primary Sjögren's syndrome (pSS), only few data from small studies on this are available.

WHAT THIS STUDY ADDS

⇒ pSS operates as an independent promoter of premature atherogenesis.
⇒ This study demonstrated that patients with pSS with organ involvement are at particularly high risk of premature intima-media thickening and plaque development.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The increased prevalence of subclinical atherosclerosis in patients with pSS emphasises the need for cardiovascular monitoring and preventive pharmacological treatment, especially when traditional cardiovascular risk factors are also present.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that primarily affects the exocrine glands through lymphocytic infiltration.[1] The prevalence, reported in the literature ranges from 1:100 to 1:1000, making pSS the most common connective tissue disease in middle-aged people.[2] In addition, approximately 50% of patients with pSS present extraglandular manifestations.[3]

In rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), chronic inflammation, particularly the formation of immune complexes, is known to impair endothelial function, leading to accelerated atherosclerosis and ultimately higher rates of cardiovascular events.[4 5] This increased cardiovascular

risk (CVR) explains much of the morbidity and mortality in patients with RA or SLE.[6 7]

In pSS, this interaction has been poorly studied, even though cardiovascular disease (CVD) is one of the leading causes of death.[8] Available data showed controversial results based on different study designs: Bartoloni *et al* found a significantly higher risk of myocardial infarction and cerebrovascular disease in a retrospective cross-sectional analysis of 1343 patients with pSS.[9] In contrast, Chiang *et al* reported that pSS was not associated with an increased risk of myocardial infarction in a nationwide prospective study from Taiwan with 5205 patients. The mean follow-up time of this observational study was 3.7 years and there was no information on disease activity or severity.[10]

However, 10 studies, including the two mentioned above, were systematically reviewed by Yong *et al*, who found further evidence that CVR may be increased in pSS.[11] In line with these findings, a recent study showed evidence of impaired endothelial function in patients with pSS compared with controls, which may appear as launching point for atherogenesis.[12] Subclinical atherosclerosis is the stage in between impaired endothelial function and a manifest CVD.

It is characterised by asymptomatic vascular damage in the form of atherosclerotic wall thickening and plaque formation and is associated with an increased risk of cardiovascular events.[13 14] The available data on subclinical atherosclerosis in pSS, defined as carotid intima-media thickening and evidence of plaque, included only few and small studies with a maximum cohort size of 64 patients, suggesting a higher prevalence of subclinical atherosclerosis.[15–20] On the other hand, there are also some data showing no difference between pSS and healthy controls, at least in an elderly population.[21] Thus, the relationship between the occurrence of subclinical atherosclerosis and pSS remains controversial, making it even more critical to conduct larger studies on this issue.

In patients with chronic disease, CVR stratification is becoming increasingly important, and several studies have investigated experimental biomarkers for their diagnostic or prognostic value.[22 23] One potential biomarker of interest is the autoantibody to oxidated low-density lipoprotein (LDL) cholesterol and its mediated complexes (Oxidized Low Density Lipoprotein antibodies (oxLDL ab)).

Oxidative stress, which has been shown to be elevated in patients with pSS, is a driver of oxLDL formation.[24 25] During this process, LDL is modified by reactive oxygen species into negatively charged oxLDL.[26] OxLDL plays a major role in the development and progression of atherosclerosis due to its proinflammatory, toxic and chemotactic properties towards macrophages, monocytes and other immune cells.[27 28] Antibodies to oxLDL, which might prevent the aforementioned effects, appear to have a protective effect in several studies,[29 30] although some studies show a detrimental function.[31 32]

The aim of our study was to investigate whether patients with pSS develop earlier or more severe subclinical atherosclerosis compared with matched healthy controls. We also investigated whether there were subgroups at higher risk and whether or not oxLDL ab might play a role in this cohort.

METHODS

Study design

This prospective monocentric cohort study was designed as a cross-sectional study and included patients with pSS, who regularly attended the rheumatological outpatient clinic or the interdisciplinary outpatient infusion clinic of Medical University Hannover between September 2021 and March 2022. Contemporaneously a gender- and age-matched control cohort was recruited in a 2:1 ratio through a multimedia call for participation.

Participants

All included patients fulfilled the ACR/EULAR 2016 classification criteria[33] and had symptoms for at least 5 years.

Exclusion criteria for all participants were known to manifest atherosclerotic end-stage diseases, such as myocardial infarction or stroke, as well as malignant diseases in the past 5 years, other systemic inflammatory diseases or currently existing pregnancy (figure 1). After matching for gender and age, a further 18 controls were excluded to ensure comparability of the cohorts in terms of age and sex distribution. All participants gave written informed consent.

Data collection

A comprehensive standardised questionnaire was completed with all participants and included disease-related symptoms, associated diseases, comorbidities, traditional cardiovascular risk factors (CRFs), family history and previous diagnostics. In addition, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) Scores were calculated.[34] Organ involvement (OI) included lung, kidney, skin and liver manifestations, as well as vasculitis, myositis and peripheral and central nervous system involvement.

Carotid ultrasound was performed using the GE LOGIQ P9 and a consistent optimised preset profile for the 10 MHz linear transducer. To ensure comparability and quality, measurements were performed according to the Mannheim Consensus recommendations.[35] The actual measurements were performed by two independent angiologists in a blinded fashion after the physical examination. In the rare case of divergent measurement results, the protocol foresaw the use of the mean value of the two measurements. Carotid intima-media thickness (cIMT) was manually measured three times on both sides at the posterior arterial wall approximately 1 cm proximal to the carotid bulb (figure 2). The mean was calculated and considered pathological in age-adjusted gradations according to Chambless *et al*.[36]

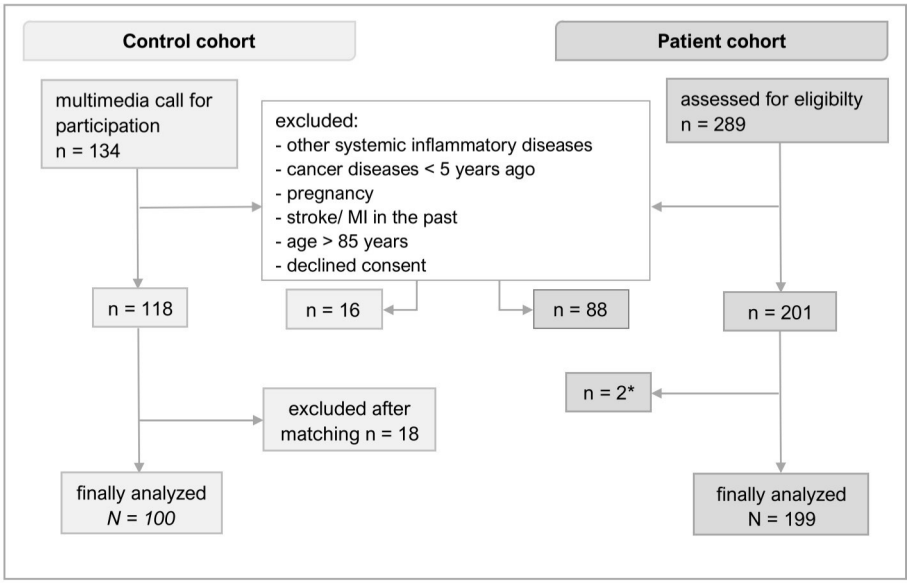

Figure 1 Study design. *Diagnosis of cancer recurrence and multiple sclerosis shortly after study inclusion. MI, myocardial infarction.

In addition, plaque extent was detected and quantified. Plaque was defined according to Touboul *et al* as "focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value".[35]

Blood samples were collected from all participants on the day of enrolment under fasting conditions for clinical markers of CVR, including HbA1c and serum lipid profile as well as lipoprotein A and oxLDL ab.

Analysis of IgG-oxLDL ab in serum samples was performed using Immundiagnostik AG ELISA K7809 according to the manufacturer's protocol (Bensheim, Germany).

Statistical and graphical analysis

R V.4.2.1 with the R-Studio IDE was used for data analysis. Data processing was performed using 'Tidyverse' packages. Descriptive statistics are presented as medians and IQRs unless otherwise stated.

Main analyses for cIMT were performed using 'lme4' and 'lmerTest'. Due to the hierarchical data structure (two cIMT measurement points per person: left and right), hierarchical linear models were conducted with cohort as level 2 predictor and participants as clusters. Since the fixed effects were of paramount interest, full maximum likelihood method was used.

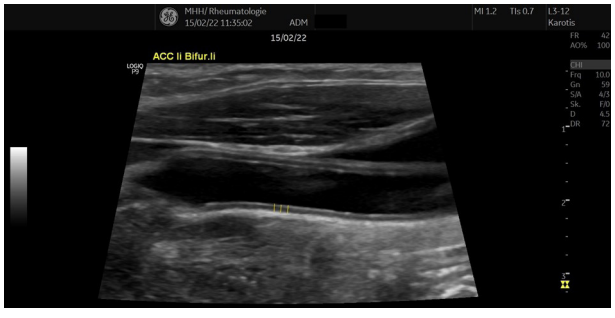

Figure 2 Ultrasound image of a left common carotid artery with thickened cIMT. Yellow lines show the measurement of cIMT according to the Mannheim Consensus. cIMT, carotid intima-media thickness.

Propensity score matching was performed to ensure that pSS and control participants did not differ significantly with regard to traditional CRFs. Therefore, cases were matched for age, sex, Body Mass Index, arterial hypertension, tobacco consumption inpack years (PY), HbA1c, serum high-density lipoprotein (HDL) cholesterol, serum LDL cholesterol, positive family history of CVDs, pre-existing diagnosis of hypercholesterolaemia and pre-existing diagnosis of diabetes mellitus (online supplemental data 1). The packages 'MatchIt', 'Optmatch', 'lmtest', 'sandwich' and 'cobalt' were used and propensity scores were estimated using a generalised linear model. Moreover, optimal pair matching was applied, which selects pairs using absolute paired distances within the matched sample.

For cohort comparisons before and after matching, continuous variables were considered non-parametric and compared using the Kruskal-Wallis test. Discrete variables were compared using the χ^2 test or Fisher's exact test.

The extent of plaque was scored as a categorical variable with four levels: Participants had either no, small, intermediate or severe plaque extent. 'Small extent of plaque' was defined as the presence of only one small plaque (<8 mm length/<1 mm thickness). 'Intermediate extent of plaque' was characterised by the presence of one tiny plaque in both carotid arteries or several small plaques in one carotid artery. Participants with a larger extent of plaque were categorised as having 'severe extent of plaque'. Due to highly skewed cell distributions, the two highest plaque levels were combined into 'intermediate and severe plaque extent' for further analysis. Ordered logistic regression was performed to estimate

Table 1 Summary of cohort demographics

			Subgroups*	
	Control cohort (n=100)	Total pSS cohort (n=199)	pSS without organ involvement (n=84)	pSS with organ involvement (n=115)
Age (years)	59.6 (50.7–64.3)	58.9 (50.5–65.2) p=n.s.†	54.9 (44.0–62.0)	60.7 (54.8–67.8) p<0.001†
Male sex (n, %)	19 (19.0)	38 (19.1) p=n.s.‡	12 (16.7)	26 (29.2) p=n.s.‡
Tobacco consumption (pack years)	0 (0–8)	0 (0–10) p=n.s.†	0 (0–5)	0 (0–13) p=n.s.†
Body Mass Index (kg/m^2)	25.2 (22.3–27.8)	25.1 (22.2–29.6) p=n.s.†	24.8 (21.8–28.7)	25.4 (22.4–29.8) p=n.s.†
Arterial hypertension (n, %)	25 (25.0)	73 (36.7) p=n.s.‡	23 (27.4)	50 (43.5) p=0.025‡
Number of antihypertensive drugs	0 (0–0.3)	0 (0–1) p=n.s. †	0 (0–0)	0 (0–1) p=0.006a
Preknown hypercholesterolaemia (n, %)	20 (20.0)	54 (27.1) p=n.s.‡	16 (19.0)	38 (33.0) p=0.036‡
Preknown diabetes mellitus (n, %)	2 (2.0)	13 (6.5) p=n.s.‡	3 (3.6)	10 (8.7) p=n.s.‡
Positive family history (n, %)§	33 (33.0)	103 (51.8) p=0.002‡	49 (58.3)	54 (47.0) p=n.s.‡
HbA1c (%)	5.3 (5.0–5.5)	5.3 (4.9–5.5) p=n.s.†	5.2 (4.9–5.4)	5.3 (5.0–5.7) p=0.037†
Serum LDL cholesterol (mmol/L)	2.98 (2.5–3.8)	2.92 (2.4–3.5) p=n.s.†	2.9 (2.3–3.5)	2.94 (2.4–3.6) p=n.s.†
Serum HDL cholesterol (mmol/L)	1.49 (1.2–1.8)	1.62 (1.3–2.0) p=n.s.†	1.65 (1.4–2.0)	1.53 (1.2–2.0) p=n.s.†

Unless otherwise stated median and (IQR) are reported. Comparative analyses were performed between the control cohort and the total pSS cohort and, independently, between the pSS subgroups with and without organ involvement.HbA1c - Hemoglobin A1c
*All comparisons were made between the two subgroups, not with the control cohort.
†Kruskal-Wallis test.
‡Fisher's exact test.
§Positive, if first-degree relatives were affected by cardiovascular diseases.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; pSS, primary Sjögren's syndrome.

the cohort's effect on the plaque extent using the 'MASS' package. The resulting log odds scale was converted to a proportional OR to ensure interpretability.

Subgroup analyses were conducted to estimate the association of additional indicators with cIMT and plaque, respectively. Due to the high skewness of some indicators, the corresponding variables were log-transformed and then considered parametric. OI was defined as the presence of pSS features in the following systems: kidney, lung, CNS and PNS, as well as vasculitis and myositis.

p<0.05 was considered significant and all p values are two-tailed unless otherwise stated.

RESULTS

Cohort demographics

199 patients with pSS and 100 healthy controls were enrolled in this study. Cohort demographics are summarised in table 1. 38 patients with pSS (19.1%) were male with a median age of 61.3 years (53.3–67.8). Female patients had a median age of 58.6 years (50.2–65.0). Concerning traditional CRFs, the patient cohort did not differ systematically from the controls (table 1), except for a positive family history of cardiovascular events, reflecting a genetic predisposition (p=0.003 according to Fisher's exact test). Moreover, a descriptively but not significantly higher proportion of patients with hypertension (p=0.057 according to Fisher's exact test) was observed for participants in the pSS cohort. It was also notable that the cohorts did not differ significantly in terms of laboratory parameters collected at baseline, that is, HbA1c, LDL and HDL (ps>0.108).

Disease-related parameters are shown in table 2. Only 29 of 199 patients (14.6%) had no objectifiable dryness but fulfilled the ACR/EULAR 2016 classification criteria based on the presence of SSA/Ro antibodies and a pathological salivary gland biopsy.[33] In total, salivary gland biopsy results were available for 123 of 199 cases (61.8%). Histopathology was graded according to the Chisholm

Table 2 Summary of disease-related parameters in patients with pSS

	Total cohort	pSS with OI	pSS without OI
ESSDAI Score	n=199	n=115	n=84
Constitutional symptoms, n (%)	51 (25.6)	33 (28.7)	18 (21.4)
Lymphadenopathy, n (%)	28 (14.1)	17 (14.8)	11 (13.1)
Glandular involvement, n (%)	34 (17.1)	12 (10.4)	62 (73.8)
Articular involvement, n (%)	140 (70.4)	77 (70.0)	63 (75.0)
Cutaneous involvement, n (%)	18 (9.0)	18 (15.7)	0 (0.0)
Pulmonary involvement, n (%)	31 (15.6)	31 (27.0)	0 (0.0)
Renal involvement, n (%)	4 (2.0)	4 (3.5)	0 (0.0)
Muscular involvement, n (%)	20 (10.1)	20 (17.4)	0 (0.0)
Peripheral nervous system involvement, n (%)	74 (37.2)	74 (64.3)	0 (0.0)
Central nervous system involvement, n (%)	22 (11.1)	22 (19.1)	0 (0.0)
Haematological involvement, n (%)	103 (51.8)	61 (53.0)	41 (48.8)
Biological involvement, n (%)	78 (39.2)	43 (37.4)	36 (42.9)
Total score, points (IQR)	14 (8–23)	18 (12–26)	6 (4–9)
Laboratory values *at investigation date*			
CRP >10 mg/dL, n (%)	16 (8.0)	13 (11.3)	3 (3.6)
Rheumatoid factor positive, n (%)	45 (22.6)	17 (14.8)	28 (33.3)
ANA >1:160, n (%)	130 (65.5)	73 (63.5)	57 (67.9)
Alpha-fodrin antibody positive, n (%)	65 (33.0)	40 (34.8)	25 (29.8)
Presence of SSA (Ro) antibody, n (%)	96 (48.5)	54 (47.4)	42 (50.0)
Presence of SSB (La) antibody, n (%)	29 (14.6)	8 (7.0)	21 (21.0)
Hypergammaglobulinaemia, n (%)	37 (18.6)	20 (17.4)	17 (20.2)
Sicca symptomatology			
Path. Saxon test, n (%)	110 (55.3)	67 (58.3)	43 (51.2)
Path. Schirmer test, n (%)	128 (64.3)	72 (62.6)	56 (66.7)
No objectifiable dryness, n (%)	29 (14.6)	14 (12.2)	15 (17.9)
Salivary gland biopsy			
Chisholm and Mason grade ≥3, n (%)	98 (79.7)	59 (74.7)	39 (86.7)
Duration since initial diagnosis, month	50 (23–107)	49 (29–89)	63 (15–146)
Duration since 1st manifestation, month	136 (82–224)	133 (80–199)	140 (85–236)
ESSPRI Score	5.0 (2.7–7.3)	5.0 (3.7–6.7)	5.2 (3.3–7.1)

Unless otherwise stated median and (IQR) are reported. In the right half of the table, the pSS cohort was divided according to the presence of OI, as reflected in the corresponding ESSDAI categories. Calculations are based on the number of patients in the group described above, with the exception of salivary gland biopsy results. These results were only available for 124 patients, 79 in the pSS subgroup with OI and 45 in the pSS subgroup without OI.
ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; OI, organ involvement; pSS, primary Sjögren's syndrome.

and Mason Score[37] with grade 3 and higher being considered pathological.[33]

The median disease duration was 4.2 years (1.9–8.9), while the median time since the reported initial manifestation was 11.3 years (6.8–18.7).

115 (57.8%) of patients with pSS had at least one organ system involved. The most common OI was peripheral nervous system involvement with 37.2% (n=74), mainly represented by a chronic inflammatory demyelinating polyneuropathy or small fibre polyneuropathy.

Results on cIMT

Comparison of the total cohorts of controls (n=100) and patients with pSS (n=199) showed a significant overall difference in cIMT, with patients displaying a higher cIMT (M=0.71, SD=0.12) than their matched controls

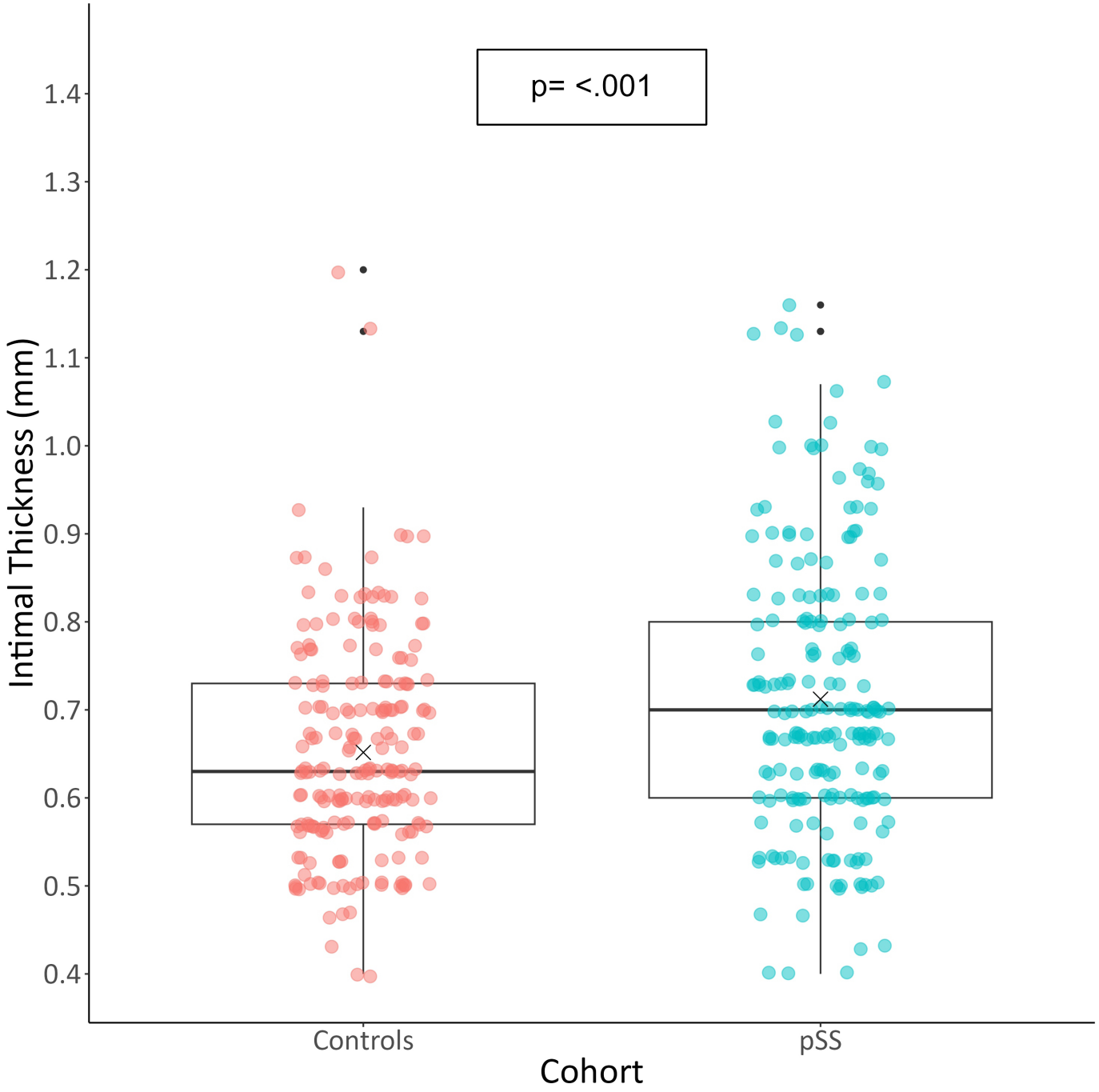

Figure 3 cIMT-density plot of matched sample (n=100 participants in each cohort) showing the cIMT distribution by group. X indicates cohort-specific cIMT means, that is, 0.65 mm for control cohort and 0.71 mm for pSS cohort. Significance level indicates main effect for cohort in hierarchical regression predicting cIMT. cIMT, carotid intima-media thickness; pSS, primary Sjögren's syndrome.

(M=65, SD=0.15, p<0.001; figure 3). In addition, the increase in thickness with progressing age was significantly higher in pSS (p=0.034) (figure 4). To illustrate the premature onset of intima-media thickening, participants were stratified into age subgroups by decade after the propensity score matching and cIMT measurements were compared between patients with pSS and controls. This analysis demonstrated that cIMT of patients in their 50s (M=0.70 mm, SD=0.13) did not substantially differ from cIMT of controls in their 60s (M=0.70 mm, SD=0.09). Even clearer results were seen in patients with pSS in their 60s (M=0.74 mm, SD=0.13) who descriptively had a cIMT-like controls in their 80s (M=0.72 mm, SD=0.10), indicating an earlier onset and accelerated progression of subclinical atherogenesis in pSS. After performing the propensity score matching, both cohorts contained 100 subjects each. The overall difference in the cIMT remained significant (M_{pSS}=0.71, SD_{pSS}=0.16; M_{HC}=0.65, SD_{HC}=0.12; p<0.001; figure 3). Additionally, subgroups were also analysed (online supplemental

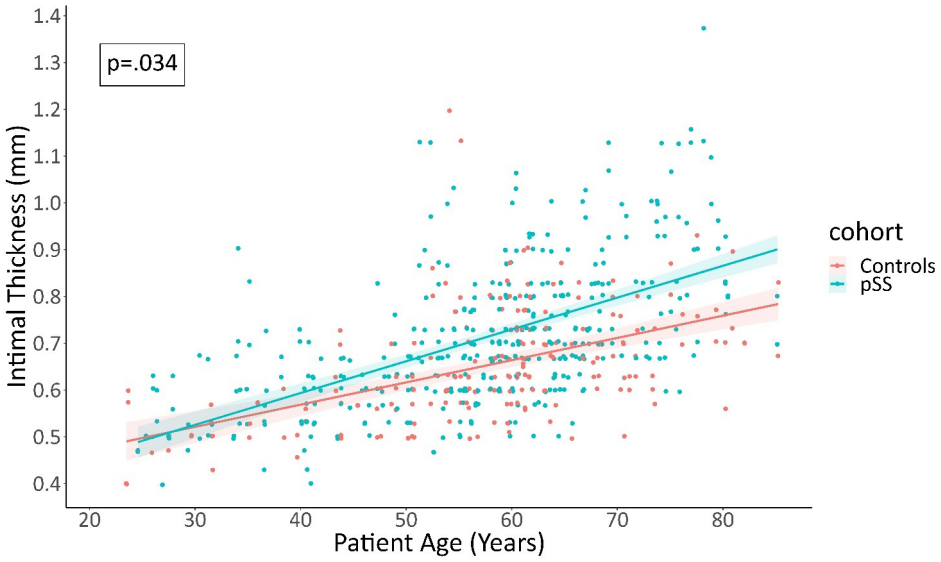

Figure 4 Scatter plot showing the correlation between cIMT and age, subdivided by cohorts. Each person is represented by two dots (left and right cIMT) and a linear regression line was calculated to illustrate the differences in increasing cIMT. cIMT, carotid intima-media thickness; pSS, primary Sjögren's syndrome.

data 4). When the cohort was divided by gender, both female and male patients with pSS showed significantly increased cIMT compared with their control counterparts when controlling for participants' age ($M_{pSS♀}$=0.69, $SD_{pSS♀}$=0.15; $M_{HC♀}$=0.64, $SD_{HC♀}$=0.12; $M_{pSS♂}$=0.77, $SD_{pSS♂}$=0.17; $M_{HC♂}$=0.70, $SD_{HC♂}$=0.11; p<0.009). For female participants only, a significant interaction with age was observed (p=0.006), indicating that cIMT increases significantly stronger with increasing age in patients with pSS. No such interaction was found for male participants, which may be an effect of limited power (p=0.510; online supplemental data 2).

Furthermore, we aimed to investigate the effect of disease duration on cIMT. Therefore, disease duration was normalised to the patients' age of the total cohort to calculate a ratio of lifetime spent with the disease. However, no relationship between disease duration proportional to the patient's age and cIMT was found (p=1.000; online supplemental data 3).

Similarly, none of the laboratory values tested (alpha-fodrin antibodies, SSA/Ro antibodies, SSB/La antibodies, antinuclear antibodies or rheumatoid factors) in the total cohort showed a significant association with an increased cIMT (online supplemental data 4).

Despite attempts at patient enrolment to characterise steroid exposure, the varying and time-dependent nature of steroid dosing made accurate quantification impossible. As a surrogate for steroid exposure, a subanalysis based on end-OI was performed.

Patients with OI had a significantly thicker carotid intima-media (M=0.73, SD=0.15) compared with patients without OI (M=0.68, SD=0.15, p=0.025; online supplemental data 6). Focusing on this, there was no significant cIMT difference between the control cohort and patients with pSS without OI (p=0.081).

Comparisons were made between the subgroups of patients with and without OI in terms of traditional CRFs. There were some significant differences between these cohorts (table 1). Patients with OI were on average 6.6 years older (M_{OI}=59.85, SD_{OI}=12.05; M_{no_OI}=53.26, SD_{no_OI}=13.28; p<0.001), had a significantly higher prevalence of arterial hypertension (p=0.025) and the presence of hypercholesterolaemia (p=0.036; table 1 for descriptive details).

Hydroxychloroquine (HCQ) therapy also presented no significant association with cIMT (p=0.999). Dividing the pSS cohort with HCQ therapy by the presence of OI revealed a descriptively but not significantly different pattern when age was added as a covariate (p=0.230; online supplemental data 5).

For MTX, we additionally compared patients with pSS with and without OI. Results indicate that participants with OI had a significantly shorter overall duration of MTX medication (M_{OI}=8.23, SD_{OI}=34.3; M_{no_OI}=11.89, SD_{no_OI}=23.82; p=0.028). This finding is consistent with the current EULAR therapy recommendations, which recommend the use of rituximab, cyclophosphamide, immunoglobulins and mycophenolate mofetil instead of MTX in patients with Sjögren's syndrome with severe OI.

However, OI showed no association with absolute or current MTX use (ps>0.355).

Examining the joint association of ESSPRI and ESSDAI with cIMT, the ESSPRI Score showed no relation with cIMT (p=0.289), whereas a higher ESSDAI Score tended to be linked to a thicker carotid intima-media (β=0.00, p=0.054).

Results on the extent of plaque

The extent of plaque, categorised into three groups, was compared with the no-plaque group and showed

significant differences in cIMT across all groups (online supplemental data 7). Patients have a 1.82 (95% CI 1.14 to 2.95) times greater chance of having plaques than controls (online supplemental data 8). The odds of having plaque are also 1.74 times higher for patients with OI than for those without (95% CI 1.02 to 3.01); online supplemental data 9).

Absolute plaque classification (plaque yes vs no) was neither associated with a higher ESSDAI or ESSPRI Score or longer disease duration nor with any measured laboratory parameters except for SSB/La antibody positivity (β=−0.93, p=0.031; online supplemental data 4). Similarly, when comparing the duration of treatment with HCQ, no difference in plaque extent was observed (p=0.156). When comparing the presence of subclinical atherosclerosis, that is, plaque and/or increased cIMT, as a composite endpoint, patients were significantly more likely to have subclinical atherosclerosis than controls (β =0.72, p=0.004). To attempt to understand the influence of pSS on atherosclerosis, a logistic regression combining classical risk factors along with pSS status across the entire cohort was performed. Although age had the greatest impact (β=0.04, p=0.0003), it could be shown that pSS independently increased the likelihood of subclinical atherosclerosis (β=0.73, p=0.010). In the subsequent multivariate analysis, pSS independently increased the risk by 2.08 (95% CI 1.19 to 3.64).

Results on anti-oxLDL ab

Comparison of oxLDL ab showed no significant difference between patients and controls (OD_{pSS}=2761.8, OD_{HC}=2558.9; p=0.895). We found that patients with pSS with atherosclerotic plaque in the carotid artery tended to have lower oxLDL ab levels than patients without atherosclerotic plaques (p=0.052). However, there was no significant association between oxLDL ab levels and the cIMT (p=0.516).

OxLDL ab levels tended to be higher in patients with pSS with OI than in those without (p=0.056). Similar results were observed when oxLDL ab was correlated with higher ESSDAI Scores (r=0.27, p<0.001), SSA/Ro ab (r=−0.16, p=0.026), hypergammaglobulinaemia (r=−0.37, p<0.001) and positive Schirmer test results (r=0.16, p=0.028; online supplemental data 4).

DISCUSSION

Our results show that carotid intima-media thickening occurs significantly earlier and faster in patients with pSS than in controls, especially from the age of 50 (figure 3). In addition, patients have a higher risk of plaque development (online supplemental data 8). We investigated that OI is the most relevant factor in patients with pSS, which additionally increases the risk of subclinical atherosclerosis within the patient cohort. OxLDL ab are significantly elevated in patients with higher disease activity. To our knowledge, this is the first study to prospectively compare a well-matched large cohort of patients with pSS with controls in terms of cIMT, plaque extent and oxLDL ab levels.

Burden of atherosclerotic formation and CVD

Premature atherosclerosis in patients suggests that atherosclerotic lesions occur earlier and more severely than in matched controls. Our results are consistent with recently published studies showing that patients with pSS suffer from earlier and more frequent cardiovascular events, which could be well explained by accelerated progression of atherosclerosis.[17 38]

Considering the association with disease duration, we decided to include age as a covariate by calculating a ratio of lifetime under disease. This took into account that advanced age is known to be a major independent risk factor for atherosclerosis.[39] Lifetime under disease showed no association with either cIMT or plaque extent, similar to what Gravani *et al* reported.[15] In contrast, other previous studies reported a correlation between disease duration and the extent of subclinical atherosclerosis, but without taking patients' age into account.[20] Furthermore, the time of diagnosis does not automatically match the time of disease onset. While disease duration does not appear to have an impact, we can report a descriptive association with disease activity and a significant association with specific OI, which has only been partially shown in previous studies.[21]

Looking more closely at the subgroups, it seemed that the difference in cIMT between patients and controls is mainly driven by OI. This suggests that this subgroup in particular is at increased risk. Consistent with these results, there was also an increased incidence of traditional CRFs in this subgroup. The increased rate of hypertension is particularly noteworthy. It has been shown several times in the literature that traditional CRFs have an increased prevalence in patients with pSS.[9 40] This could be attributed to the fact that systemic inflammatory activity leads to premature vascular stiffening via endothelial damage and therefore favours the development of arterial hypertension.[41] At the same time, arterial hypertension, especially if not adequately treated, also leads to a progression of atherosclerotic lesions. Thus, systemic autoimmune disease in general, and Sjögren's syndrome in particular, may act as an accelerator in this spiral of atherosclerotic vascular damage.[5 12 42]

Molecular link of inflammation and atherogenesis

It is well known that atherosclerosis is based on an interaction between traditional CRFs, inflammatory events and immunological mechanisms.[43] In several autoimmune rheumatic conditions, there is a significantly higher prevalence of atherosclerosis compared with the general population.[5 12 42] This correlation is not unexpected, as similar mediators and inflammatory mechanisms are involved in atherosclerosis and autoimmune rheumatic diseases.[17] Since patients with pSS have an overactivated immune system and chronic inflammation, this suggests that the underlying pathology contributes

to the accelerated process of atherogenesis. One major overlap is in endothelial cell activation and another can be found in the type I interferon (IFN) pathway.

Endothelial cells are central to the pathogenesis of atherosclerosis. Their activation leads to the upregulation of various cell adhesion molecules, such as ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1). These molecules are known biomarkers of endothelial cell damage and have been found to be significantly upregulated in pSS, suggesting a link between pSS and atherosclerosis.[44] In the next step, immune cells are recruited and migrate into the vessel wall. Macrophages then take up oxLDL via Toll-like receptors (TLRs) to turn into foam cells.[17] This process also represents a potential link to the pathology of pSS, as upregulation of TLRs has been observed in both mouse models and humans.[45] It is therefore reasonable to assume that the uptake of oxLDL via TLRs is increased in the context of pSS. In addition, macrophages also promote the development of atherosclerosis through oxidative stress by releasing reactive oxygen species (ROS) stimulates the formation of oxLDL, which in turn increases lipid accumulation and foam cell formation. Interestingly, neutrophils from patients with pSS showed significantly increased ROS production compared with neutrophils from healthy subjects.[46] Again, this is a connection to the pathology of pSS, as several studies have shown increased oxidative stress in pSS.[25]

Another interface between the pathogenesis of pSS and atherosclerosis is the IFN-1 pathway. IFN-alpha upregulation has been reported in lip biopsies and peripheral blood cells, as well as in blood plasma of patients with pSS.[46 47] The proinflammatory environment as a consequence of enhanced type I IFN signalling may be involved in the pathogenesis of pSS-associated atherosclerosis.[17]

These observations suggest numerous molecular interfaces between the pathology of pSS and that of atherosclerosis. However, as CRFs such as hypertension or dyslipidaemia also tend to have a higher prevalence in patients with pSS, it is difficult to distinguish the exact contribution of the traditional CRFs to the development and progression of atherosclerosis from that of molecular autoimmune and inflammatory processes.

OxLDL antibodies

The role of oxLDL in the context of autoimmune diseases, such as pSS, is particularly controversial and has not been extensively studied. Cinoku *et al* revealed that patients with pSS had significantly lower oxLDL ab levels than healthy controls. However, with 63 patients, they were less than one-third the size of our cohort.[48] Within this pSS cohort, those with higher oxLDL ab levels had an increased disease activity index, higher SSA/Ro ab levels and lower plaque rates.[48] We confirmed these observations with regard to the ESSDAI Score, SSA/Ro antibodies in our sample.

These findings suggest a protective role for oxLDL ab regarding the extent of plaque, although the underlying molecular mechanisms are poorly understood.

There are several approaches to elucidate the protective function of oxLDL ab. One possible explanation is that oxLDL ab help to clear oxLDL by forming immune complexes.[49] Another hypothesis suggests antibody consumption in plaque as a reason for lower antibody levels in patients with pSS with plaque formation.[50] A study in mice indicates that oxLDL ab may block oxLDL uptake by macrophages, resulting in less foam cell formation and thus suppressing the progression of atherosclerosis.[51] Although the exact mechanisms are unclear, the presumed protective role of oxLDL ab has been demonstrated in animal models,[51] healthy humans[29] and several diseases such as RA[52] and coronary heart disease.[49]

Considering the common B-cell hyperactivity in pSS, we developed the hypothesis that increased B-cell activity could lead to increased production of oxLDL ab. The potential protective effect in terms of antibody consumption suggested by some studies may be superimposed on this increased production.[49 50] This is consistent with our finding that higher disease activity (ESSDAI), and correspondingly greater B-cell overactivity, are associated with higher oxLDL-ab levels. This theory needs to be evaluated by further studies with larger cohorts.

As the exact molecular mechanisms remain unclear, we cannot clearly attribute protective functions to oxLDL ab and underline once again the need for further large-scale studies.

Individual CVR stratification

Considering the results of our study and previous studies showing an increased risk of CVD in this patient group,[9 11 38] it is clear that clinicians need to pay more attention to CVR stratification in patients with pSS. At the same time, however, a disease-specific risk stratification, such as Adjusted Global Anti-Phospholipid Syndrome Score for antiphospholipid syndrome, is still missing.[53] Whether by using an independent score or for example by modifying the QRISK3 Score, a CVR assessment is needed for each patient with pSS.[53] In this way, we aim to identify those patients at particularly high CVR.

Strengths and limitations

Our study offers a clearly described and large patient cohort with well-defined organ manifestations followed in a prospective study design, as well as strictly matched controls. We were also the first to analyse distinct subgroups and thereby identify further aggravating risk factors, especially the OI.

Contrary to previous studies on this issue, our cohort includes a high number of patients with organ manifestations, including an over-represented male proportion (n=38/199) and a large number of patients with polyneuropathy (n=74/199) compared with the proportion in the total population. The differences especially in biomarker status have been published before, showing

less prevalence of Ro Ab and ANA titre.[54] This circumstance is due to the university medicine selection bias and could lead to an overestimation of the real effect of vascular damage and premature atherosclerosis for the total population of patients with pSS. With regard to this, we aimed to compare the pSS subgroups with the control cohort.

Another limitation is due to our study design: With the cross-sectional design, no follow-up assessment is possible and the effects of any drugs, such as HCQ, can only be sparsely assessed. In addition, differences in the use of glucocorticoids were not taken into consideration, so their possible effect on vascular lesions and CVR was not directly addressed. 96% of patients with pSS received glucocorticoids during their clinical course. This was particularly the case for patients with pSS with organ manifestations, such as interstitial lung disease. As the duration, dose of glucocorticoids and documentation of prednisolone prescription varied widely, we could not take this into account for the analysis. Further, longitudinal studies are needed to analyse whether glucocorticoids play a significant role in the development of subclinical atherosclerosis.

Finally, our findings strongly support the need for further longitudinal prospective studies to analyse whether particularly high-risk patients may benefit from antiplatelet therapy with low-dose acetylsalicylic acid, HMG-CoA reductase inhibitors or Doppler ultrasound screening. In addition, clinicians need to assess and treat traditional CRFs, and it remains to be investigated whether cardiovascular treatment targets for patients should be more stringent. Based on our results, patients with pSS with OI are likely to be the subgroup that benefits most from preventive strategies.

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Contributors Study design and concept: NZ, DE and KS. Methodology: NZ, SB, DE, KS and AAD. Formal analysis and investigation: NZ, SB, MA, CLZ, SB, EK, TS, GS, VG and GA. Writing—original draft preparation: NZ and MA. Writing—review and editing: NZ, MA, SB, KS, AAD, VG, TW and DE.

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Competing interests Novartis did not contribute to the study design, analyses or data interpretation. The oxLDL antibody analyses were performed as a commissioned service by Immundiagnostik AG, Bensheim, Germany, under the direction of Dr Franz Paul Armbruster, without further information on the samples. Immundiagnostik AG therefore had no influence on the analyses or the interpretation of the data.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of Medical University Hannover approval (8179_BO_S_2018). Participants gave informed consent to participate in the study before taking part.

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