CHRONIC RHEUMATIC INFLAMMATORY CONDITIONS AND CARDIOVASCULAR HEALTH

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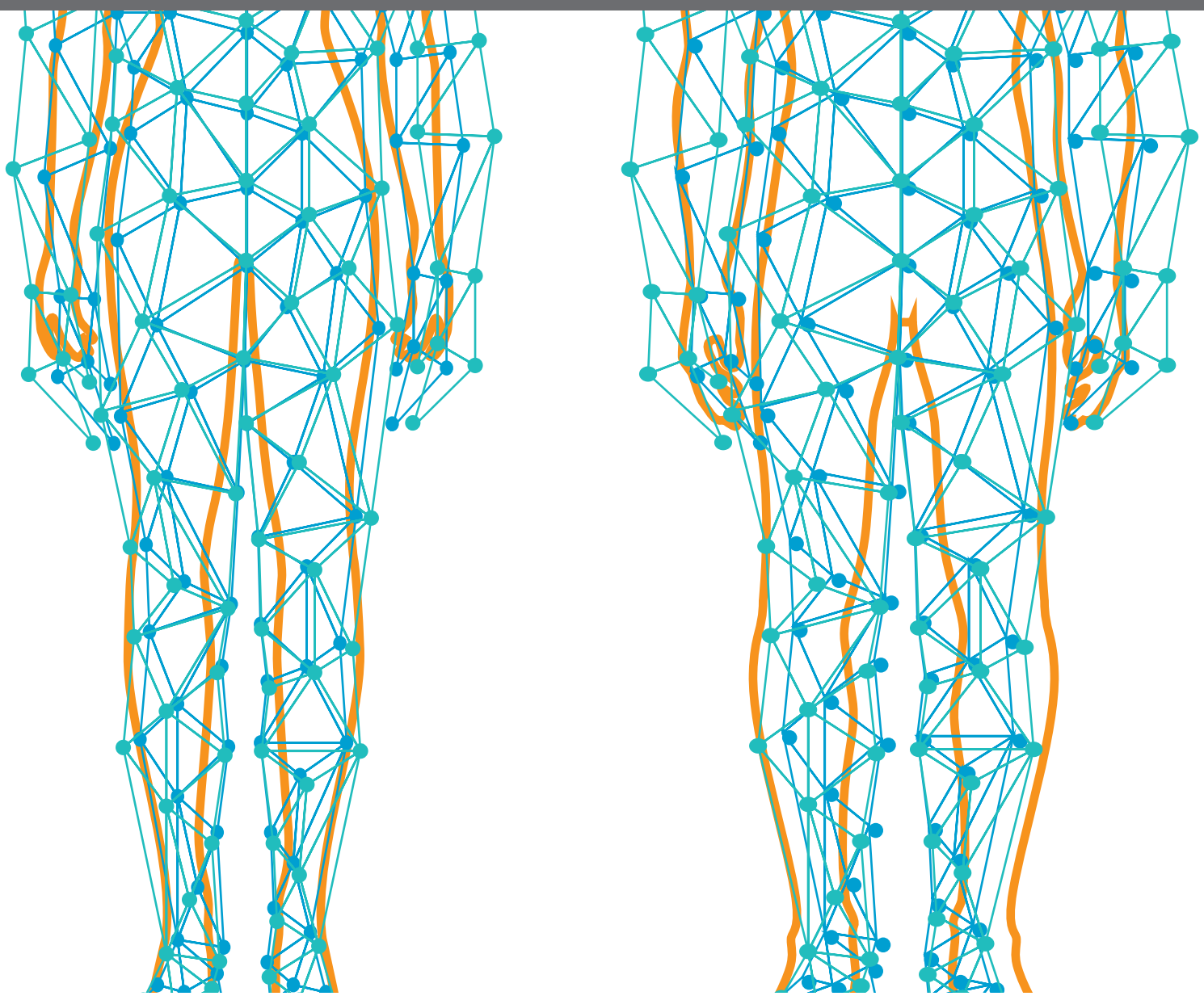

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CHRONIC RHEUMATIC INFLAMMATORY CONDITIONS AND CARDIOVASCULAR HEALTH

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Editorial: Chronic rheumatic inflammatory conditions and cardiovascular health

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Editorial on the Research Topic
Chronic rheumatic inflammatory conditions and cardiovascular health

Patients with chronic inflammatory rheumatic diseases (IRD), such as systemic lupus erythematosus (SLE), chronic arthritis and vasculitis, have a higher risk of developing premature cardiovascular disease (CVD) (1, 2). The multifactorial characteristic of this condition is thought to result from an interaction of inflammation, metabolic factors, therapy- and disease-related factor. Standardized mortality ratios in patients with IRD are higher than those in the general population (3); this increased and commonly premature mortality is mainly due to cardiovascular events (CV). Interestingly, this increased risk of CVD in rheumatoid arthritis (RA) is comparable to that observed in type 2 diabetes mellitus (4). Dampening disease activity has been associated with reduction in the CV mortality of patients with IRD; furthermore treatment with anti TNF or DMARDs seem to reduce CV events (5). European League Against Rheumatism's (EULAR) evidence-based recommendations for CV risk management in patients with RA and other forms of IRD strongly support the use of algorithms to stratify the CV risk of patients with inflammatory arthritis. Briefly, to avoid the underestimation of CV risk, the EULAR task force recommends a 1.5 multiplication factor in patients with RA who meet two of the three following criteria: disease duration longer than 10 years, presence of rheumatoid factor or anti-CCP antibodies, and extra-articular manifestations (6). Taking together these observations, with this special issue the impact on cardiovascular health was assessed in the management of patients with several rheumatic conditions including chronic arthritis, connective tissue disease and vasculitis.

A systematic review on arterial stiffness in vasculitis was conducted, particularly focusing on ANCA vasculitis, Behcet disease and Takayasu Arteritis; vascular properties impairment, as measured by Pulse wave velocity, is reported in most subtypes of vasculitis, underlining the importance of an effective—and early—treatment of conventional CV risk factors, and calling for additional investigation on further ways to mitigate the risk excess (Lo Gullo et al.).

Skoog et al. reported that the examination—through an extended ultrasound protocol—of brachiocephalic and common carotid arteries can provide a very high diagnostic sensitivity in patients with suspected giant cell arteritis without affecting the specificity when temporal and axillary findings are indecisive. Kuret et al. investigated some markers potentially helpful in predicting giant cell arteritis relapses suggesting that IL-23 might be a promising biomarker of uncontrolled and active disease and could give early indication of upcoming relapses.

An update about cardiovascular risk in arthritis was also provided. Argnani et al. in a big Italian study reported that RA patients had higher incidence of atrial fibrillation (incidence rate ratio, IRR 1.28), heart failure (IRR 1.53), stroke (IRR 1.19), and myocardial infarction compared to controls . On the other hand, as reported by Schirmer, patients with spondyloarthritis, psoriatic arthritis and rheumatoid arthritis have a prevalence of CVD that is 8.7, 12.8, and 18.7% respectively (Yagensky and Schirmer). Degboè et al. reported a higher prevalence of cardiovascular risk factors (CVRs), as well as a higher prevalence of major adverse cardiovascular events in PsA compared to the general population. The CVR is higher in the PsA population than in the controls either using SCORE and QRISK2 equations or using SCORE- PsA and QRISK2-PsA equations. Hupin et al. investigated the autonomic function in RA, and in particular the parasympathetic tone, using the heart rate recovery (HRR), which improved after 1 and 2 year by guided physical activity. As regards physical activity, Garcia et al. describes the beneficial effect of personalized training program to improve aerobic activity and glycated hemoglobin in Sjogren Syndrome. Svensson et al. found impaired microcirculation in systemic lupus erythematosus as reflected by peak oxygen saturation even in the younger ages, and higher Augmentation index as compared to controls. Young people with childhood-onset rheumatic disease is known to have increased risk of CVD and Ciurtin et al. in a review describe some potential ways to improve cardiovascular safety in this population; Mondal et al., instead, describe different aspects of cardiac dysfunction in Juvenile dermatomyositis. As regards therapeutic and drug-related issues, the effects of ketogenic diet on CV outcomes in arthritis are reviewed by Ciaffi et al., reporting a favorable effect specially in RA. Soòs et al. analyzed a possible effect of anti TNF on CV system; they found that anti-TNF treatment may increase ACE and ACE2 in the sera of RA and Ankylosing spondylitis patients and may be associated with disease duration, markers of inflammation and vascular pathophysiology. Toussirot et al. describe the CV risk in spondyloarthritis with highlights on the use of bDMARDs (TNF and probably IL-17i) and specific treatment strategies, as favorable impact on CV risk and disease prognosis.

Sonographic crystal deposits and subclinical inflammation were observed in a study performed by Calabuig et al. in patients with intercritical gout; tophi and a positive Power Doppler signal were linked to carotid atherosclerosis, while the association between hyperuricemia/gout and an increased CVD risk was described by Zhu et al. in a big cohort of patients with long follow up. On the other hand, in a meta-analysis (Zhang et al.) suggests that neither allopurinol nor febuxostat significantly modify—increasing or reducing—the risk of major adverse cardiovascular events in hyperuricemic patients with or without gout.

This special issue aimed to provide an up-to-date state of the art of this constantly evolving picture.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Cardiovascular Safety of Febuxostat and Allopurinol in Hyperuricemic Patients With or Without Gout: A Network Meta-Analysis

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Background: Hyperuricemia is a common metabolic disease and has become a public health problem because of its increasing prevalence and association with comorbidities. Allopurinol and febuxostat are recommended as the first-line treatments for hyperuricemia and gout. But cardiovascular safety between febuxostat and allopurinol is still controversial. The purpose of this study is to compare the cardiovascular safety of XOIs and placebo in hyperuricemic patients with or without gout.

Methods: PubMed, Embase via OVID, Cochrane Library, CNKI, Wanfang, and VIP were searched from their earliest records to February 8th 2021. ClinicalTrials.gov was also searched for unpublished data. The reference lists of included studies and relevant review articles investigating the cardiovascular safety of XOIs in hyperuricemia patients are screened for potentially eligible studies. Randomized controlled trials (RCTs) evaluating allopurinol (100∼900 mg/d), febuxostat (20∼120 mg/d), or placebo for hyperuricemia were included. The outcomes were incidence of MACE, non-fatal MI, non-fatal stroke, and cardiovascular death. We conducted a Bayesian random-effects network meta-analysis on the included randomized controlled trials using the Markov Chain Monte Carlo simulation method. The grading of recommendations assessment, development, and evaluation (GRADE) approach was used to assesses the certainty of the evidence.

Results: Ten RCTs with 18,004 participants were included. The network estimates showed that there was no significant difference observed among febuxostat, allopurinol, and placebo regarding outcomes. The certainty of the evidence ranged from very low to moderate. The probabilities of rankings and SUCRA showed that compared to placebo, febuxostat, and allopurinol might prevent adverse cardiovascular events.

Conclusion: Febuxostat is not associated with increasing risk of adverse cardiovascular events compared to allopurinol; and compared to placebo, whether febuxostat and allopurinol reduce the risk of adverse cardiovascular events remains uncertain.

Keywords: febuxostat, allopurinol, hyperuricemia, network meta-analysis, cardiovascular safety, Bayesian framework

INTRODUCTION

Hyperuricemia is a metabolic disease caused by disorders in purine metabolism or reduced uric acid excretion and develops into gout with prolonged elevation of serum urate (1). Hyperuricemia is "traditional risk factor" for cardiovascular diseases with hyperlipidemia, hypertension, and diabetes (2–5). However, the causation between hyperuricemia and cardiovascular diseases remains debated (6). Although this causation was suggested by a recent Mendenlian randomization study (7), cohort studies showed a U-shaped association between sUA (serum uric acid) and the incidence of cardiovascular diseases (8). This means that both elevated and very low levels of sUA can be linked to cardiovascular risk.

To prevent gout flares and other comorbidities, urate-lowering drugs are commonly used for patients with hyperuricemia (9). There are three main categories of urate-lowering drugs: xanthine oxidase inhibitors (XOIs) (e.g., allopurinol and febuxostat), uricosurics (e.g., probenecid, benzbromarone, and lesinurad), and recombinant uricase (e.g., pegloticase). In many countries, allopurinol and febuxostat are recommended as the first-line treatments for hyperuricemia and gout (10–12). Febuxostat is often considered more effective in urate-lowering than allopurinol, and febuxostat used for patients with renal dysfunction (30 ml/min < GFR < 89 ml/min) does not require dose adjustment (13–15). However, it remains unclear whether urate-lowering drugs may improve long-term cardiovascular outcomes. A recent trial linked long-term febuxostat to a mildly increased risk of cardiovascular death (16), when the results were not validated in another large trial (17). In this systematic review, we focus on the cardiovascular outcomes of XOIs (e.g., allopurinol and febuxostat) for hyperuricemic patients using a network meta-analysis.

METHODS

We conducted this study in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist for network meta-analyses (18). This network meta-analysis was registered on International Prospective Register of Systematic Review (PROSPERO, CRD42021244788).

Literature Search and Eligible Criteria

We comprehensively searched the PubMed, Embase via OVID, Cochrane Library, CNKI (China National Knowledge Infrastructure), Wanfang, and VIP electronic databases to identify relevant studies published until February 8th, 2020. ClinicalTrials.gov was also searched for unpublished data. The reference lists of included studies and relevant review articles investigating the cardiovascular safety of XOIs in hyperuricemia patients are screened for potentially eligible studies. Based on the PICOS (Participants, Intervention, Comparison, Outcome, and Study design) framework, the key terms searched in this study were hyperuricemia, drug therapy, febuxostat, allopurinol, and randomized controlled trial.

The inclusion criteria were as follows: (a) Participants: adult patients (>18 years) with a diagnosis of hyperuricemia with or without gout. (b) Interventions/comparisons: febuxostat, allopurinol or placebo. (c) Outcomes: major adverse cardiovascular events (MACE; composite endpoint of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death), nonfatal myocardial infarction (MI), nonfatal stroke and cardiovascular death. (d) Study design: randomized controlled trials of 4 weeks or more of treatment and follow-up duration. The exclusion criteria were as follows: (a) acute gout or secondary gout, (b) animal experiments, (c) poor-quality studies (random sequence generation, allocation concealment, and blinding approaches are all assessed as high risk based on the Cochrane bias risk tool), (d) patients with moderate or severe hepatic impairment (value, ascites, lower limb edema, icterus, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× reference or increased prothrombin time >2× reference value), severe renal impairment (eGFR <15 mL/min), or advanced cancer, and (e) studies published in a language other than Chinese or English.

Screening Process, Data Extraction, and Risk of Bias

Two authors (SZ, TX) independently screened titles and abstracts based on the inclusion and exclusion criteria identified in section Literature Search and Eligible Criteria. Studies identified as potentially relevant were then checked via full-text review. This screening process continued until all remaining literature was checked. Discrepancies were resolved by discussion between these two researchers and, if necessary, by consulting the third member (NS) of our team.

Two reviewers (SZ, TX) independently extracted individual study data and entered them into an electronic database. Discrepancies were resolved through discussion with a third reviewer (NS). These study data included the first author's name, publication year, interventions/comparisons, outcomes, durations, and baseline characteristics of patients including sex and age. We used Intention-to-treat sample sizes when available.

Two members (SZ, TX) of the research team used the Cochrane bias risk tool by RevMan version 5.4 to independently assess the risk of bias of all included studies (19). Any discrepancies were resolved by discussion with a third reviewer (NS).

Treatment Nodes

Treatment nodes were grouped by drugs. Only the common dose of each drug was eligible. Considering the different recommended doses of drugs in different countries, the common dose was defined as 20–120 mg/d for febuxostat, and 100–900 mg/d for allopurinol. We drew network plots with the *multinma* package in R (version 4.0.3) (20).

Statistical Analysis

We conducted a network meta-analysis of randomized controlled trials that assessed the cardiovascular safety of febuxostat and allopurinol using a random-effects model and consistency model. This analysis was estimated in a Bayesian framework (21). Odds

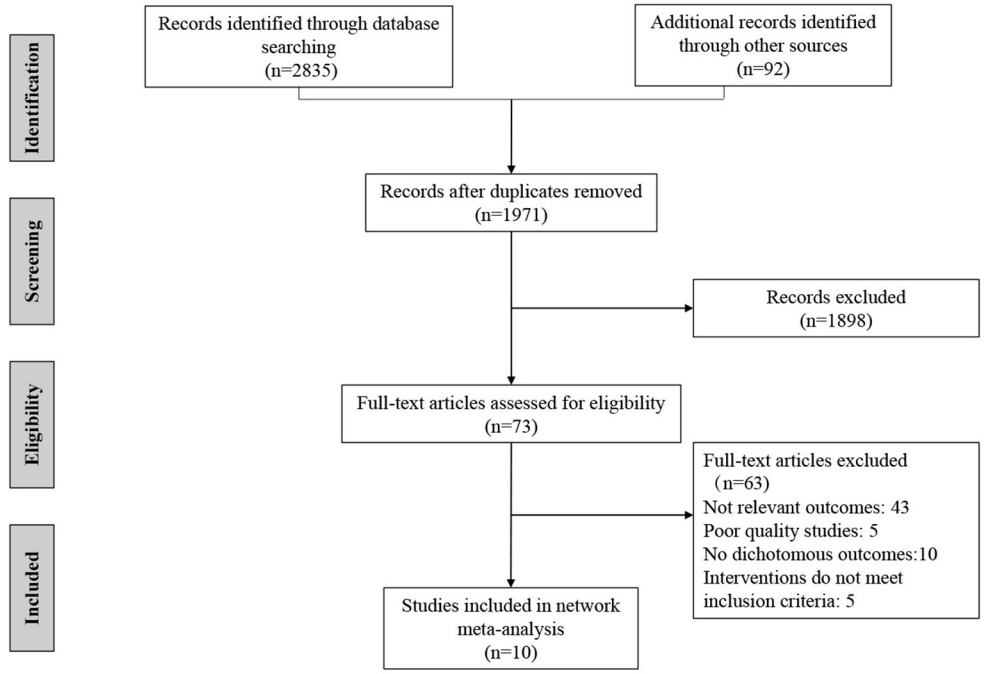

FIGURE 1 | Flow diagram of literature search and selection.

ratios (ORs) and 95% credible intervals (CIs) were used to report the effect size for assessing cardiovascular safety. We used the Markov chain Monte Carlo method (22), built up four chains, and set 160,000 iterations after an initial burn-in of 40,000 and a thinning of one. We assessed local incoherence and obtained indirect estimates by node splitting models (23). We calculated the probabilities of the surface under the cumulative ranking curve (SUCRA) to rank treatments (24). We performed sensitivity analysis by excluding trials without double blinding.

In this analysis, $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using the *gemtc* package in R (Version 4.0.3) (25).

The Certainty of Evidence

The certainty of evidence was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for network meta-analysis (26–28). Two members of the research team assessed the certainty for each comparison as high, moderate, low, or very low, based on consideration of the risk of bias, incoherence, inconsistency, indirectness, intransitivity, publication bias, and imprecision. Discrepancies were resolved by discussions.

RESULTS

Characteristics of Eligible Studies

After screening 1,971 citations and 73 full texts, 10 randomized controlled trials met the inclusion criteria in our systematic review (**Figure 1**). The included trials were conducted in 4 countries or regions (USA, Canada, Japan, and Europe), and most of trials were registered (9/10, 90%), all of which were published in English. Among the included studies, seven were two-arm studies and three were three-arm studies. **Table 1** presents the baseline characteristics of the included studies (16, 17, 29–36). The mean age of the participants was ranged from 50 to 76 years old, and the proportion of males ranged from 69% to 97%. Six trials assessed all four outcomes, two trials assessed three outcomes, and two trials assessed two outcomes. The length of follow-up ranged from 24 to 312 weeks.

Risk of Bias of Included Studies

The assessment of the risk of bias of the included studies is presented in **Supplementary Figure 2**. Three studies had high risk in the domain of blinding of participants and outcome assessment (16, 29, 31). All other included studies were evaluated at low risk of bias in all domains.

Results of Network Meta-analysis

The network plots of each outcome are presented in **Figure 2**. **Figure 3** presents the results of our network meta-analysis and the certainty of evidence for all network estimates. Detailed results of the network meta-analysis and the certainty of evidence for all comparisons and outcomes are presented in the **Supplementary Table 3**. Detailed results of node split analysis are provided in the **Supplementary Figure 3**. The results of the sensitivity analysis are presented in the **Supplementary Table 5**.

MACE

Ten randomized controlled trials including 18,004 subjects reported the incidence of MACE. The intervention nodes

TABLE 1 | Characteristics baseline of randomized controlled trials.

Study ID	Register number/trial name	Location	No. of patients	*N*	Intervention	Age	Male (%)	Outcomes	Length of follow-up (weeks)
White et al. (16)	NCT01101035	USA	7,190	3,098	Febuxostat 40~80 mg/day	64.3 ± 9.6	84.1%	①②③④	312
				3,092	Allopurinol 300~600 mg/day	64.7 ± 9.6	83.8%		
Mackenzie et al. (17)	EudraCT 2011-001883-23	Europe	6,128	3,063	Febuxostat 80~120 mg/day	71.0 ± 6.4	85.5%	①②③④	312
				3,065	Allopurinol 100~900 mg/day	70.9 ± 6.5	85.0%		
Tanaka et al. (29)	UMIN0000112911	Japan	483	239	Febuxostat 10~40 mg/day	69.1 ± 10.1	79.5%	①②③④	104
				244	Placebo	69.1 ± 10.7	81.1%		
Becker et al. (30)	FACT	USA, Canada	760	256	Febuxostat 80 mg/day	51.8 ± 11.7	95.0%	①④	52
				251	Febuxostat 120 mg/day	52.0 ± 12.1	97.0%		
				253	Allopurinol 300 mg/day	51.6 ± 12.6	96.0%		
Kojima et al. (31)	NCT01984749	Japan	1,070	537	Febuxostat 10~40 mg/day	75.4 ± 6.7	69.1%	①②③④	156
				533	Allopurinol 100~900 mg/day	76.0 ± 6.5	69.0%		
Kimura et al. (32)	UMIN000008343	Japan	441	219	Febuxostat 10~40 mg/day	65.3 ± 11.8	77.6%	①②③	108
				222	Placebo	65.4 ± 12.3	77.0%		
Dalbeth et al. (33)	NCT010783	USA	314	157	Febuxostat 40 mg/day	51.4 ± 12.4	91.1%	①②④	104
				157	Placebo	50.1 ± 11.7	92.4%		
Saag et al. (34)	NCT01082640	USA	96	32	Febuxostat 30 mg BID	67.3 ± 11.11	78.1%	①②③④	52
				32	Febuxostat 40~80 mg QD	63.6 ± 8.15	81.3%		
				32	Placebo	66.3 ± 12.05	81.3%		
Givertz et al. (35)	NCT00987415	USA	253	128	Allopurinol 100~600 mg/day	63.7 ± 15.0	86.0%	①④	24
				125	Placebo	62 ± 14.25	78.0%		
Becker et al. (36)	NCT00430248	USA	2269	757	Febuxostat 40 mg/day	52.5 ± 11.68	95.4%	①②③④	26
				756	Febuxostat 80 mg/day	53.0 ± 11.79	93.9%		
				756	Allopurinol 200~300 mg/day	52.9 ± 11.73	93.8%		

①, MACE (composite endpoints of non-fatal MI, no-fatal stroke or cardiovascular death); ②, non-fatal MI (myocardial infarction); ③, non-fatal stroke; ④, cardiovascular death.

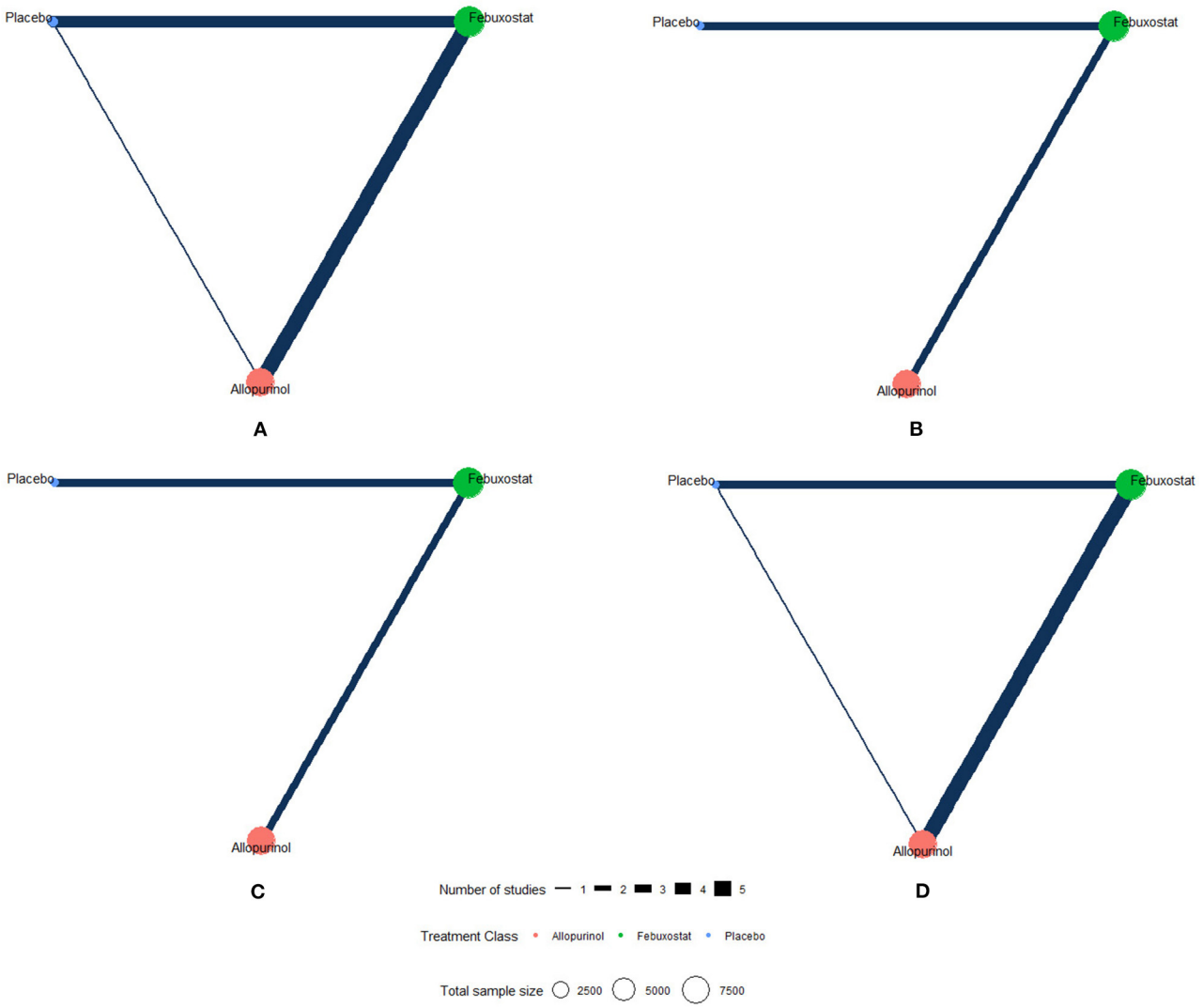

FIGURE 2 | Network plots of each outcome. The network of eligible studies for different outcomes. Different color of nodes represents different treatment. The node sizes correspond to the number of participants that investigated the treatments. The thickness of edges represents the number of trials. A lack of line indicates that there were no head-to-head trials between two treatments for this outcome. **(A)** MACE (major adverse cardiovascular events), **(B)** non-fatal MI (myocardial infarction), **(C)** non-fatal stroke, and **(D)** cardiovascular death.

included in this network meta-analysis were allopurinol, febuxostat, and placebo. There were no significant differences in either pairwise or network estimates. The certainty of evidence was moderate for all comparisons.

The global I^2 of pairwise was 10.7% and the global I^2 of consistency model was 0%. The node split analysis showed that the results were consistent. The results of sensitivity analysis were mostly similar to the results of main analysis.

Non-fatal MI

Eight randomized controlled trials including 16 991 subjects reported the incidence of non-fatal MI. The intervention nodes included were allopurinol, febuxostat, and placebo. There were no significant differences in either pairwise or network estimates. The certainty of the evidence was moderate for febuxostat compared with allopurinol, placebo compared with febuxostat, and very low for placebo compared with allopurinol.

The global I^2 of pairwise was 0% and the global I^2 of consistency model was 0%. There was no node split analysis of this outcome due to no loop. The results of sensitivity analysis were similar to the results of main analysis.

Non-fatal Stroke

Seven randomized controlled trials including 16 677 subjects reported incidence of non-fatal stroke. The intervention nodes included were allopurinol, febuxostat and placebo. There were no significant differences in either pairwise or network estimates. The certainty of the evidence was moderate for febuxostat

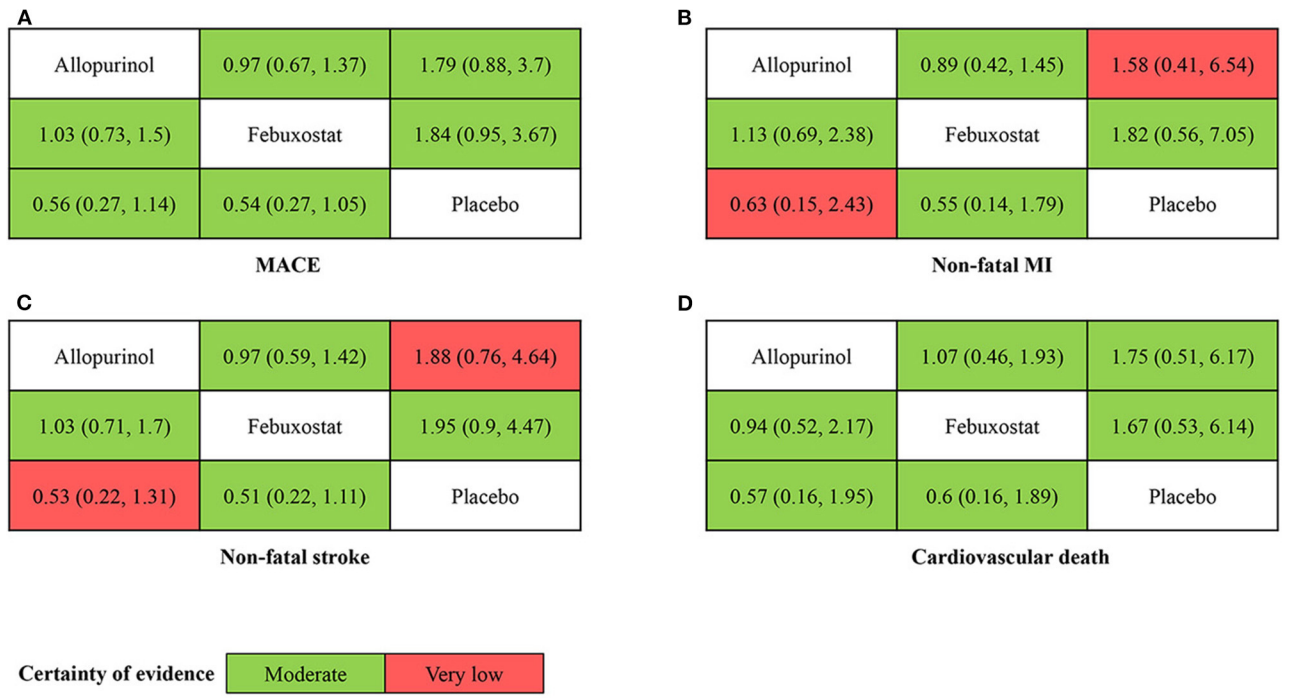

FIGURE 3 | League table of each outcome. Each number is an odds ratio (=column/row), and 95% confidence interval. Different color represents different certainty of evidence. OR < 1 favors the drug in the column. **(A)** MACE (major adverse cardiovascular events), **(B)** non-fatal MI (myocardial infarction), **(C)** non-fatal stroke, and **(D)** cardiovascular death.

compared with allopurinol, placebo compared with febuxostat, and very low for placebo compared with allopurinol.

The global I^2 of pairwise was 3.9% and the global I^2 of consistency model was 3.9%. There was no node split analysis of this outcome due to no loop. The results of sensitivity analysis were similar to the results of main analysis.

Cardiovascular Death

Nine randomized controlled trials including 17,563 subjects reported incidence of cardiovascular death. The intervention nodes included were allopurinol, febuxostat, and placebo. There were no significant differences in either pairwise or network estimates. The certainty of the evidence was moderate for all comparisons.

The global I^2 of pairwise was 23.6% and the global I^2 of consistency model was 13.7%. There was no node split analysis of this outcome due to no loop. The results of sensitivity analysis were similar to the results of main analysis.

Rankings and SUCRA

The rank probabilities of febuxostat, allopurinol, and placebo is shown in **Figure 4**, rank-heat plot based on SUCRA is presented in **Figure 5**. Detailed data is shown in **Supplementary Table 4**. According to **Figures 4**, **5**, The differences of rank probabilities and SUCRA values between febuxostat and allopurinol are not significant; although network estimates showed no significant differences, the rank probabilities and SUCRA values of febuxostat and allopurinol display marked difference over placebo.

DISCUSSION

This network meta-analysis provides an overview of the evidence regarding the cardiovascular safety of febuxostat and allopurinol in people living with hyperuricemia. This result indicated that neither allopurinol nor febuxostat needs a concern of cardiovascular safety with very low to moderate certainty. Additionally, neither drug improves cardiovascular outcomes in people with hyperuricemia.

After FDA issued a boxed warning on febuxostat (37), more and more clinical trials have been devoted to focus on the cardiovascular safety of XOIs (17, 38–42). However, the conclusions of these trials were not unanimous. Until now, therefore, it remains unclear whether XOIs increase the risk of adverse cardiovascular events. The results of our network meta-analysis can provide reference for clinicians to treat patients with hyperuricemia using XOIs in terms of cardiovascular safety. To the best of our knowledge, this is the first Bayesian network meta-analysis of febuxostat, allopurinol, and placebo investigating cardiovascular outcomes as the primary outcomes. Before our studies, several systematic reviews were conducted to evaluate urate-lowering drugs in terms of cardiovascular safety. Two systematic reviews and meta-analyses that focused only on composite endpoints found

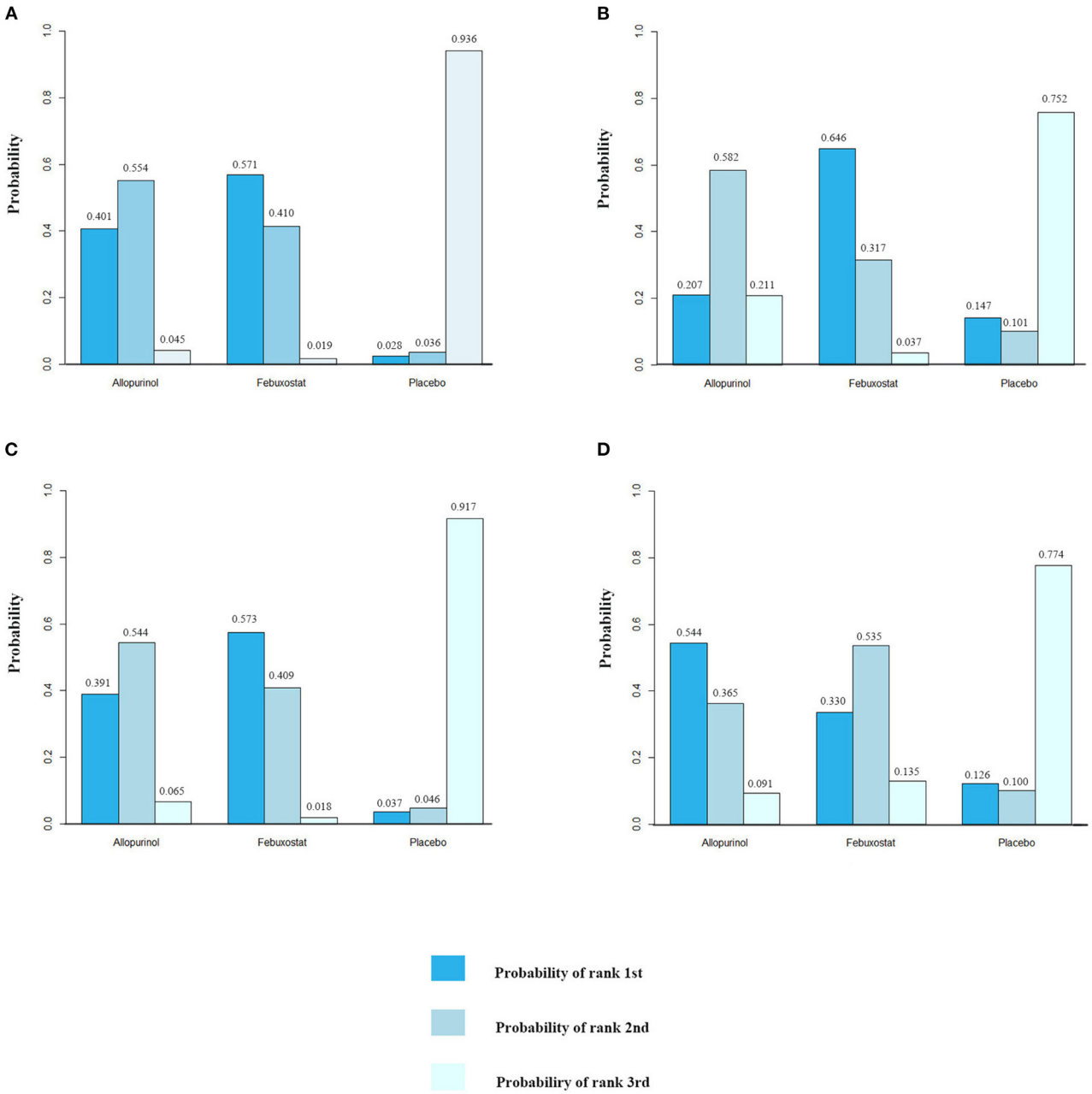

FIGURE 4 | Rank diagram of febuxostat, allopurinol, and placebo for different outcomes. The numbers on the vertical axis represent the probability. **(A)** MACE (major adverse cardiovascular events), **(B)** non-fatal MI (myocardial infarction), **(C)** non-fatal stroke, and **(D)** cardiovascular death.

that XOIs did not significantly reduce the risk of MACE (43, 44). This conclusion is consistent with our network estimates. Another systematic review and meta-analysis revealed that urate-lowering treatments might increase cardiovascular mortality (45), which included nonrandomized and retrospective studies, and that may be the reason why the conclusion of this study is different from ours. Although previous evidences suggested a significant benefit from allopurinol intake in increasing flow-mediated dilation in humans (46, 47), the results of our network meta-analysis did not indicate this cardiovascular benefit of allopurinol for patients with hyperuricemia. Actually, whether patients with asymptomatic hyperuricemia should be treated with urate lowering drugs remains controversial. Some guidelines recommended that urate lowering drugs should be used for asymptomatic hyperuricemia (9, 48), whereas others suggested that the benefits of urate lowering drugs would not overweigh the treatment costs or potential risks (14, 49). The results of our network meta-analysis indicated that for patients with

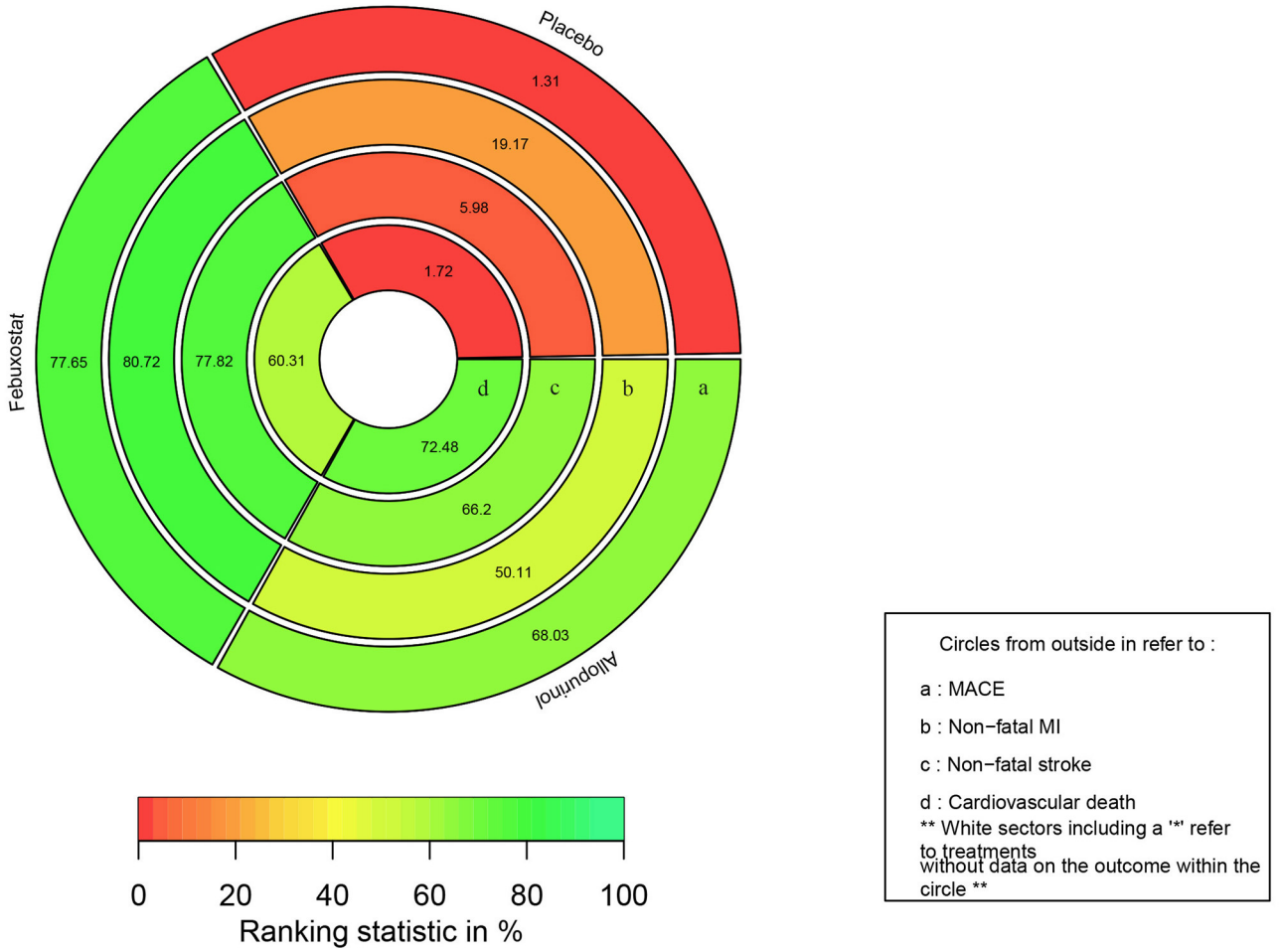

FIGURE 5 | Rank-heat plot based on SUCRA. Each sector is colored according to the SUCRA (Surface under the cumulative ranking) value of the corresponding treatment and outcome. The scale consists of the transformation of three colors: red (0%), yellow (50%), and green (100%), and each color is associated with a different evaluating indicator. MACE, major adverse cardiovascular events; MI, myocardial infarction.

hyperuricemia, XOIs did not increase the risk of adverse cardiovascular events.

The debates of CARES and FAST introduced heterogeneity in our study (16, 17). The reasons for the difference between the two results may be as follows: first, the baseline characteristics of the two trials were different, including the proportion of patients with established cardiovascular disease at baseline, the severity of cardiovascular disease, the severity of gout, and the proportion of patients with established urate lowering therapy. These differences at baseline might lead to different cardiovascular prognoses. Second, the doses of study medication were different. In CARES, doses of allopurinol were 200∼600 mg/day, and doses of febuxostat were 40∼80 mg/day. In FAST, doses of allopurinol were 100∼900 mg/day, and doses of febuxostat were 80∼120 mg/day. Although this difference reflected the different dose ranges for the two XOIs approved by regulatory agencies in North America and Europe, it is worth considering that the risk of adverse events generally increases with the increase of drug dose. Compared to FAST, lower doses of febuxostat in CARES lead to an increase in cardiovascular risk, in our opinion, therefore, the conclusion of FAST is more reliable. Third, the proportion of patients discontinued treatments, and the loss rate of follow-up of CARES was much higher than that of FAST, so the bias of CARES was greater than that of FAST, which further strengthens our view that the conclusion of FAST is more reliable. Fourth, differences in sponsors, practitioners and procedures may also lead to differences in the final conclusions.

The main limitation of our study is the limited quality of evidence. Limited quality of evidence is mainly due to imprecision which may be caused by the limited number of RCTs, resulting in the dependence on indirect comparisons of some network estimates. This problem would be resolved with the augmentation of high-quality RCTs. The second limitation is that our inclusion criteria were not highly strict so that some participants with comorbidities such as hypertension, diabetes, coronary artery diseases, and other diseases were included in our network meta-analysis. The third limitation is the short duration of some RCTs included in the present study. To obtain more

reliable results, further studies may require longer duration. But our results are still convincing due to the following reasons. First, the dosage of the drug may be adjusted according to the actual situation. Second, patients with hyperuricemia often have different comorbidities. Third, node split analysis showed consistence in outcomes and heterogeneity is low. Fourth, the results of the sensitivity analysis were mostly similar to the results of our main analysis.

CONCLUSION

This network meta-analysis suggests that neither allopurinol nor febuxostat increases or reduces the risk of major adverse cardiovascular events. However, current evidence does not support the cardiovascular benefits of XOIs. Due to the differences between large randomized controlled trials and real-world practice (50), real-world studies with long-term follow-up durations are warranted to validate the findings in our study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SZ and TX were in charge of study design, data collection and interpretation, the quality assessment of evidence, and manuscript preparation. SL critically reviewed the manuscript and provided revisions. QS, LW, and ZA were involved statistical analysis. NS was involved in data collection, data interpretation, and the quality assessment of evidence. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.698437/full#supplementary-material

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ORIGINAL RESEARCH
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Cardiovascular Effect of Physical Exercise on Primary Sjogren's Syndrome (pSS): Randomized Trial

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Objective: To evaluate the effects of an exercise program on aerobic capacity, echocardiographic parameters, metabolic profile, quality of life and safety in patients with primary Sjogren's syndrome in a randomized trial.

Methods: 60 women with pSS were evaluated from the SF-36 Short-Form Health Survey (SF-36) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) questionnaires. The participants performed ergospirometry and echocardiography; blood samples were collected to evaluate the metabolic profile. Patients were randomly divided into 2 groups: a training group that participated in the supervised training program and a control group. All variables were analyzed at baseline and after 28 weeks for both groups and we performed an intention-to-treat analysis. The training program consisted of 16 weeks of resistance exercises and, after, the exercise became aerobic. Patients and coaches were not blinded, contrary to the evaluators of all examinations/procedures and data analysts. Statistical analysis included Wilcoxon's rank sum test, chi-square test, and ANOVA test. P values < 0.05 were considered to be statistically significant.

Results: The 2 groups were homogeneous at baseline. The training group showed a significant improvement in oxygen maximum volume (VO2max) and anaerobic threshold (AT). Comparison of the training group and control group after 28 weeks showed a significant difference relating to VO2max and in AT. We did not find statistically significant diference in echocardiographic parameters, metabolic profile and in questionnaires SF-36 and ESSDAI.

Conclusions: This study showed significant improvement in aerobic capacity and glycated hemoglobin after a supervised training program in patients with pSS with safety.

Keywords: Sjogren' s syndrome, quality of life, physical activity, metabolic syndrome, subclinical cardiovascular disease

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INTRODUCTION

Primary Sjogren's syndrome (pSS) is an autoimmune disease characterized by exocrine glandular dysfunction secondary to a local inflammatory reaction (1). It predominantly affects women between the fifth and seventh decades of life, with an estimated prevalence of 0.04–0.06% worldwide (2). Since the salivary and lacrimal glands are the main sites of lymphocyte infiltration, they

account for the highest prevalence of symptoms associated with pSS, such as dry mouth and eyes (98 and 93%, respectively) (3). However, approximately one-third of pSS patients experience extra-glandular symptoms (4).

Recent studies have shown an increased cardiovascular risk (CVR) in patients with pSS. Bartoloni et al. reported that the prevalence of coronary and cerebrovascular diseases was higher in 788 female patients with pSS than in 4,774 healthy women (5). Zoller et al. followed patients with autoimmune diseases from 1987 to 2008 and found that the risk of acute myocardial infarction in patients with pSS was twice as high as that of the general population (6). A higher frequency of traditional risk factors, such as systemic arterial hypertension, diabetes mellitus (DM), and dyslipidemia (7, 8) in patients with pSS cannot explain the increased CVR observed, indicating that pSS is an independent risk factor for cardiovascular disease (6, 9).

Although the data are still scarce and inconsistent, some studies report an association between disease characteristics and increased CVR. For example, the presence of Ro/SSA autoantibodies has been shown to be associated with a diagnosis of subclinical atherosclerosis (10, 11), however, other studies have not been able to corroborate these results (5, 11). Clinical and laboratory data have also shown that parotitis and leukopenia may be associated with endothelial dysfunction and subclinical cardiovascular injury; however, to date, no other studies have confirmed these findings (12, 13).

More than 50% of pSS patients experience intense and incapacitating fatigue (14), which in turn promotes a sedentary lifestyle and increases CVR (15). Ng et al. found that the physical activity levels were 50% lower in individuals with pSS, as well as a marked reduction in moderate-to high intensity activities when compared to a control group (16). Strombeck et al. compared the aerobic capacity between pSS patients and healthy control subjects, reporting a reduction of ∼11% in the maximal oxygen consumption (VO2max or VO2peak) of the pSS group and demonstrating that cardiac function is associated with pSS (17).

Physical exercise is one of the pillars of prevention for cardiovascular events. In addition to controlling metabolic risk factors, it promotes direct cardioprotection during ischemia-reperfusion, thereby attenuating tissue death and allowing greater maintenance of cardiac function. Although the mechanisms underlying this protective response are not yet clear, it is believed that nitric oxide metabolism, antioxidant systems, and cardiac opioids are involved in the process (18).

Thus, the objective of our study was to evaluate the impact of supervised physical exercise on aerobic capacity, echocardiographic parameters, metabolic profiles, quality of life, and disease activity in patients with pSS.

MATERIALS AND METHODS

This study was approved by the Ethics Research Committee of the Federal University of São Paulo (Unifesp) (opinion 503606/2013) and registered in the Brazilian Registry of Clinical Trials (Trial RBR-3V3ZMD). All the patients signed a free and informed consent (FIC), and all the principles outlined in the Declaration of Helsinki were followed.

Eligibility Criteria

For the study, we recruited female patients between the ages of 18 and 90 years with an established diagnosis of pSS according to the 2002 American-European Consensus Group (4). The exclusion criteria included the diagnosis of secondary Sjogren's syndrome, history of cardiac and/or pulmonary diseases, an articular inflammation that prevents physical exercise, participation in a regular physical exercise regimen for more than 4 weeks in the 6 months prior to recruitment, and pregnancy.

The clinical, laboratory, and imaging examinations were performed at facilities located at the Hospital São Paulo and the Center for Studies in Psychobiology and Exercises (in Portuguese, Centro de Estudos em Psicobiologia e Exercícios—CEPE).

The patients who agreed to participate in the study and met the eligibility criteria were divided into two groups: the physical exercise group (EG) and the control group (CG). In the CG, patients followed the standard pSS visit and treatment protocol without additional intervention.

Randomization and Blinding

Prospective study participants were invited to participate in the study by the principal investigator. After the eligibility assessment, the names of the included patients were given to an individual blinded to study who was responsible for the random generation of the allocation sequence and distribution of the intervention envelopes to the participants. The blinded randomization of patients into the EG or CG groups was conducted in a 1:1 ratio using Microsoft Excel (Microsoft Corp., Redmond, VA, USA). The volunteers received opaque, closed envelopes during their first visit, and opened by the patients in the presence of the coach on the second visit. Unlike examination/procedure evaluators and data analysts, the patients and coaches were not blinded to the study.

Intervention

The groups were analyzed at baseline (T0) and after 28 weeks (T28). Under the guidance and supervision of a physiotherapist or physical education professional, the training was carried out in groups of five patients at the CEPE premises twice a week.

The program was divided into two phases. The first phase consisted of 16 weeks of resistance exercises in a 45-min circuit, and each muscle group was exercised for three sets of 12 repetitions each. In the first training session, we tested the maximal number of repetitions for each muscle group with a gradual increase technique to determine the maximum voluntary contraction (MVC), which consists of the heaviest weight the subject can shift during a complete movement without compensation. The training was individually designed to ensure that each patient performed the repetitions with 80% of the MVC. A new MVC assessment was performed every 2 weeks to make necessary adjustments. The circuit included the extensor chair (quadriceps), inclined leg press (quadriceps, hamstring muscles, gluteal muscles), horizontal leg press (calf muscles), abductor and adductor chair (abductor and adductor muscles, respectively),

direct threading (biceps), French press (triceps), lateral elevation of the upper limbs (shoulder), crucifix (pectoral muscles), and bent-over row (grand dorsal muscle).

The second phase began after week 17, at which time the patients were switched to an aerobic exercise regimen while using an ergometer (the same one used in the ergospirometric test) and an electromagnetic braking cycle (Lode Excalibur Sport, Groningen, The Netherlands) coupled to a computerized gas analyzer (Quark CPET, Cosmed, Italy). Throughout phase 2, the training intensity and duration progressively increased. At weeks 17 and 18, the load was 20 to 39% of the VO2 max for 20 min; at weeks 19, 20, and 21, the load was increased to 40 to 59% of the VO2 max for 30 min. The training duration was then increased, while maintaining the same load, to 40 min and 50 min between weeks 22 and 24 and a load of 60 to 84% of the VO2 max in the last 3 weeks of the study. The ergometric test at T0 provided data for the maximum oxygen consumption. After making the appropriate percentage calculations, the intensity (in watts) corresponding to each incremental range to be used on the bike was established. The patients were instructed to maintain their exercise rate at between 60 and 70 rotations per min (rpm) and perform a 5-min warm-up on the bike before officially starting the workout.

Subjects in the EG who did not exercise at least 75% of the planned study time, or who were absent from more than two consecutive training sessions, were excluded.

Outcome Measures

In a previous study, an average improvement of 12,5% in aerobic capacity was observed after performing aerobic exercise (19). Therefore, the primary endpoint of this study was to assess improvements of at least 15% in the patients' aerobic capacity compared to the baseline. This was accomplished by measuring the VO2 max using ergospirometry. Secondary endpoints included an intragroup assessment of the aerobic threshold (AT) and maximal heart rate through ergospirometry, echocardiographic parameters, metabolic profile, quality of life, and safety.

Variable Analysis

Ergospirometry: patients were instructed not to consume stimulant foods or perform intense physical activity in the 24 h prior to the first visit. They were also told to wear comfortable clothes and sneakers and only eat light meals up to 1 h before the examination.

After a 3-min analysis of the gases, a progressive test was started, with an intensity increase of 10 watts every minute until the subject reached the maximum voluntary exhaustion, and the patients were reminded to maintain a pedaling frequency between 60 and 70 rpm. When the maximum effort was reached, the test was interrupted, and the patient was encouraged to maintain a low speed for two min to recover and an additional minute to record the vital signs and gas data. VO2 max and AT, expressed in mL/kg/min, were calculated using a gas analyzer. The maximal heart rate, measured concomitantly with the VO2 max, was also recorded.

Clinical evaluation, metabolic profile, and questionnaires: The patients were instructed to observe a 12-h fast. They underwent a medical evaluation to collect clinical and physical examination data and completed the validated Portuguese version of the Short-Form Health Survey SF-36 (20) and the EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) (21).

Peripheral blood was collected from the patients to evaluate disease activity, glycemic metabolism (fasting glycemia and glycated hemoglobin—HbA1c), lipidemic profile (total cholesterol, HDL and LDL fractions, and triglycerides), and the presence of autoantibodies. Urine samples were also collected.

Doppler echocardiography: a Doppler echocardiography was performed for each patient by an experienced cardiologist. Parasternal images were obtained along the longitudinal axis of the patients in the left lateral decubitus position. The dimensions of the left ventricle (LV) and thickness of the posterior and septal walls were measured using standard bidimensional echocardiography in M-mode, while the left ventricle ejection fraction (LVEF) was obtained according to the modified Simpson method. Left ventricular diastolic dysfunction (LVdd) was measured using the tissue Doppler according to the diastolic myocardial velocities obtained from the mitral ring in the septal and lateral basal segments of the LV by the apical cut of the four chambers. All the procedures were performed at T0 and T28 and at a maximum of 72 h after the last EG training session.

Sample Size Estimate

A study performed by Strombeck et al. (17), in which they evaluated the aerobic capacity of pSS patients using the VO2 max, reported a mean of 28.7 mL/kg/min. Using a 90% test power and a significance level of 0.05, we estimated that 26 patients would be required to detect aerobic capacity improvements of at least 15% after the intervention.

Statistical Analyses

We performed an intention-to-treat analysis of the patients who withdrew from the study after replicating the examination and questionnaire results from T0 to T28. Data are presented using descriptive statistics (mean ± standard deviation, absolute number, and percentage). The Shapiro-Wilk test was used to verify the hypothesis of a normal distribution of the data. The analyses were performed using the R program version 3.3.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria), with a significance level of 5% ($p < 0.05$). The student's t-test was used for data with a normal distribution and the Wilcoxon test was used for data with a non-normal distribution. We used the Chi-square test to evaluate categorical variables and analysis of variance (ANOVA) to compare intergroup and intragroup variability. The effect of the intervention was verified using repeated-measures ANOVA.

RESULTS

The patients were recruited between January 2014 and June 2015 at the Hospital São Paulo/Unifesp, the Hospital do Servidor Público Estadual, and the Universidade de Santo Amaro, as well

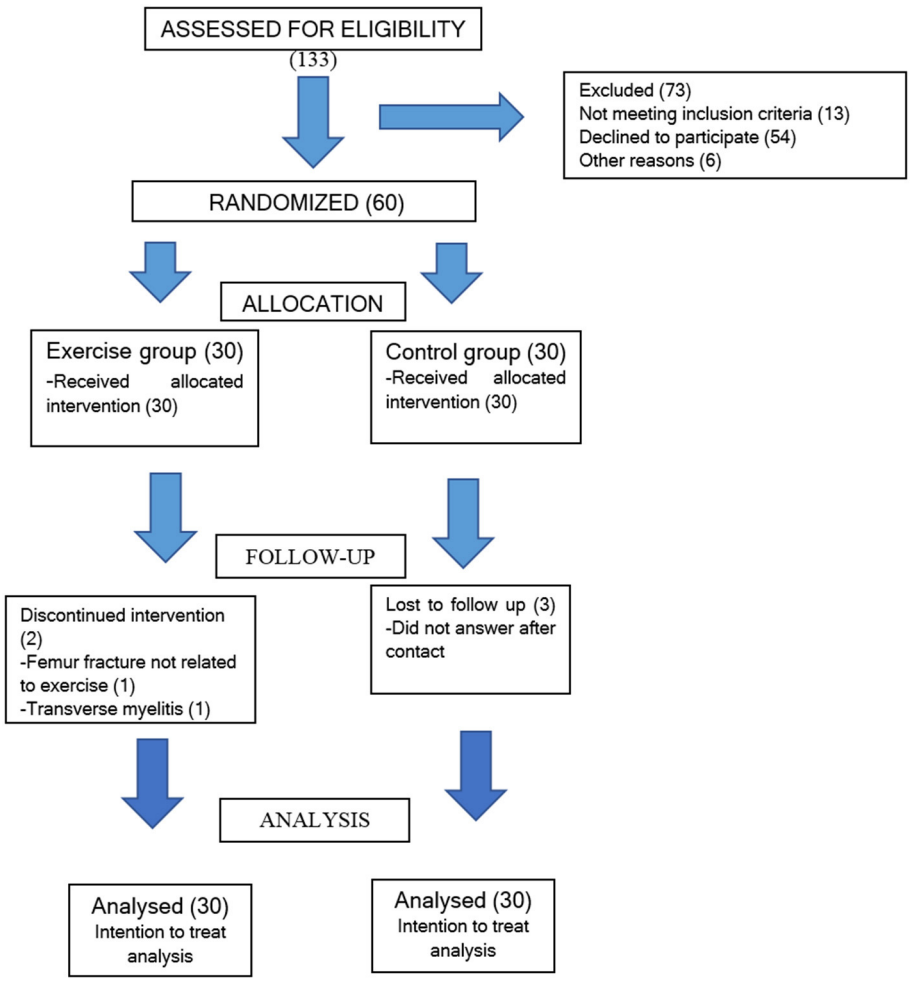

FIGURE 1 | Flow diagram of participants through each stage of the trail.

as through specific social network groups where the study was publicized (https://www.facebook.com).

The study was performed between February 2014 and February 2016. Patient recruitment is shown in **Figure 1**. Except for the ESSDAI, all data were normally distributed. Thus, the evolution of this variable was performed using Wilcoxon's non-parametric statistics.

Twenty-eight patients completed the exercise protocol, with average adherence 82% (22, 96 weeks), with minimum and maximum adherence of 78,57 (22 weeks) and 96,42% (27 weeks), respectively. Patient withdrawal from the study in the EG occurred at weeks 11 and 18, while all losses in the CG occurred at T28.

The baseline data of the groups were similar, except for the higher prevalence of antiSSB/La in the EG (17/30−56.7 vs. 8/30−26.7%, respectively, $p = 0.018$) and the greater use of corticosteroids in the CG (28/30−93.3 vs. 21/30−70%, respectively, $p = 0.02$) (**Table 1**).

Ergoespirometry

There was a significant improvement in the VO2 max of the EG between T0 and T28, with a mean value of 17.95% (±14.85). Twenty patients (66,67%) had an increase of 15%. Among the patients who completed the exercise protocol, the minimum and the maximum increase were 3,82 and 53,45%, respectively.

After 28 weeks of supervised exercise, there was a significant increase in the VO2 max, (Δ +3,31 ml/kg/min−22.95 ± 4.01 vs. 19.64 ± 3.47, $p < 0.001$) and AT (Δ +2,7 ml/kg/min−19.56 ± 3.18 vs. 16.86 ± 2.86, $p < 0.001$) in the EG. In the CG, there was a significant decrease in the VO2 max (Δ −1,76 ml/kg/min−20.20 ± 4.16 vs. 21.96 ± 5.50, p=0.028) over the 28-week period, with no other changes to the other variables (**Table 2**).

In the intergroup evaluation, there was a significant improvement in the VO2 max [$F_{(1, 58)} = 31.43$; $p < 0.001$] and the AT [$F_{(1, 58)} = 5.41$; $p < 0.001$] in the EG compared to the CG. **Figure 2** shows intragroup evaluation in CG and EG.

Metabolic Profile, Doppler Echocardiography and Questionnaires

We found no intragroup differences in either group from baseline to the end of the study (T0 vs.T28). There were also no intergroup differences in any of these parameters.

We found a small, but significant, improvement in the HbA1c in the EG between T0 and T28 (Δ −0,13%−5.88 ± 0.73 vs. 5.75 ± 0.66, $p = 0.006$). The improvement observed in the intergroup evaluation was statistically significant in the EG compared to the CG [$F_{(1, 58)} = 4.21$; $p = 0.001$].

There were no significant differences between the groups at T28 in the intragroup evaluations of the LVEF and light LVdd. Similarly, no intergroup differences were observed between the groups.

The mean ESSDAI remained stable in the CG group. We also found no significant differences between the two groups at T28.

Both groups showed significant improvements in all the domains of the SF-36 questionnaire; however, the intergroup analysis showed no relationship with the intervention.

No harm or unintended effects occurred in either group.

TABLE 1 | Clinical and demographic characteristics of the EG and CG groups at baseline.

	Control ($n = 30$)		Exercise ($n = 30$)		p
Age (years)	55.77	(10.42)	60.43	(12.20)	0.124
Disease d (years)	5.73	(4.55)	6.15	(4.20)	0.572
Symptoms d (years)	12.80	(8.62)	12.33	(7.27)	0.894
BMI	26.60	(4.11)	27.35	(4.20)	0.493
SAH	10	(33.3)	12	(40.0)	0.592
DM	5	(16.7)	3	(10.0)	0.448
DLP	5	(16.7)	11	(36.7)	0.080
Smoking					
Previous	4	(13.3)	4	(13.3)	0.601
Current	1	(3.3)	0	(0.0)	0.601
ESSDAI	3.43	(3.35)	2.47	(3.48)	0.151
VAS fatigue	6.50	(2.90)	6.93	(2.25)	0.736
ANF	22	(73.3)	23	(76.7)	0.766
RF	15	(50.0)	12	(40.0)	0.436
SSA/RO	17	(56.7)	19	(63.3)	0.598
SSB/LA	8	(26.7)	17	(56.7)	0.018
Diagnosis					
AP	13	(43.3)	10	(33.3)	0.598
Autoantibodies	17	(56.7)	19	(63.3)	0.598
Systemic Status	16	(53.3)	11	(36,7)	0.329
Drugs					
DMARD	13	(43.3)	11	(36.7)	0.268
Corticoid	28	(93.3)	21	(70.0)	0.020

Values are mean and standard deviation for continuous variables and absolute number and percentage for categorical variables. Disease d, disease duration; Symptoms d, symptoms duration; BMI, body mass index; SAH, systemic arterial hypertension; DM, diabetes mellitus; DLP, dyslipidemia; ESSDAI, EULAR Sjogren's Syndrome Disease Activity Index; AVS, analog visual scale; ANF, antinuclear factor; RF, rheumatoid factor; SSA/Ro, antiSSA/Ro antibody; SSB/La, antiSSB/La antibody AP, anatomopathological; DMARD, disease-modifying antirheumatic drugs.

DISCUSSION

Low aerobic capacity has been studied for more than two decades as an independent risk factor for cardiovascular mortality and overall mortality (22, 23). Low aerobic capacity can be objectively evaluated with an ergospirometry examination through the calculation of the VO2 max. Conversely, evidence shows that aerobic exercise helps in the treatment and control of cardiovascular risk factors such as hypertension, diabetes and obesity and can reduce the risk of cardiac events with efficacy similar to that of pharmacological treatments (24, 25).

Strombeck et al. were the first to demonstrate that women with pSS have a lower aerobic capacity than age-matched healthy controls (28.7 vs. 32.4 mL/kg/min) (16). In 2017, Dassouki et al. reported a lower aerobic capacity (22.5 ml/kg/min ± 3.5 vs. 24.6 ± 3.6), lower functionality, and higher levels of fatigue and osteoarticular pain in pSS patients than in those without pSS (26). Our study showed the aerobic capacity in pSS similar to Dassouki et al., with a mean value of 21.96 ml/kg/min ± 5.5 in the CG and 19.64 mL/kg/min ± 4.16 in the EG and with no significant differences between the groups.

We started our exercise program with 16 weeks of resistance training to increase muscular strength and functional capacity to improve aerobic training performance and decrease the occurrence of exercise-related injuries. After the 28-week program ended, we observed an increase of 17.95 ± 14.85% in the VO2 max of the EG, whereas the CG showed a significant decrease in this same parameter. We observed a significant improvement in the EG AT, considered a useful parameter for measuring training progress (27).

To date, only two studies have analyzed the effects of physical exercise on the aerobic capacity of patients with pSS. Strombeck et al. assessed nine patients for 12 weeks. Their program included walking three times a week, but only one of these sessions was supervised. The authors reported a significant improvement in the VO2max of these patients compared to the 10 healthy volunteers in the control group (19). In 2019, Miyamoto et al. followed 23 patients in a supervised walking program three times a week for 16 weeks and showed positive results in aerobic capacity compared to 22 participants in the control group (28).

Although data for other rheumatic diseases are still scarce, the number of studies in this field has been increasing. Ayan et al. recently published a systematic review evaluating the effects of physical exercise on patients with systemic lupus erythematosus (SLE). Of the 14 articles selected for their review, there were 13 studies involving adults with exercise programs ranging between 6 and 12 weeks. All the studies analyzed the impact of aerobic exercise, but only one combined this modality with resistance exercises. Five studies used aerobic capacity as a variable, and four observed a significant difference in the VO2max after the intervention. Thus, although the study's authors determined that the quality of the analyzed evidence was not high, the review showed that physical exercise can increase the aerobic capacity of patients with SLE (29).

Another systematic review evaluated 17 randomized controlled trials that analyzed the effects of exercise on patients

TABLE 2 | Assessment of the VO_2 max, AT e HR max variables in the EG and CG groups before and after 28 weeks.

		TIME POINTS			
	N	T0	T28	Δ	*p*
VO_2 max (ml/kg/min)					
CG	30	21,96 ± 5,5	20,2 ± 4,16	−1,76	0,028
EG	30	19,64 ± 3,47	22,95 ± 4,01	+3,31	<0,001
p intergroup		0,056	0,012		
AT (ml/kg/min)					
CG	30	18,61 ± 3,67	17,8 ± 2,82	−0,81	0,163
EG	30	16,86 ± 2,86	19,56 ± 3,18	+2,7	<0,001
p intergroup		0,065	0,041		
HRmax (bpm)					
CG	30	144 ± 18,3	139,9 ± 20,9	−4,1	0,106
EG	30	137,9 ± 16,3	142,1 ± 18,8	+4,2	0,106
p intergroup		0,405	0,405		

VO_2 max, maximum oxygen consumption; AT, aerobic threshold; HR max, maximum heart rate; bpm, beats per minute. P values provided by Anova method.

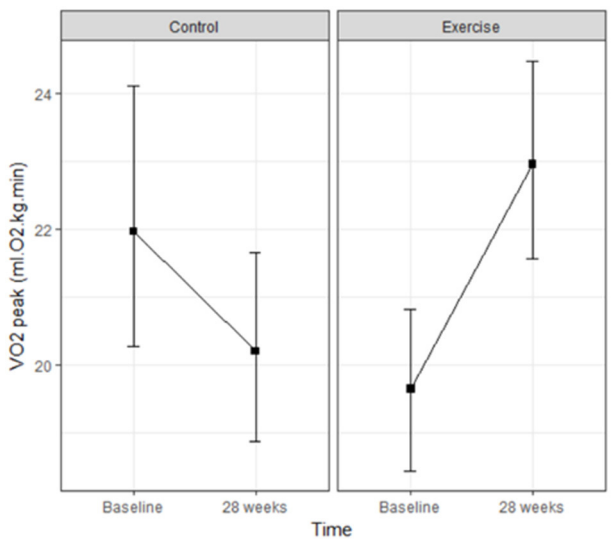

FIGURE 2 | Mean VO2 peak values at each of the evaluation times in the control and exercise groups [$F_{(1, 58)} = 31.43$; $p < 0.001$].

with rheumatoid arthritis. Although the studies included differing exercise programs did not include descriptions of intervention monitoring, the authors concluded that medium-to high-intensity exercise can improve aerobic capacity and is therefore recommended as part of an overall treatment plan for patients with rheumatoid arthritis (30).

The effects of exercise on glycemic and lipidemic metabolism are widely known. Previous research has shown that exercise enhances glycemia and insulin sensitivity, which leads to better prevention and control of type 2 DM (31, 32). Exercise has also been shown to promote an increase in HDL levels and decreases in LDL, VLDL, and triglyceride levels (33).

In the present study, we did not observe any changes in the participants' cholesterol profiles, but there was a small, but significant improvement in the glycated hemoglobin levels. We believe that this benefit would be greater with increasing exercise frequency, as structured exercise training of more than 150 min per week is associated with greater declines in glycated hemoglobin compared to 150 min or less per week (34). To date, however, no studies demonstrated a link between exercise and the metabolic profile of patients with pSS.

Only one study has evaluated the lipidemic profile of SLE patients who underwent an aerobic exercise program twice a week for 12 weeks, but no improvements in the metabolic parameters measured were observed (35). This lack of change in cholesterol levels after exercise may be related to the presence of various pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interferon gamma, as these proteins interfere with cholesterol synthesis and degradation (36). Previous studies have shown that these factors can reduce the activity of lipoprotein lipase, an enzyme associated with HDL synthesis (37).

Stavropoulos-Kalinoglou et al. conducted a 6-month intervention for RA patients, with aerobic exercises in the first 3 months and aerobic exercise in combination with resistance exercise until the end of the study. The patient HDL cholesterol levels underwent clinically significant changes by the end of the program, but there were no changes in the glycemic profile or total cholesterol and its components (38).

Echocardiographic analyses of pSS patients htipically show a silent impairment of the myocardium, mainly consisting of LV systolic and diastolic dysfunction. The mechanism underlying this dysfunction is still unknown, but it may be associated with Raynaud's phenomenon of coronary microcirculation or direct myocardial tissue injury caused by autoantibodies (39). Bayram et al. reported a higher prevalence of LV dysfunction in women with pSS (40). Similar results were reported by Vassiliou et al. and Manganelli et al. in pSS patients and Elnady et al. and Aslan et al. in patients with SLE and RA, respectively (40–43). In our study, 55.33% of the patients presented with LV diastolic dysfunction, with no changes in systolic function as measured by the ejection fraction.

Sarajlic et al. followed RA patients for 1 year enrolled in a moderate-to-intense unsupervised exercise program for 30 min on most days, with 2 weekly 45 min circuit sessions combining aerobic and resistance exercise. In the second year, the patients were encouraged to maintain their activity levels. There were no changes observed in the patients' LV systolic function, but there was an improvement in diastolic dysfunction seen after 1 year. The authors suggested that this is related to aerobic capacity, suggesting that impaired myocardial relaxation may be associated with a low VO2max (44). Although physical exercise promotes cardiac remodeling and thus improves ejection fraction and diastolic dysfunction, we did not observe any changes in the echocardiographic parameters evaluated in our study, probably due to shorter duration of the protocol.

As noted in the Miyamoto et al. study, the patients in our study did not experience worsened disease activity, confirming the

safety of the exercise program (28). Similar results were observed in previous studies of patients living with SLE and RA (29, 30).

In our study, the patients presented low quality of life scores according to the SF-36 questionnaire, which aligns with other studies (45). Both groups improved in all the domains tested; however, similar to the results reported by Strombeck et al. and Miyamoto et al., we did not observe a significant difference between the two groups by the end of the program (27, 28). We agree with Miyamoto et al. that the number of meetings between CG and health professionals may have been a factor in raising mood, motivation and effort, which may influence the results for this group. Studies on quality of life for individuals with SLE have produced controversial results. Seven studies have used the SF-36 questionnaire for assessments after physical exercise for this population. In three, there were no improvements in any of the observed parameters, whereas the other studies reported significant improvements in up to three domains (29).

Our study had some limitations. This was a small, single-center study. In a larger sample, differences at baseline may be more defined. The recommendation to prescribe physical exercise for patients with pSS follows the standard prescription of exercise for healthy individuals in terms of intensity, duration, and frequency (46). In our study, however, the exercise program we designed followed the first two parameters, but the frequency was below the recommended minimum, (three times a week) because of the availability of volunteers (47). Even so, it was possible to promote the improvement of aerobic capacity, which has already been seen in patients with limited cutaneous Systemic Sclerosis (48).

In conclusion, ours results show that regular physical exercise based on personalized and supervised training can safely increase the aerobic capacity of patients with pSS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Research Committee of the Federal University of São Paulo (Unifesp) (opinion 503606/2013). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Rheumatoid Arthritis and Cardiovascular Risk: Retrospective Matched-Cohort Analysis Based on the RECORD Study of the Italian Society for Rheumatology

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Background: Rheumatoid arthritis (RA) is associated with an increase in cardiovascular (CV) risk. This issue maybe not only explained by a genetic component, as well as by the traditional CV risk factors, but also by an underestimation and undertreatment of concomitant CV comorbidities.

Method: This was a retrospective matched-cohort analysis in the Italian RA real-world population based on the healthcare-administrative databases to assess the CV risk factors and incidence of CV events in comparison with the general population. Persistence and adherence to the CV therapy were also evaluated in both groups.

Results: In a RA cohort (*N* = 21,201), there was a greater prevalence of hypertension and diabetes with respect to the non-RA subjects (*N* = 249,156) (36.9 vs. 33.4% and 10.2 vs. 9.6%, respectively), while dyslipidemia was more frequent in the non-RA group (15.4 vs. 16.5%). Compared with a non-RA cohort, the patients with RA had a higher incidence of atrial fibrillation (incidence rate ratio, IRR 1.28), heart failure (IRR 1.53), stroke (IRR 1.19), and myocardial infarction (IRR 1.48). The patients with RA presented a significantly lower persistence rate to glucose-lowering and lipid-lowering therapies than the controls (odds ratio, *OR* 0.73 [95% *CI* 0.6–0.8] and *OR* 0.82 [0.8–0.9], respectively). The difference in the adherence to glucose-lowering therapy was significant (*OR* 0.7 [0.6–0.8]), conversely no statistically significant differences emerged regarding the adherence to lipid-lowering therapy (*OR* 0.89 [95% *CI* 0.8–1.0]) and anti-hypertensive therapy (*OR* 0.96 [95% *CI* 0.9–1.0]).

Conclusion: The patients with RA have a higher risk of developing CV events compared with the general population, partially explained by the excess and undertreatment of CV risk factors.

Keywords: rheumatoid arthritis, cardiovascular risk, real-world population, cardiovascular events, prevalence

INTRODUCTION

The pathophysiology of rheumatoid arthritis (RA) involves a complex interplay of environmental and genetic factors, leading to chronic synovial inflammation and joint damage (1). Beyond synovitis, the patients with RA are at high risk of developing cardiovascular disease (CVD) (2), as inflammation plays a pivotal role in the pathogenesis of CVD (3). Therefore, the patients with RA have approximately a double risk of atherosclerotic CVD, stroke, heart failure, and atrial fibrillation (AF) compared with the general population (2–4). Furthermore, the patients with active RA, differently from the general population, have increased CV events and mortality, paradoxically associated with the reduced circulating lipid levels (5). In fact, the lipid functions are abnormal in RA (5). Several studies have shown an increased CVD risk since the early stages of RA, and mortality linked to the CV events increases along with disease duration (6–8). As the degree of CVD involvement in RA correlates with the degree of systemic inflammation, conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) and biologic (b)DMARDs protect from the CV events (9), while chronic corticosteroids increase the CVD risk (3).

Although this high risk of CVD has been well documented and known for decades, the patients with RA still receive the suboptimal primary and secondary CVD preventive cares with respect to other high-risk subjects, and one of the most important clinical unmet needs in RA relates to improving the CVD preventive strategies (10). To note, the excess of CVD risk in the patients with RA is in part connected to an underestimation of the concomitant CV comorbidities, as well as to their suboptimal management (4), beyond the relevance of a genetic component in CVD development documented by several studies (11). In this regard, well-established risk charts, such as the Systematic COronary Risk Evaluation (SCORE) were found to underestimate the actual CV risk of patients with RA (12). Because of that, non-invasive techniques, such as the carotid ultrasound are used to identify the patients with RA who are at high risk of cardiovascular events (13).

In Italy, no solid data are available regarding the CV risk and CV risk factors in RA, as well as no data, were reported regarding the persistence and adherence to CV risk-lowering therapy. The analyses in a national context are important due to the differences in disease and patients' management. Thus, we conducted an analysis in Italian RA real-world population with the main objectives (i) to assess the CV risk factors, CV events, and overall mortality in the patients with by comparing them with the general population; (ii) to compare the persistence and adherence with the CV risk-lowering therapy in the patients with RA vs. non-RA. For these purposes, we took advantage of the RECord linkage Of Rheumatic Disease (RECORD) study promoted by the Italian Society for Rheumatology, aiming to set up a national surveillance system to monitor the health burden of rheumatic diseases in Italy.

PATIENTS AND METHODS

Study Design

This was a retrospective matched cohort study, performed using data of the RECORD project promoted by the Italian Society for Rheumatology, aimed to implement an algorithm to identify the patients with RA using the administrative healthcare databases (AHDs) information and to measure the prevalence, incidence, and mortality of RA (14, 15). The RECORD data cover the period 2004–2013.

The data sources for the RECORD project were the AHDs of Lombardy, an Italian region with more than 10,000,000 inhabitants (about 16% of the entire Italian population). The entire Italian population is covered by the National Health Service (NHS), and in Lombardy, an automated system of AHDs has been created to collect a variety of information (16). The source registry is an electronic database that contains the fields that are built as an obligatory menu, limiting the possible errors and missing data.

The study was approved by the ethical committee of the Pavia University Hospital (deliberation of March 12, 2012) and it has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Study Population

The target population in the RECORD project included all the residents of Lombardy, aged 18 years and older. In the RECORD project, a cohort of patients with RA was identified applying the aforementioned algorithm (14). Each RA case was matched with the four patients with non-RA, during the same period, by gender and age. For each patient, the clinical and pharmacological history covering the period 2004–2013 was available.

In our analysis, we excluded all the subjects with a CV event that occurred between 2004 and 2008. All the patients were followed from January 2009 until the first CV event, emigration, death, or end of follow-up (31 December 2013), whichever came first.

Variables and Statistical Analysis

The CV risk factors (hypertension, dyslipidemia, or diabetes mellitus [DM]) frequencies were extracted and the difference in terms of the proportion of subjects with CV risk factors was assessed by performing the χ^2 test in the period between January 01, 2004, and December 31, 2008.

The CV events taken into consideration in these study analyses were myocardial infarction, ischemic stroke, heart failure, and AF, classified with the diagnosis-related group 24 (DRG-24) and the International Classification of Diseases, 9th revision-Clinical Modification (ICD9-CM) codes (**Supplementary Material**). If a patient presented more than one CV event during the same hospitalization, all the incident events were taken into consideration. The comparison between the incidence rates (1,000 person/years) of CV events in the patients with RA and non-RA was carried out using the univariate and multivariate Poisson models, with the following covariates included: gender, age, and CV risk factors. The subjects with hypertension, dyslipidemia, or DM as well as patients on treatment for CV risk factors were identified by means of the data relating to the therapeutic prescriptions, Anatomical Therapeutic Chemical classification system codes (ATC, **Supplementary Material**), or to the presence of certifications for the aforementioned diseases.

The difference between the patients in the RA group and non-RA group for CV risk factors therapies was assessed by performing the χ^2 test. The patients not presenting a CV risk-lowering drug therapeutic discontinuity during the follow-up $\geq$90 days (median time frame for the renewal of prescription) were considered persistent to the drug therapy. A patient was defined as adherent to the CV risk-lowering treatment when the proportion of day covered (PDC) by the treatment for at least 80% of his/her follow-up, taking into account multiple treatments for a specific indication (17). In case of treatment overlap, the overlapping days were considered once. To calculate the PDC, the amount of drug purchased by the patient was considered and this quantity was divided by the defined daily dose.

Three logistic regression models were applied, defining persistence or adherence to the therapy as outcome and presence or absence of RA as covariate adjusting for age and sex. The association estimates were reported as odds ratio (*OR*) and relative 95% *CI*. No formal sample size estimation was made for this observational retrospective study as we analyzed all the eligible RA subjects with a high number of matched non-RA cases.

All the hypothesis tests were two-sided and the *p*-values for statistical significance were set at 0.05. All the analyses were performed using an R statistical software 3.3 version (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The CV Events and CV Risk Factors

The RA cohort consisted of 21,201 patients with 16,098 (76%) women and a median age of 61.7 years ($\pm$13.7), whereas the non-RA cohort was represented by 249,156 subjects with 179,407 (72%) women and a median age of 62.5 years ($\pm$14.4). Regarding the presence of CV risk factors, rates of hypertension and DM were higher in the patients with RA (36.9 vs. 33.4%, $p < 0.001$, and 10.2 vs. 9.6%, $p = 0.004$, respectively), while the rate of dyslipidemia was higher in the patients with non-RA (16.5 vs. 15.4%, $p < 0.001$).

Among the patients with RA, 1,769/21,201 (8.3%) subjects had at least one CV event during the follow-up, whereas 16,381/249,156 (6.6%) non-RA subjects had at least one CV event in the same period.

Some subjects had simultaneously (i.e., in the same hospitalization) more than one CV event. Among the RA cases, 1,618 subjects had one event and 151 had two events. Among the non-RA cases, 14,661 subjects had only one event, 1,707 had two events, and 13 had three events.

The development of the first CV event was associated with the presence of each CV risk factor and RA acted as an independent risk factor for the development of the first CV event (incidence rate ratio [IRR] 1.39 [1.3–1.5], $p < 0.001$). In addition, the patients with RA have an increased risk of death compared with the non-RA subjects from any cause (IRR 1.35 [1.3–1.4] $p < 0.001$). Two thousand and nineteen patients with RA (9.5%) and 20,273 (8.1%) non-RA subjects deceased during the follow-up.

More specifically, the incidence rates of AF, heart failure, and acute myocardial infarction were significantly higher in the patients with RA than in the non-RA group (IRR 1.17, 1.35 and 1.39, respectively; $p < 0.001$) (**Table 1**). In addition, a higher incidence of stroke occurred in the RA group, with a *p*-value not statistically significant (crude IRR: 1.10 [*CI* 1.0–1.3], $p = 0.171$).

The presence of CV comorbidities, such as hypertension and DM lead to an increase in the adjusted incidence of AF (IRR 2.03 and 1.18, respectively; all $p < 0.001$), whereas the subjects with dyslipidemia had a risk of developing AF similar to those not affected by this comorbidity (0.99, $p = 0.663$).

The patients with RA, DM, or hypertension had a significantly higher risk of developing heart failure (IRR 1.54, 1.82, and 1.62, respectively; $p < 0.001$), while dyslipidemia did not act as an independent CV risk factor for the development of this event (IRR 1.02, $p = 0.665$).

The presence of RA, DM, hypertension, or dyslipidemia correlated independently with the risk of developing myocardial infarction (IRR 1.48, 1.50, 1.57, and 1.58, respectively; $p < 0.001$).

Regarding stroke, the patients with RA had an increased risk of developing this CV event compared with the control group when adjusting for pre-specified confounders (IRR 1.19, $p = 0.012$).

All details matching the CV events and CV risk factors for both groups are reported in **Table 2**.

Persistence and Adherence

Regarding treatment for the CV risk factors, 80% patients with RA and 80.2% patients with non-RA with hypertension had at least one prescription of anti-hypertensive drug ($p = 0.677$), among the patients with DM, 73.3% RA vs. 80.9% non-RA had hypoglycemic treatment ($p < 0.001$), and among the patients with dyslipidemia, 71.8% RA vs. 77.2% non-RA ($p < 0.001$) had at least one prescription for lipid-lowering therapies. No statistically significant differences occurred in the two groups regarding the therapeutic persistence for antihypertensive drugs (44 vs. 45%, *OR* 1.01 [0.9–1.1], $p = 0.78$). On the other hand, the patients with DM-RA had a lower persistence to hypoglycemic treatment (46 vs. 54%, *OR* 0.73 [0.7–0.8], $p < 0.001$), and dyslipidemia RA to lipid-lowering therapies (29 vs. 33%, 0.82 [0.8–0.9], $p < 0.001$) than the non-RA group.

TABLE 1 | Incidence rates of cardiovascular (CV) events in the patients with and without RA (per year, per 1,000 person).

CV event	RA, N	RA, IR [95%CI]	non-RA, N	non-RA, IR [95%CI]	IRR	*p*-value
Atrial fibrillation	687	7.01 [5.9–8.1]	6,964	5.98 [5.7–6.3]	1.17 [1.1–1.3]	<0.001(***)
Heart failure	402	4.10 [3.2–5.0]	3,546	3.04 [2.8–3.3]	1.35 [1.2–1.5]	<0.001(***)
Myocardial infarction	603	6.15 [5.1–7.2]	5,140	4.41 [4.2–4.7]	1.39 [1.3–1.5]	<0.001(***)
Stroke	228	2.33 [1.7–3.0]	2,464	2.11 [1.9–2.3]	1.10 [1.0–1.3]	0.171

CV, cardiovascular; CI, confidence interval; IR, incidence rate; IRR, incident rate ratio; RA, rheumatoid arthritis; IRR, were adjusted for age, sex, and CV risk factors.
****Highly significant.*

TABLE 2 | Assessment of the relationship between CV risk factors and CV events.

	Atrial fibrillation	Heart failure	Stroke	Myocardial infarction
	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]
RA	1.28 [1.2–1.4]	1.54 [1.4–1.7]	1.19 [1.0–1.4]	1.48 [1.4–1.6]
Hypertension	2.03 [1.9–2.1]	1.82 [1.7–2.0]	1.49 [1.4–1.6]	1.57 [1.5–1.6]
DM	1.18 [1.1–1.3]	1.62 [1.5–1.7]	1.52 [1.4–1.7]	1.50 [1.4–1.6]
Dyslipidemia	0.99 [0.9–1.0]	1.02 [0.9–1.1]	0.98 [0.9–1.1]	1.58 [1.5–1.7]

DM, diabetes mellitus; IRR, incidence rate ratio; RA, rheumatoid arthritis.

No statistically significant differences emerged regarding the adherence to lipid-lowering therapy (*OR* 0.89 [0.8–1.0], $p = 0.054$) and antihypertensive therapy (*OR* 0.96 [0.9–1.0], $p = 0.179$) between the two groups, whereas the patients with RA showed less adherence to the glucose-lowering treatments than the non-RA subjects (*OR* 0.70 [0.6–0.8], $p < 0.001$).

DISCUSSION

The patients with RA have increased mortality and morbidity compared with the general population (18). There are no univocal reports that explain these data, as they vary according to the type of cohort and the care setting examined. Nevertheless, the increase in mortality in RA is largely attributable to the CV events (19).

In Italy, solid data are not available regarding the distribution of CV risk factors and their correlation with the onset of new CV events in patients with RA. The present analysis aimed to fill this gap and to investigate if the CV events are a consequence of suboptimal drug utilization.

Regarding the presence of CV risk factors, in the analyzed cohort there was a greater prevalence of hypertensive subjects in the patients with RA (36.9 vs. 33.4%). A wide variability regarding the prevalence of hypertension in the patients with RA has been documented (20, 21): a higher prevalence of hypertension among the patients with RA could be affected by the lack of analysis of confounding variables because of the comparison of patients coming from different care settings (20). For example, the prevalence of hypertension and diabetes was found to be increased in the Spanish individuals with RA compared with matched controls (22). Glucocorticoid-induced DM might partially explain the excess diagnosis of DM in the patients with RA.

The prevalence of dyslipidemia in the RA group (15.4 vs. 16.5%) was significantly lower than in the control group and this data could be explained with the "lipid paradox" (23, 24), however, it was not possible to assess the disease activity in the population under examination. Our RA cases have a higher prevalence of DM than the control group (10.2 vs. 9.6%). From the analysis of the data available in the literature, the conflicting elements emerged: a 2011 meta-analysis documented an increased prevalence of DM in the patients with RA (25), whereas other studies did not show statistically significant differences in the prevalence of DM in women with or without RA (26). According to our data, the baseline data from the Spanish inflammatory arthritis registry Cardiovascular in rheumatology (CARMA) showed a lower prevalence of hypercholesterolemia than the matched controls (22).

During the follow-up, 18,150 patients presented at least one CV event: 1,769 (8.3%) among the RA group and 16,381 (6.6%) in the non-RA group, respectively. Compared with the control group, the patients with RA have a 30% higher overall incidence of CV events. These data appear superimposable to those available in the literature that the patients with RA have also a higher incidence of AF, heart failure and myocardial infarction, and stroke compared with the control group, in line with data previously reported in the patients with RA (27–30). To note, data after 5 years of follow-up from the prospective CARMA project in patients with inflammatory arthritis, unlike expected, showed that the frequency of CV events did not increase in the patients with RA compared with the control groups. At that time, the CARMA project member speculated on the protective effect of the biologic therapy administered to a high number of patients, due to the favorable effect of biologics on the insulin resistance, lipid composition, and other beneficial metabolic effects mediated by these agents, as well as the effect on reducing inflammation. Likewise, the greater knowledge of the EULAR recommendation

for the management of traditional CV risk factors among the members of the CARMA project may also have explained these favorable results (31). The discrepancy supports the gap in proper stratification and treatment of the patients with RA in our cohort.

From the results of our study, RA, hypertension, and DM act as the independent risk factors for the development of AF and heart failure. Furthermore, the presence of RA acts as an independent risk factor for the development of myocardial infarction and for mortality, indicating that disease-specific risk factors play an important role.

Evaluating the data regarding pharmacoutilization of drugs for CVD, it emerged that the patients with RA have lower persistence to the glucose-lowering and lipid-lowering treatments than the control group, and, when persistent, are less adherent to glucose-lowering therapy, confirming the previous reports (32). These results indicate that careful monitoring for DM and hyperlipidemia for persistent treatments of related drugs are needed in the patients with RA.

The main strengths of the study are represented by the absence of selection bias, the large sample size with no loss to follow-up, and the duration of the follow-up. Furthermore, this report presents the largest matched-cohort study on CV risk in the patients with RA and non-RA ever reported in Italy with no missing information as the RECORD database covers all the events of interest generated by the target population. The main limitation is linked by the retrospective design of an administrative database. In fact, the use of data extracted from the administrative databases lacks some clinical information that could influence the CV risk. An essential part of CV risk management consists of a screening of five traditional parameters: blood pressure, smoking status, body weight, blood glucose, and lipid profile (33, 34). For the present analyses, data on smoking status and body weight were not available. In addition, the acquired data are limited to the actually delivered prescriptions and no information was available regarding the reasons for primary non-adherence to the treatments or for the suspension of the therapies. To note that we analyzed data registered only during hospitalizations with underestimation of events due to the lack of events that occurred both in the out-patient regimen and in patients deceased before the hypothetical hospitalization.

The differences in treatment and CV risk factors only partially justify the increase in CVD risk that could be explained by the pathophysiological characteristics of RA.

Considering the results of our study that ascertain a central role of RA and the traditional CV risk factors in the onset of new CV events, it is essential to translate into practice the programs of surveillance and management of traditional CV risk factors, proper CV risk assessment taking into account the disease-specific characteristics (i.e., lipid paradox) as well as in assessing the adherence of patients to CVD risk-lowering therapy.

In conclusion, data emerging from this study confirm that the patients with RA have a higher risk of developing CV events including AF, heart failure, stroke, and myocardial infarction, as well as an increased mortality rate compared with the general population, even independently from the presence of other CV comorbidities. CV risk factor management should be an essential part of the care of patients with RA. Although relevant international guidelines exist, there are still major gaps in the knowledge and risk factor management implementation in these patients' groups and CV risk should be assessed according to the national guidelines as they may differ among the countries.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Pavia University Hospital (deliberation of 12/March/2012) and it has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AZan, CS, AZam, and GC: study conception and design. AZan, CS, GG, ES, and GC: acquisition of data. LA, AZan, CS, AZam, and GC: analysis and interpretation of data. CS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in drafting the article or revising it critically for important intellectual content, and approved the final version to be submitted for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.745601/full#supplementary-material

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Impaired Microcirculation and Vascular Hemodynamics in Relation to Macrocirculation in Patients With Systemic Lupus Erythematosus

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Introduction: Systemic lupus erythematosus (SLE) is associated with premature cardiovascular disease (CVD) and mortality, unexplained by traditional risk factors. Impairment of microcirculation and vascular hemodynamics may represent early signs of vascular affection. We hypothesized that studies of microcirculation and pulse waves may provide additional information, compared to ultrasound (US) alone, for the detection of early vascular disease in SLE.

Methods: Sixty well-characterized SLE-patients (52 women, eight men; mean age 43.21 ± 1.3 years) characterized by lupus nephritis (LN; $n = 20$), antiphospholipid syndrome (APS; n = 20) or skin and joint involvement ($n = 20$) and 60 healthy controls were included. Microcirculatory peak oxygen saturation (OxyP) was evaluated using a novel combined laser Doppler flowmetry/diffuse reflectance spectroscopy method. Pulse waves were recorded in the radial artery by the aid of applanation tonometry in order to calculate central augmentation index (AIx75). Intima-media thickness (IMT) and plaque occurrence were evaluated using high frequency US, in carotid and central arteries.

Results: Lower OxyP (84 ± 8 vs. 87 ± 5 %, $p = 0.01$) and higher AIx75 (17.3 ± 13.9 vs. 10.0 ± 14.2 %, $p = 0.005$) were seen in the SLE cohort. OxyP was inversely correlated with IMT in internal carotid artery (ICA), ($R = -0.32$, $p = 0.01$). AIx75 correlated with IMT in common carotid artery (CCA), ($R = 0.36$, $p = 0.005$), common femoral artery (CFA), ($R = 0.43$, $p = 0.001$), and ICA ($R = 0.27$, $p = 0.04$). AIx75 correlated negatively with OxyP ($R = -0.29$, $p = 0.02$). SLE-patients with plaque had lower OxyP values (80 ± 8 vs. 85 ± 7 %, $p < 0.001$) and higher AIx75 (23.0 ± 11.6 vs. 15.5 ± 14.2 %, $p < 0.001$) compared to those without plaque.

Conclusion: Impaired microcirculation and vessel hemodynamics were observed in SLE. These methods correlated with IMT and plaque occurrence. The importance of early macro- and micro-circulatory vascular affection for increased risk of CVD in SLE will be followed-up in future studies.

Keywords: SLE, microcirculation, augmentation index (AIx), ultrasound, intimal medial thickness (IMT), microvascular dysfunction

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune inflammatory disease primarily affecting young females (1). Patients with SLE have an increased risk of cardiovascular disease (CVD) with accelerated atherosclerosis and higher mortality rates compared to the general population (2, 3). In middle-aged female patients with SLE, the increased risk for coronary heart disease can be as high as 50-fold (4).

To evaluate the risk of CVD, ultrasound (US) with measurements of intima media thickness (IMT) constitutes a validated and established method to assess early atherosclerosis (5). Previous studies of cardiovascular risk in SLE, including IMT and plaque assessment, have focused mainly on common carotid artery (CCA), (3, 6, 7). In a previous study from our group, we found an increased number of plaques in SLE compared to age- and sex-matched healthy controls using high frequency US of multiple vessel areas. In addition, we observed increased wall thickness with predominantly medium echogenic appearance in several arterial areas, predominantly in the aortic arch (8). This appearance can be seen in several inflammatory diseases (9, 10), with increasing age, (11) or as an early sign of atherosclerosis (12). Compared to inflammatory vessel wall appearance, atherosclerosis presents with a more heterogeneous, irregular vessel wall thickness.

Arterial stiffness in large arteries is considered as a decisive factor for systolic pressure and is a predictor of cardiovascular events (13). Pulse wave analysis (PWA) presented as augmentation index (AIx) is a measure of the universal cardiovascular condition and is altered by changes in for instance peripheral vascular tone and arterial stiffness.

According to prior studies (14), an increase in AIx has predictive value for future cardiovascular events and mortality. In hypertension, monitoring of AIx for risk assessment is recommended, although aging is a contributing factor for arterial stiffness (15). Earlier studies of women with SLE have indicated increased stiffness of their elastic central arteries as measured with pulse wave velocity (PWV), (16, 17). This may be one factor contributing to the increased cardiovascular risk seen in this cohort.

Several tools to assess microcirculation have been used clinically, i.e., capillaroscopy, infrared thermography and different laser techniques measuring microcirculation perfusion (18). Studies with different types of laser-based measurements to investigate microcirculation perfusion in SLE have been performed, but studies are scarce (18–20).

For evaluation of microcirculation in the skin, we employed a novel fiber-optic system that combines laser Doppler flowmetry (LDF) and diffuse reflectance spectroscopy (DRS). The system estimates red blood cell tissue fraction, speed resolved perfusion and oxygen saturation (21, 22). Previous studies using this method have shown that the system can discriminate blood perfusion from different blood-flow speeds (23), which may enable measurement of healthy and dysfunctional microcirculatory flow. The system has also been used to study microcirculatory perfusion in patients with type-2 diabetes (24) and in the Swedish Cardiopulmonary bioImage Study (SCAPIS), a large population-based cohort of men and women aged 50–65 year (25).

The aim of this study was to assess vascular hemodynamics in relation to macrocirculation in patients with SLE. We hypothesized that microcirculation and pulse waves may provide additional information, compared to ultrasound (US) alone, for the detection of early vascular disease in SLE.

MATERIALS AND METHODS

Subjects

The study population (**Supplementary Table 1**) has previously been described in detailed (8) and was part of a regional Swedish quality register (26). Patients above 63 years of age were excluded due to increased age-dependent background risk of atherosclerosis (27), whereas only patients ≥23 years of age were considered. In order to compose a balanced study population, the 60 patients were stratified into three phenotypic subgroups with different manifestations of SLE. The subgroups were matched between each other 1:1:1 according to sex and age; 20 cases met the renal disorder ACR criterion, i.e., lupus nephritis (LN) in the absence of antiphospholipid syndrome (APS); 20 cases met the APS criteria (28) in the absence of LN; and 20 cases had exclusively skin and joint involvement in the absence of LN and APS (8, 26).

Acquired organ damage was assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) damage index (SDI) and disease activity by the SLE disease activity index 2000 (SLEDAI-2K) for each patient, recorded from their closest regular visit to rheumatologist (29, 30). Mean time between examination and disease activity assessment was 3.8 months. 50/60 cases (83%) were of Caucasian ancestry.

Sixty healthy age- and sex-matched (i.e., 1:1 to the 60 SLE cases), non-medicated (except for contraceptives) controls without clinical signs of inflammatory or atherosclerotic disease, were examined using the same protocol (US, microcirculation and vascular hemodynamics) as for the patients. The healthy controls were all of Caucasian ethnicity and hospital employees.

Background Variables

Height, weight, waist circumference and sagittal abdominal diameter were measured in all subjects. Variables concerning

Abbreviations: ACE, Angiotensin-converting enzyme; ACR, American college of rheumatology; AIx, Augmentation Index; AIx75, Augmentation Index normalized to heart rate 75; APS, Antiphospholipid syndrome; ARB, Angiotensin II receptor blocker; AXA, Axillar artery; CCA, Common carotid artery; CFA, Common femoral artery; DRS, Diffuse reflectance spectroscopy; hsCRP, High sensitive C-reactive protein; CVD, Cardiovascular disease; HDL, High-density lipoprotein; ICA, Internal carotid artery; IMT, Intima-media thickness; LDF, Laser Doppler flowmetry; LDL, Low-density lipoprotein; LN, Lupus Nephritis; MCTD, Mixed connective tissue disease; OxyP, Peak oxygen saturation; PWA, Pulse wave analysis; PWV, Pulse wave velocity; PORH, Post occlusive reactive hyperemia; SCA, Subclavian artery; SCAPIS, Swedish Cardiopulmonary BioImage Study; SFA, Superficial femoral artery; SDI, SLICC Damage Index; SLICC, Systemic Lupus International Collaborating Clinics; SLE, Systemic lupus erythemathosus; SLEDAI, SLE disease activity index; US, Ultrasound.

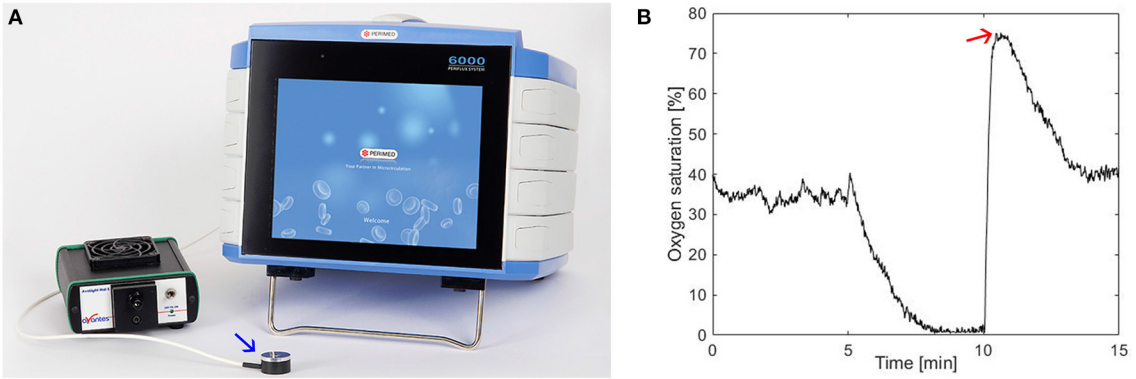

FIGURE 1 | (A) The PeriFlux 6000 EPOS (Perimed) system with the probe (blue arrow) which was placed on the left forearm. **(B)** Oxygen saturation (%), baseline, during arterial occlusion (between 5 and 10 min), and in the post-ischemic. Red arrow denotes oxygen saturation peak.

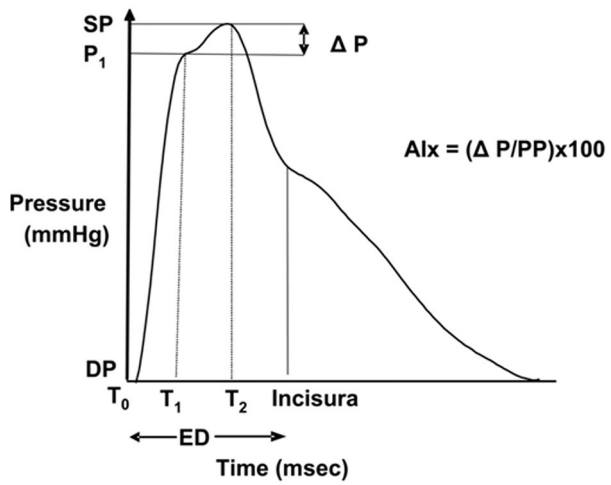

FIGURE 2 | Pulse pressure waveform, T0 indicates the start of the waveform; T1, duration from start of waveform to the first peak (outgoing pressure wave); T2, duration from start of waveform to the second peak (reflected pressure wave); ED, ejection duration; SP, central aortic systolic pressure; DP, central aortic diastolic pressure; P1, height difference between the minimum pressure and the pressure at the first peak; ΔP, difference between maximal pressure (central aortic systolic pressure) and P1, pressure at the first peak; PP, pulse pressure; and AIx, augmentation index. Image with permission from AtCor Medical.

age, sex, smoking habits, physical activity, and ongoing pharmacotherapy were collected by oral request and medical records. Physical activity was defined as activity with increased heart rate (occasions/week). Blood pressure was determined with oscillometric technique (Dinamap PRO 200 Monitor, Critikon, Tampa, FL, USA).

Microcirculation

Microcirculatory oxygen saturation was assessed with PeriFlux 6000 EPOS system (Enhanced Perfusion and Oxygen Saturation, Perimed, Järfälla, Sweden). A sphygmomanometer cuff was placed on the left upper arm, the probe (with both DRS and LDF) of the EPOS system (**Figure 1A**) was attached on the left forearm, ∼10 cm below the cuff. A baseline measurement period of 5 min was followed by a 5-min suprasystolic occlusion of the upper arm ending with a 5-min post-ischemic measurement. Assessment of peak oxygen saturation was performed in the post-occlusive reactive hyperemia phase (PORH), (**Figure 1B**). PORH refers to the increase in blood flow that follows vascular occlusion involving endothelial vasodilatation. Based on the results of Jonasson et al., OxyP was selected as the most robust value to report (25, 31). This parameter reflects overall microcirculatory function associated with vasodilator capacity and is better than perfusion values to discriminate between diseased patients and healthy controls.

Pulse Wave Analysis

PWA was performed with applanation tonometry (SphygmoCor® system, model MM3, AtCor Medical, Sydney, Australia), of the right radial artery. The locally recorded peripheral pressure waveform is traced by partly compressing the artery with an external high fidelity pressure probe (tonometer). Augmentation index adjusted to heart rate 75 (AIx75) was calculated. AIx is defined as [(Difference between the second and first systolic peak pressure)/Pulse Pressure] x100. This index denotes the relative aortic pulse pressure amplification in late systole from reflection waves (**Figure 2**). All measurements were made in at least duplicate, a mean of two reliable measurements (defined and calculated by SphygmoCor software as "operator index") was calculated (32).

Ultrasound

Ultrasound measurements were performed with a GE Logic E9 US system (LOGIQ E9 XDclear 2.0 General Electric Medical Systems US, Wauwatosa, WI, USA) with L2-9 MHz and C1-6 MHz transducers. IMT was measured in the common carotid artery (CCA), internal carotid artery (ICA), subclavian artery (SCA), axillar artery (AxA), common femoral artery (CFA), superficial femoral artery (SFA) and the aortic arch. Both sides were investigated. The procedure of IMT measurements

TABLE 1 | Detailed characteristics of included patients and controls presented as mean ± SD or *n* (%).

	All SLE (*n* = 60) Mean ± SD	Controls (*n* = 60) Mean ± SD
Background variables		
Age at examination (years)	43.2 ± 11.3	43.01 ± 11.4
Female gender, *n* (%)	52 (87)	52 (87)
Duration of SLE (years)	12.0 ± 9.4	N/A
SDI	0.8 ± 1.1	N/A
SLEDAI-2K	2.0 ± 2.1	N/A
Serologically active clinically quiescent SLE, *n* (%)	29 (48)	N/A
Lupus nephritis, *n*	20	N/A
APS, *n*	20	N/A
Skin & Joint, *n*	20	N/A
Traditional risk factors and laboratory data		
Body mass index (BMI) (kg/m²)	26.0 ± 4.2**	24.0 ± 3.3
Waist circumference (cm)	92.4 ± 12.1***	83.0 ± 10.0
Sagittal abdominal diameter (cm)	20.6 ± 3.9**	18.8 ± 2.7
Ever smoker (former or current), *n* (%)	14 (23) ***	0
Physical activity (times/week)	1.4 ± 1.6	1.8 ± 1.7
Systolic blood pressure (mm Hg)	115 ± 26	112 ± 18
Diastolic blood pressure (mm Hg)	73 ± 11*	68 ± 8
Diabetes mellitus, *n* (%)	1 (2)	0
Raynaud's phenomenon, *n* (%)	16 (27)	9 (15)
Estimated glomerular filtration rate (mL/min/1,73 m²)	84 ± 16	Not available
Total cholesterol (mmol/L)	4.7 ± 1.0	4.9 ± 1.1
High-density lipoprotein (HDL) (mmol/L)	1.6 ± 0.5	1.7 ± 0.4
Low-density lipoprotein (LDL) (mmol/L)	2.6 ± 0.8	2.6 ± 0.9
Triglycerides (TG) (mmol/L)	1.1 ± 0.7	1.2 ± 0.6
Anti-dsDNA (IU/mL)	86 ± 200	N/A
Complement protein 3 (g/L)	1.0 ± 0.2	N/A
Complement protein 4 (g/L)	0.2 ± 0.1	N/A
High-sensitivity CRP (mg/L)	2.2 ± 2.8	2.0 ± 3.7
Medical treatment, ongoing		
Antimalarial agents, *n* (%)	54 (90)	0
Antihypertensives, *n* (%)	20 (33)	0
Beta-blockers, *n* (%)	5 (8)	0
ARB/ACE inhibitors, *n* (%)	15 (25)	0
Other antihypertensives, *n* (%)	4 (7)	0
Glucocorticoid therapy *n* (%)	31 (52)	0
Mean daily Prednisolone dose (mg)	4.5	0
Warfarin therapy, *n* (%)	11 (18)	0
Antiplatelet therapy, *n* (%)	11 (18)	0
Statin therapy *n* (%)	5 (8)	0
DMARD therapy, *n* (%)	27 (45)	0
Mycophenolate mofetil, *n* (%)	16 (27)	0
Methotrexate, *n* (%)	5 (8)	0
Azathioprine, *n* (%)	3 (5)	0
Sirolimus, *n* (%)	2 (3)	0
Dehydroepiandrosterone, *n* (%)	1 (2)	0
Biologics, *n* (%)	4 (7)	0
Bortezomib, *n* (%)	1 (2)	0
Rituximab, *n* (%)	1 (2)	0
Belimumab, *n* (%)	2 (3)	0

*SLE patients compared to all controls.*p<0.05, **p<0.01, ***p<0.001.*
ACE, angiotensin converting enzyme; APS, Antiphospholipid syndrome; ARB, angiotensin II receptor blocker; CRP, C-reactive protein; DMARDs, Disease Modifying Anti-Rheumatic Drugs; LN, lupus nephritis; N/A, not applicable; SDI, SLICC/ACR damage index; SLE, Systemic lupus erythematosus.

has been described previously (8). The IMT cut-off value of ≥0.9 mm in CCA was chosen due to the latest ESH/ESC hypertension guidelines (33). For the aortic arch a higher cut-off value (≥1.2 mm) was chosen due to generally higher aortic arch IMT values among our healthy controls and according to results from earlier studies (34). Subjective vessel wall assessment regarding wall appearance and plaque occurrence was performed in carotid and central arteries as described earlier (8).

Laboratory Measurements

As previously described (8), standard cardiovascular and inflammatory laboratory tests, including lipid profile, plasma creatinine and C-reactive protein with high-sensitive technique (hsCRP), anti-double-stranded DNA antibodies, and plasma complement protein 3 (C3) and 4 (C4), were controlled for at the closest regular visit to rheumatologist (35).

Examination Procedure

The participant had to rest 15 min before the test, which was performed in a room with a temperature of 25°C, dim lighting and no outer disturbances. A standardized examination procedure was used in all individuals. The examination procedure started with US measurements followed by bilateral blood pressure measurements and pulse wave analysis of the right radial artery. The examination procedure ended with evaluation of microcirculation.

All participants were asked to refrain from coffee and nicotine use 4 h prior to the measurements.

The same vascular sonographer performed all physiologic examinations and the following off-line measurements. The sonographer was blinded to which subgroup of SLE the patients belonged, but not to whether the participants were patients or controls.

Statistical Methods

AIx75, OxyP and IMT are presented as mean ± SD. Differences between the whole SLE group and controls were calculated using Student's *t*-test. χ^2 test was performed for categorical variables. Differences between subgroups were calculated using one-way ANOVA with Bonferroni *post hoc* test. Pearson's correlation test, as well as univariate linear regression were used to test any relationship between AIx75 and OxyP and each of the variables in **Table 1**. Multivariate linear and logistic regression were used to examine factors explaining AIx75 and OxyP. All variables significant in the univariate model were combined and a stepwise procedure was performed eliminating non-significant ($p \geq 0.05$) variables until a multiple model with only significant variables remained. For missing data, no imputation analysis was performed. Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY USA).

Ethics Considerations

Oral and written informed consent was obtained from all patients and healthy controls. The study protocol was performed according to the Declaration of Helsinki and approved by the Regional Ethics Board in Linköping (ref. M75-08, 2013/33-31 and ref. 2017/572-32).

RESULTS

Basic demographics, laboratory data and ongoing medical therapies are shown in **Table 1**. Seventeen of the 60 patients (28%) had low-density lipoprotein (LDL) levels >3.0 mmol/L), but all patients on regular statin therapy ($n = 5$) showed LDL levels ≤2.7 mmol/L. No significant differences were seen between SLE and controls except for body mass index (BMI), waist circumference, sagittal abdominal diameter, diastolic blood pressure and smoking habits.

Microcirculation and Pulse Wave Analysis

The average OxyP of the entire SLE group was significantly decreased compared to controls 84 ± 8 vs. 87 ± 5 % ($p = 0.01$). No significant differences with regard to the phenotypic SLE subgroups were found, although the LN group had the lowest values (82 ± 10 %). AIx75 values were increased in SLE patients compared to controls (17.3 ± 13.9 vs. 10.0 ± 14.2 %, $p = 0.005$). No significant differences with regard to the phenotypic subgroups were found, although the APS group showed the highest values (18.8 ± 15.2 %). When comparing gender, no significant differences were found for OxyP, whereas AIx75 differed significantly. AIx75 in females was 19.0 ± 13.7 vs. men 6.8 ± 10.7 % ($p < 0.001$). In controls, AIx75 for females was 11.6 ± 13.3 vs. men −0.6 ± 15.8 % ($p = 0.02$).

A significant inverse correlation was observed between OxyP and AIx75 ($R = -0{,}29$, $p = 0.02$).

OxyP and AIx75 in Relation to IMT

OxyP was inversely correlated with IMT in ICA, ($R = -0.32$, $p = 0.01$). IMT in other vessel areas was not correlated with OxyP.

We observed a difference in OxyP between (1) controls, (2) patients with normal IMT in the aortic arch without plaque, (3) patients with increased IMT in the aortic arch without plaque, and (4) patients with plaque (87 ± 5, 87 ± 6, 83 ± 9, 80 ± 8 %, respectively, $p = 0.001$). As demonstrated in **Figure 3A**, a significant difference was seen between controls and patients with plaque, and between patients with normal IMT in the aortic arch without plaque and patients with plaque.

AIx75 correlated with IMT in CCA ($R = 0.36$, $p = 0.005$), CFA ($R = 0.43$, $p = 0.001$) and ICA ($R = 0.27$, $p = 0.04$). Other vessel areas showed no significant correlation with AIx75.

AIx75 in the groups mentioned above were 8.9 ± 15.0, 13.9 ± 13.8, 18.2 ± 14.7, and 23.1 ± 11.7 %, respectively, ($p = 0.04$). AIx75 differ significantly between controls and patients with plaque (**Figure 3B**).

When comparing patients with or without plaque, regardless of normal or increased IMT in the aortic arch, the group with plaque had lower OxyP values (80 ± 8 vs. 85 ± 7 %, $p < 0.001$) and higher AIx75 (23.0 ± 11.6 vs. 15.5 ± 14.2 %, $p < 0.001$) compared to those without plaque.

Relation of OxyP to Traditional and SLE Associated Risk Factors

Relation between OxyP and traditional and disease associated risk factors are shown in **Table 2**. In the univariate analysis of OxyP, waist circumference, sagittal abdominal diameter, presence of Raynaud's phenomenon, angiotensin II receptor blocker (ARB)/angiotensin-converting enzyme (ACE) inhibitor treatment, and statin therapy, were related to OxyP. However, when all significant variables were included in a multiple linear regression model, only the presence of Raynaud's phenomenon ($p = 0.04$) and statin therapy ($p = 0.001$) were negatively associated with OxyP ($R = 0.51$).

OxyP was not associated with age (**Figure 3C**), duration of SLE, SDI, SLEDAI-2K, C3, C4 or anti-dsDNA levels.

Self-reported physical activity (occasions/week) were not associated with OxyP, neither in SLE nor in controls.

Relation of AIx75 to Traditional and SLE Associated Risk Factors

Relation between AIx75 and traditional and disease associated risk factors are shown in **Table 2**. In the univariate analysis of AIx75, age, female sex, SLE duration, SDI, waist circumference, sagittal abdominal diameter, diastolic blood pressure, total cholesterol, high- density lipoprotein (HDL), triglycerids, C3/C4, hsCRP and beta-blocking therapy, correlated with AIx75. eGFR and physical activity correlated negatively with AIx75.

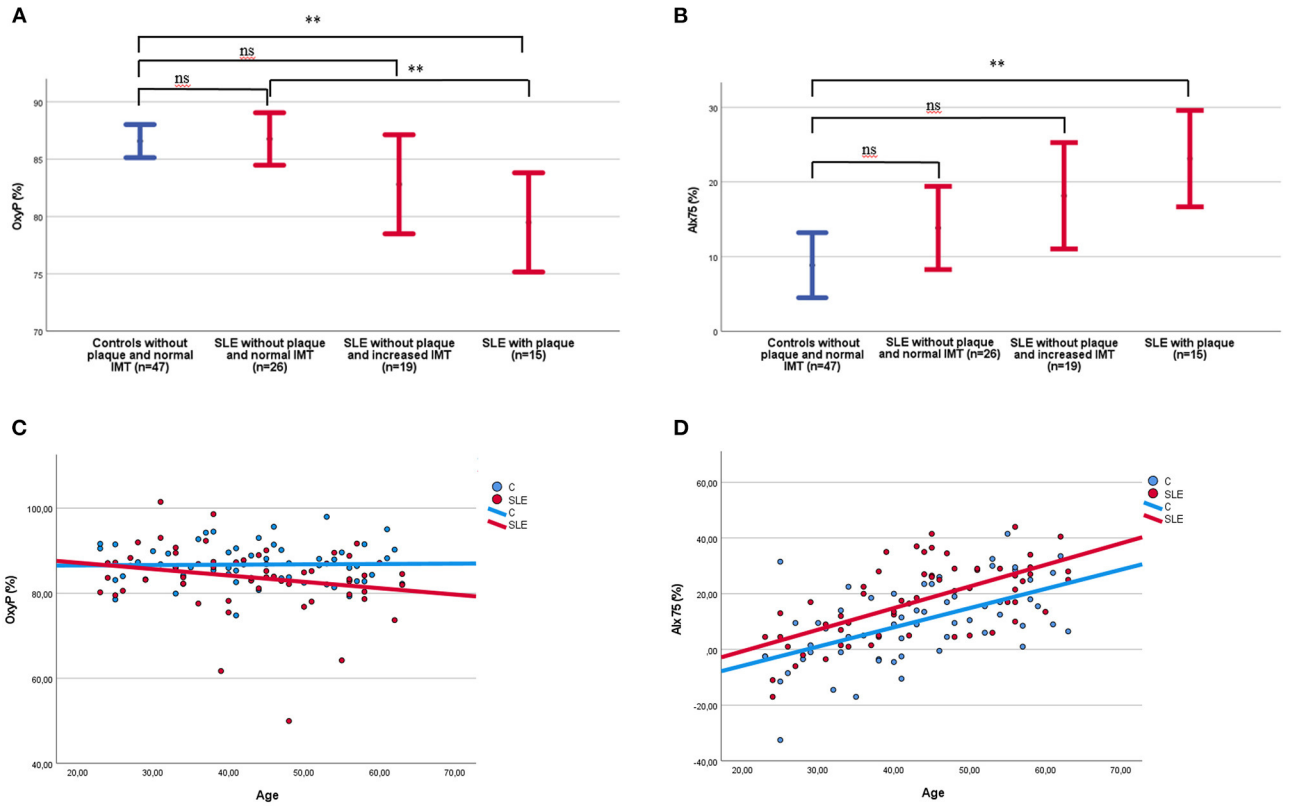

FIGURE 3 | (A) OxyP (%) among patients and controls shown in relation to increased IMT in the aortic arch and plaque occurrence. Two controls with plaque were excluded in the figure. IMT, intima media thickness; OxyP, peak oxygen saturation; SLE, systemic lupus erythematosus. **(B)** AIx75 (%) among patients and controls shown in relation to increased IMT in the aortic arch and plaque occurrence. Two controls with plaque were excluded in the figure. IMT, intima media thickness; SLE, systemic lupus erythematosus. **(C)** OxyP among patients and controls shown in relation to age, SLE; $R = -0.22$ (ns), Controls; $R = 0.02$ (ns), **(D)** AIx75 (%) among patients and controls shown in relation to age. SLE $R = 0.63$ ($p < 0.001$); Controls $R = 0.56$ ($p < 0.001$). $^{**}p < 0.01$.

When all significant variables were included in a multiple linear regression model, age (**Figure 3D**), ($p < 0.001$), female sex ($p < 0.001$) and diastolic blood pressure ($p < 0.001$) remained as significant risk factors for AIx75 ($R = 0.63$).

There was a significant difference in AIx75 in relation to self-reported physical activity in SLE. For no physical activity AIx75 was 19.4 ± 13.1 % ($n = 31$), for physical activity 1–3 times/week 18.31 ± 2.5 % ($n = 23$), and for physical activity ≥4 times/week 3.1 ± 17.1 % ($n = 6$), ($p = 0.02$). In the controls, no significant differences were seen.

Age Impairment on OxyP and AIx75 in SLE and Healthy Controls

As OxyP was lower, and AIx75 was higher, in SLE patients compared to controls, and as OxyP tended to decrease with age in SLE but not in controls (**Figure 3C**), we analyzed OxyP and AIx75 in different age groups (**Figures 4A,B**). In SLE, decreased OxyP levels were found in all age groups ($p < 0.001$). Increased AIx75 levels were found in three of four age groups ($p < 0.001$, ns in the youngest group).

DISCUSSION

This study of well-characterized SLE patients with clinically low disease activity showed impaired microcirculatory reactivity assessed by OxyP, and signs of premature arterial aging assessed by pulse wave recordings, when compared to healthy controls. Significant correlations with IMT in different vascular areas and plaque occurrence were also detected.

For assessment of microcirculation in SLE, prior studies have used different methods such as capillaroscopy, laser imaging techniques and infrared thermography (18).

In this study we used a novel fiber-optic method combining LDF/DRS for estimating oxygen saturation in the microcirculation of the skin in absolute units (21, 22). Microcirculatory function measures peak oxygen saturation after arterial occlusion. The post-occlusive reactive hyperemia phase refers to the increase in blood flow that mirror the endothelial vasodilatation function. The method is new but validated (23) and can detect disturbed microcirculatory flow in the skin not previously described for this patient group.

We observed that patients with SLE had impaired microcirculation as reflected by OxyP, compared to healthy

TABLE 2 | OxyP and AIx75 related to background variables, traditional risk factors, laboratory tests and medical treatment in a univariate regression model among all 60 patients with SLE.

All SLE ($n = 60$)	**OxyP**		**AIx75**	
	B	***p*-value**	**B**	***p*-value**
Background variables				
Age at examiantion (years)	−0.150	NS	0.776	**<0.001**
Male gender	0.050	NS	−12.149	0.020
Duration of SLE (years)	−0.082	NS	0.529	0.005
SLICC/ACR damage index	0.105	NS	3.444	0.030
APS	1.139	NS	2.150	NS
LN	−2.315	NS	−1.075	NS
Skin & Joint	1.177	NS	−1.075	NS
Traditional risk factors and laboratory tests				
Body mass index (BMI) (kg/m²)	−0.274	NS	0.665	NS
Waist circumference (cm)	−0.632	0.010	0.987	0.030
Sagittal abdominal diameter (cm)	−0.175	0.040	0.404	0.006
Ever smoker (former or current)	−3.387	NS	0.905	NS
Physical activity (occasions/week)	1.141	NS	−2.375	0.034
Systolic blood pressure (mm Hg)	−0.044	NS	0.104	NS
Diastolic blood pressure (mm Hg)	−0.111	NS	0.774	**<0.001**
Raynaud's phenomenon	−5.811	0.010	5.415	NS
Estimated glomerular filtration rate (mL/min/1,73 m²)	0.039	NS	−0.347	0.002
Total cholesterol (mmol/L)	−0.640	NS	6.176	0.001
High-density lipoprotein (HDL) (mmol/L)	−0.201	NS	9.734	0.013
Low-density lipoprotein (LDL) (mmol/L)	−0.259	NS	3.567	NS
Triglycerides (TG) (mmol/L)	−1.828	NS	6.188	0.010
Anti-dsDNA (IU/mL)	−0.004	NS	−0.013	NS
Complement protein 3 (g/l)	−5.697	NS	0.354	0.006
Complement protein 4 (g/l)	−15.669	NS	0.262	0.040
High-sensitivity (hs) CRP (mg/L)	−0.021	NS	1.410	0.030
Medical treatment, ongoing				
Antimalarial agents	−4.899	NS	−0.176	NS
Antihypertensives	−2.138	NS	0.003	NS
Beta-blockers	−3.792	NS	13.700	0.030
ARB/ACE inhibitors	−6.492	0.005	2.567	NS
Other antihypertensives	−4.752	NS	6.732	NS
Glucocorticoid therapy	−3.519	0.080	1.896	NS
Mean daily dose (mg)	−0.712	0.070	−0.129	NS
Warfarin therapy	−2.033	NS	−1.420	NS
Antiplatelet therapy	0.176	NS	0.214	NS
Statin therapy	−12.727	**<0.001**	11.409	NS
DMARD therapy	−3.627	NS	−0.328	NS

Red boxes denote variables remaining significant in multiple analysis. Bold p-values represent p < 0.001. OxyP, Peak oxygen saturation; AIx75, Augmentation Index correlated for heart frequency 75; ACE, angiotensin converting enzyme; APS, antiphospholipid syndrome; ARB, angiotensin II receptor- blocker; B, Beta coefficient; CRP, C-reactive protein; DMARD, Disease Modifying Anti-Rheumatic Drugs; LN, Lupus nephritis.

controls. In healthy controls, the OxyP value were relatively stable regardless of age, whereas OxyP tended to decrease with age in patients with SLE. Stücker et al., using high-resolution two-dimensional laser Doppler perfusion imaging in a healthy group could not find age-related differences in microcirculatory perfusion (36).

Jonasson et al. demonstrated that microcirculatory perfusion is reduced in diabetic patients independent of microvascular changes in the kidneys and large-vessel stiffness (24). In the large population-based Swedish study SCAPIS, Jonasson et al. have shown that age and sex are important variables to consider in studies of microvascular function. They further analyzed groups with diabetes, hypertension and dyslipedemia and found that all these groups had lower OxyP levels compared to subjects without these diseases. The diabetic patients had the lowest values, which is in line with SLE patients in our study. The patients with

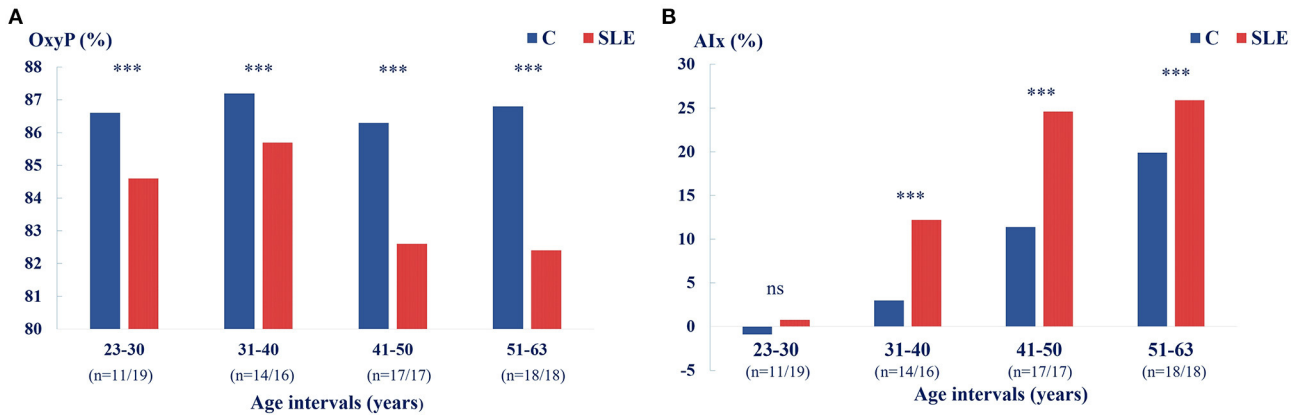

FIGURE 4 | (A) Microcirculation reflected by OxyP (%) decreases with age in SLE patients but not in controls, *** $p < 0.001$. **(B)** AIx75 (%) among patients and controls shown in relation to age groups, *** $p < 0.001$.

hypertension or dyslipidemia showed slightly higher levels, but still decreased compared to patient without these diseases. They also observed that women had higher OxyP compared to men and that age influenced the value (25). Herein, we observed impaired OxyP also in patients of younger age.

Our study showed that reduced OxyP was negatively correlated with waist circumference, sagittal abdominal diameter, presence of Raynaud's phenomenon, as well as ARB/ACE inhibitor and statin therapy in the univariate analysis. In the multivariate analysis only presence of Raynaud's and use of statins remained as negatively correlating factors. However, it should be noted that statin therapy in the study population was prescribed as either primary or secondary prophylaxis. Mosdósi et al. investigated skin perfusion in finger with laser Doppler technology in adolescents with Raynaud's and reported altered heat-induced cutaneous hyperaemia responses (37). Thus, microcirculation is impaired in patients with Raynaud's, also when examined on the upper arm.

Statin therapy has been reported to impair hyperemic blood flow measured with laser Doppler (38). One explanation of our results may be that statin therapy represents dyslipidemia possibly not treated in all aspects. Dyslipdemia in SLE is often characterized by hypertriglyceridemia and decreased levels of high-density lipoprotein cholesterol (39). In active SLE, the atherogenic lipoprotein profile may result in accumulation of triglyceride-rich proteins and development of small and dense low-density lipoprotein-cholesterol particles (40–42).

The possible mechanism of microvascular abnormalities in SLE include autoantibodies forming immune complexes that deposit in small vessels and activate endothelial cells (18). However, SLE-associated risk factors such as disease duration, acquired organ damage (SDI), disease activity (SLEDAI-2K), C3, C4 or anti-dsDNA levels did not correlate with OxyP.

Increased AIx75 was observed in the SLE group compared to controls. Belizna et al. reported that patients with APS, both primary and secondary had a significantly higher prevalence of increased IMT, arterial stiffness, and presence of plaques, independent of known cardiovascular risk factors, compared with controls (43). Possibly, due to the low number of APS patients ($n = 20$), our study could not detect any association of APS and these parameters. Brodszki et al. demonstrated that vascular stiffness was associated with SLE irrespective of secondary vasculitis or not. They suggested that other mechanisms such as shifts in the collagen/elastin ratios, besides atherosclerosis might be involved in the pathogenesis of arterial stiffness in SLE (44). Both these studies used US to evaluate stiffness in large arteries.

Stortz et al. used evaluation of carotid-femoral PWV in patients with SLE, and showed an independent correlation between eGFR and PWV in SLE patients, and they found no difference between SLE and healthy controls (45). Another study using PWV demonstrated significantly higher aortic stiffness in patients with mixed connective tissue disease (MCTD) (46). In the present study, we used pulse wave analysis with tonometry of the radial artery, which is a muscular artery. This method can be used as a surrogate measure for arterial stiffness and cardiovascular risk (13). PWA is widely used to evaluate vascular properties, as it reflects the condition of the entire arterial system. The method is valuable, validated, and used for monitoring of hypertension (15). In a large population study on patients with low risk of CVD, Janner et al. showed that AIx reaches a plateau after 60 years of age, suggesting that AIx may be a better marker of CVD risk in younger subjects (47).

However, AIx is altered by changes in peripheral vascular tone and arterial stiffness, and measurement of PWV is needed for direct assessment of arterial stiffness.

A previous study, which included post-menopausal women with SLE, observed higher aortic PWV while central blood pressure and AIx were essentially unaltered (16). This may imply that PWV is a more sensitive tool for revealing early alteration in arterial wall geometry and function in subjects with SLE, while the later stiffening of central elastic arteries also shifts the reflection sites more distally. It is thus plausible that patients with SLE reaches their AIx plateau at an earlier age while controls still increase their augmentation to catch up the gap at higher age. Shang et al. used AIx to measure arterial stiffness and found an association with global disease activity assessed by SLEDAI-2K (48).

Increased arterial stiffness, including increased AIx, has been reported with increasing age, hypertension, hypercholesterolemia, end stage renal disease, and diabetes (49). However, gender is also a factor to include (50). When all significant variables were included in a multiple linear regression model in our study, age, female sex, and diastolic blood pressure remained as significant risk factors for AIx75. For younger women arterial stiffness is lower than in aged-matched men, but this sex difference reverses during aging (51). We only had eight men in the study and the age profile did not differ compared to the women. AIx75 also correlated with IMT in multiple vascular areas.

In our study, total cholesterol and triglycerides showed association with AIx75 in the univariate, but not in the multivariate, analyses. In contrast to healthy controls, vascular stiffness was improved (lower AIx75) by physical activity in univariate analysis. This finding should be further investigated.

Peak oxygen saturation correlated inversely with arterial stiffness (AIx75) implying that both methods could add valuable information regarding vascular status in SLE.

Although our study population was well-characterized, the number of included subjects remained limited. Nevertheless, the included number of patients were comparable with many other studies investigating the increased risk of cardiovascular disease in SLE (6, 8, 16, 17, 19, 43, 44–46, 48). We admit that both BMI and smoking habits were different among SLE patients compared to the controls. It cannot be excluded that these differences might have affected the results over all. The present study was based on the identical study population as our previous study (8), which could be considered as a limitation. No specific interventions were taken to avoid potential bias. However, the topic herein was different (with focus on microcirculation and vascular hemodynamics) and the collected data thus respond to separate research questions.

Ethnicity of the study population constitutes another limitation. Mainly Caucasian individuals were enrolled, and as ethnicity is well known to affect SLE severity, extrapolation of our results to other populations should be done with caution. Evaluation of microcirculation could be difficult to compare with established methods as the way of analyzing is completely new. However, our method has been validated for various diseases. Test-retest variability was not possible to study for the microcirculation method as the hyperaemic phase could affect a second measure. The described vascular methods are to some degree operator dependent. However, as only one operator was involved, at least the potential inter-operator dependent affection on the results was eliminated.

CONCLUSION

In conclusion, our data suggest that adding non-invasive measurements of microcirculation and pulse wave analysis to standardized US of multiple arterial areas could be useful in the detection of vascular status in SLE. Impaired microcirculation as reflected by OxyP, and higher AIx were observed in SLE but not among controls, and both methods correlated with IMT and occurrence of plaque. The novel method with measurement of OxyP has not previously been studied in this group of patients but our results demonstrate that SLE patients have impaired microcirculation even in the younger ages. Further studies of microcirculation related to vascular hemodynamics in comparison to established methods for evaluation of cardiovascular risk in SLE are warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/ **Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethics Board in Linköping (ref. M75-08, 2013/33-31 and ref. 2017/572-32). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CSv, PE, CSj, and HZ contributed to the conception of this study and the study design. CSv collected and assembled data and wrote the original draft. CSv, PE, CSj, HZ, HJ, TS, and NB contributed to the analysis and interpretation of the data. All authors contributed to the critical revision of the article for important intellectual content and gave final approval of the article for submission. All authors have seen and approved the final text.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.722758/full#supplementary-material

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The Risk of Cardiovascular Diseases in Axial Spondyloarthritis. Current Insights

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There is an increased cardiovascular (CV) risk in axial spondyloarthritis (axSpA), leading to increased CV mortality and morbidity in these patients. The factors that may explain this enhanced CV risk in axSpA are multiple, including traditional CV risk factors such as smoking, but also the inflammatory process and probably the use of non-steroidal anti-inflammatory drugs (NSAIDs). The CV involvement of axSpA may be detected at an early and pre-clinical stage, using non-invasive techniques. While NSAIDs play a deleterious role in the CV risk of axSpA, TNF inhibitors seem to have a beneficial impact, but this remains to be demonstrated in specific clinical studies. More data are needed to determine the potential effects of IL-17 inhibitors on the CV risk of axSpA. CV comorbidity has been mainly assessed in the radiographic form of axSpA, while limited data are available in patients with the non-radiographic form. The current management of axSpA must consider this CV comorbidity according to the EULAR recommendations. Rheumatologists play a determinant role in the detection of CV risk and current management of these patients is focused on the control of disease activity, suppression of inflammation, screening for and management of traditional CV risk factors, as well as the restriction of NSAID use.

Keywords: ankylosing spondylitis, spondyloarthritis, cardiovascular risk, cardiovascular risk factors, atherosclerosis

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INTRODUCTION

Axial spondyloarthritis (axSpA) refers to an interrelated group of inflammatory rheumatic diseases (IRD) that primarily affect the axial skeleton (1). Radiographic changes of the sacroiliac joints are a hallmark of the disease, and enable the diagnosis of ankylosing spondylitis (AS) according to the modified New York criteria (2). The Assessment of SpondyloArthritis international Society (ASAS) has developed a set of criteria for the recognition of patients with early axSpA that includes evidence of sacroiliitis visible by magnetic resonance imaging (MRI), chronic back pain, HLA-B27 positivity and other non-articular symptoms (3). These criteria distinguish the radiographic (r-axSpA, formely AS) and non-radiographic (nr-axSpA) forms of axSpA, according to the presence or absence of structural changes of the sacroiliac joints on pelvic X-rays. When the clinical features predominate in peripheral joints, SpA may be classified as a peripheral form (pSpA).

Besides extra-articular manifestations (psoriasis, acute anterior uveitis and inflammatory bowel diseases), additional comorbidities are described in axSpA, including cardiovascular (CV) involvement (4, 5). Rheumatoid arthritis (RA) is another IRD for which there is ample evidence of an increased CV risk (6). In parallel, there is a cumulating body of evidence that axSpA may promote the development of atherosclerosis, CV manifestations and complications including myocardial infarction and/or stroke (4, 5, 7).

In this review, we analyze the evidence for CV mortality and morbidity in axSpA, as well as the traditional CV risk factors that may participate in the increased CV risk seen in axSpA patients.

MORTALITY IN axSpA

Mortality in axSpA is mostly described in AS, with limited information in nr-axSpA, due to the recent individualization of this subgroup (4, 8). This excess mortality in AS has been previously related to radiation treatment, a therapeutic option that was used until the seventies (9). However, studies on the mortality rate in AS are not concordant. In an analysis from the Mayo Clinic (Rochester, Minnesota USA) in 1979, there was no difference in mortality between male patients with AS and the general male population (10). On the contrary, other studies have reported an excess of mortality in AS, with a standardized mortality ratio (SMR) ranging from 1.6 to 1.9 (11–13) (**Table 1**). These studies took radiation therapy into account, and the increased mortality persisted even in patients who did not receive this treatment. A relationship between mortality in AS and disease duration and severity was also reported (13). A study from Norway confirmed these results (14): in a population of 677 AS patients followed in a reference center for a 34 year period, the SMR was increased in male patients [1.63; 95% confidence interval (CI): 1.29–1.97] compared to a control group. Circulatory disease was the most frequent cause of death (40%) and the factors linked to decreased survival were delayed diagnosis, an increase in acute phase reactants, work disability and the absence of NSAID use. In a series of 2,154 patients with AS from Hong Kong, the SMR was calculated to be 3.07 [2.64–3.5], and 1.89 [1.61–2.13] after adjustment for age. The most frequent cause of death was infection, ahead of CV complications (15). In nationwide cohorts of AS patients from Scandinavian countries, the (age- and sex-) adjusted hazard ratio (HR) for death among AS patients was 1.60 [1.44–1.77] with increased mortality in both male and female patients. A low level of education and general comorbidities (including CV diseases) were identified as predictors of death (16). In a Spanish study analyzing CV mortality and CV events at 5 years in different IRD, AS was found to have the highest risk of a first CV event [HR: 4.6 (1.32–15.99)], but without increased CV deaths (17). Finally, a recent meta-analysis concluded that CV mortality in AS was increased, with a relative risk (RR) of 1.46 [1.15–1.86] (18).

CARDIOVASCULAR MORBIDITY IN axSpA

Mortality in axSpA (AS) is consistently related to CV diseases and complications. In a large American administrative database comparing CV diseases in different IRD including 1,843 patients with AS, the prevalence ratios for ischemic heart disease, cerebrovascular disease and congestive heart failure ranged between 1.2 and 1.8 (19). In a retrospective cohort study conducted in Canada, and including 8,616 patients with AS, the prevalence of CV and cerebrovascular diseases increased with age, but age- and sex-stratified prevalence ratios were highest in younger people, ranging from 1.25 for cerebrovascular disease to 1.37 for ischemic heart disease (20). These results were in line with recent data from a Swedish cohort followed from 2006 to 2012, where the standardized incidence ratios (SIRs) for acute coronary syndrome and stroke were higher in patients compared to the general population (4.3 and 5.4/1,000 person years compared to 3.2 and 4.7, respectively) (21). On the contrary, the study by Brophy et al. (22) did not find an increased prevalence of acute myocardial infarction or stroke among patients with AS compared to those without AS. Different meta-analyses have examined the risk of CV diseases and/or complications in patients with axSpA. Mathieu *et al* performed such an analysis in 2011, and updated it in 2015. In the first meta-analysis, based on 11 studies, there was no significant increase in myocardial infarction or stroke in AS (23), while in the updated meta-analysis, which included 6 additional studies, there was a significant increase in both CV complications [myocardial infarction: odds ratio (OR) 1.6 (1.32–1.93) and stroke: OR 1.5 (1.39–1.62), respectively] (24). The more recent meta-analysis of 16 studies by Kim *et al* also reported a significantly higher risk of myocardial infarction in AS [RR: 1.49 (1.34–1.66) (18). The COMOSPA study was devoted to comorbidity analysis in SpA, including patients with axial or peripheral SpA (ax-SpA: 89%; pSpA: 56%]. The prevalence of ischemic heart disease and cerebrovascular disease was 2.7% [2.2–3.2] and 1.3% [0.9–1.7], respectively (25). Finally, results form a cross-sectional study in Spain were recently published. That study examined the CV burden in patients with r-axSpA and nr-axSpA by means of ultrasound assessment. The results indicated that the atherosclerotic involvement was similar between these 2 forms (26).

CARDIOVASCULAR RISK FACTORS IN axSpA

There are several possible explanations for the higher CV risk in axSpA: inflammation is a well-recognized factor for accelerated atherosclerosis in different IRD, including axSpA, while traditional CV risk factors may also play a role. In addition, specific axSpA-related cardiac manifestations (aortic insufficiency and atrioventricular conduction disturbances) may also contribute to the enhanced CV risk.

Smoking

It is now established that cigarette smoking has a negative influence on axSpA activity and severity (27). In the French DESIR cohort of patients with early SpA, smoking was associated with early disease onset, high disease activity, increased axial structural damage on X-ray, and poor quality of life (28). In the COMOSPA study, the prevalence of smoking in SpA ranged from 6 to 44%, depending on the countries (25).

TABLE 1 | Standardized mortality ratio (SMR) or hazard ratio in patients with radiographic axial spondyloarthritis.

References	Number of patients	Country	Duration of follow-up (years)	SMR/HR
Smith and Doll (9)	14,111	United Kingdom	16	SMR: 1.66
Radford et al. (11)	836	United Kingdom	13	SMR: 1.6 (men)
Karprove et al. (12)	151	Canada	27	SMR1.93 (men)
Lethinen et al. (13)	398	Finland	25.7	SMR:1.5
Bakland et al. (14)	677	Norway	33	SMR: 1.63 (men)
Mok et al. (15)	2,154	China	9	SMR: 1.88
Exarchou et al. (16)	8,600	Sweden	6	HR: 1.6

Hypertension

It is estimated that the prevalence of hypertension is higher in axSpA than would be expected in the general population (4). In a small series of patients with AS ($N = 20$), 20% had hypertension (29). In the COMOSPA study, the proportion was higher (33.5%), especially in northern European countries (25). Continuous use of NSAIDs may impact on the development of hypertension: in a prospective longitudinal r-axSpA cohort, continuous NSAID use was associated with a 12% increased risk for the development of incident hypertension compared to patients with non-continuous use or no NSAID use (30).

Diabetes and Metabolic Syndrome

In the COMOSPA study, the prevalence of diabetes was 8.8% (25). A high frequency of metabolic syndrome according to the NCEP-ATP III criteria was found in a limited series of patients with axSpA ($N = 24$; frequency: 45.8 vs. 10.9% in the controls) (31).

Obesity

A recent study found that patients with axSpA may present with increased weight: in that study, obesity was found in 22% of patients and overweight in 37%, according to the WHO criteria (32). However, body composition studies did not find an excess of fat mass, but an increased lean mass (33).

Dyslipidemia

The relationships between lipid parameters and IRD are complex. Indeed, inflammation has a wide range of effects on lipids, both quantitatively and qualitatively. Under the pressure of inflammation, both LDL and HDL cholesterol tend to decrease, but with an imbalanced atherogenic index (total cholesterol/HDL cholesterol) (34). In parallel, lipids are subject to qualitative changes, toward a pro-atherogenic profile for HDL cholesterol, and oxidation for the LDL fraction (35). All these modifications promote an increased CV risk in IRD (36). In axSpA, similar lipid changes are described. The prevalence ratio of dyslipidemia was 1.2 in a large series of patients with AS (19). In more recent series, HDL cholesterol was found to be decreased, with an elevated atherogenic index (37, 38). In addition, the levels of HDL cholesterol and apolipoprotein-A have been associated with CV complications in axSpA [HR: 3.67 (1.47–9.06) and 1.89 (1.02–3.54)] (39).

PRECLINICAL ATHEROSCLEROSIS IN axSpA

Non-invasive techniques may be used for the identification of early arterial wall changes in IRD. Ultrasonography of carotid arteries is the most widely used method, giving results on intima media thickness (IMT), pulse wave velocity (PWV) and flow mediated dilatation (FMD). It is a valid method for the identification of pre-clinical atherosclerosis with the capacity to predict future CV disease and complications (7). This method has been extensively used in RA, showing impaired endothelial function as well as arterial wall changes (40). Similar results were obtained in patients with axSpA. In two meta-analyses, IMT was reported to be increased in patients with AS (23, 41). A third recent meta-analysis of 35 studies reported an increased IMT and PWV and a decreased FMD in patients with AS, indicative of a higher risk of subclinical atherosclerosis (42). Carotid plaques are frequently observed in axSpA compared to a control population (29.7 vs. 9.4%) and the presence of such plaques correlated with acute phase reactants but not IMT (43). Endothelial dysfunction as evaluated by FMD was impaired in a series of 43 patients with axSpA compared to 40 healthy controls (44). In the cross-sectional study from Spain, there was no difference in the prevalence of carotid plaques or in carotid IMT between patients with r-axSpA and those with nr-axSpA. In addition, when using the CV risk assessment model (SCORE), the percentage of patients classified in the very high risk category was comparable between the 2 groups, indicating that the CV burden was similar in nr-axSpA and r-axSpA (26).

THE EFFECT OF TREATMENT ON CARDIOVASCULAR RISK IN axSpA

The CV impact of the treatments that are routinely used in axSpA may be bidirectional, i.e., beneficial and/or detrimental. Indeed, since atherosclerosis should be seen as an inflammatory disease, and the CV risk in IRD is largely influenced by inflammation, controlling inflammation would have a favorable impact on this comorbidity. In RA, it is well-established that methotrexate (MTX) and TNFα inhibitors (TNFi) positively influence the CV risk (45).

NSAIDs

It is well-recognized that all the NSAIDs have a negative impact on CV risk, contributing to an excess of CV complications (46). Among the different NSAID class, coxib and diclofenac were

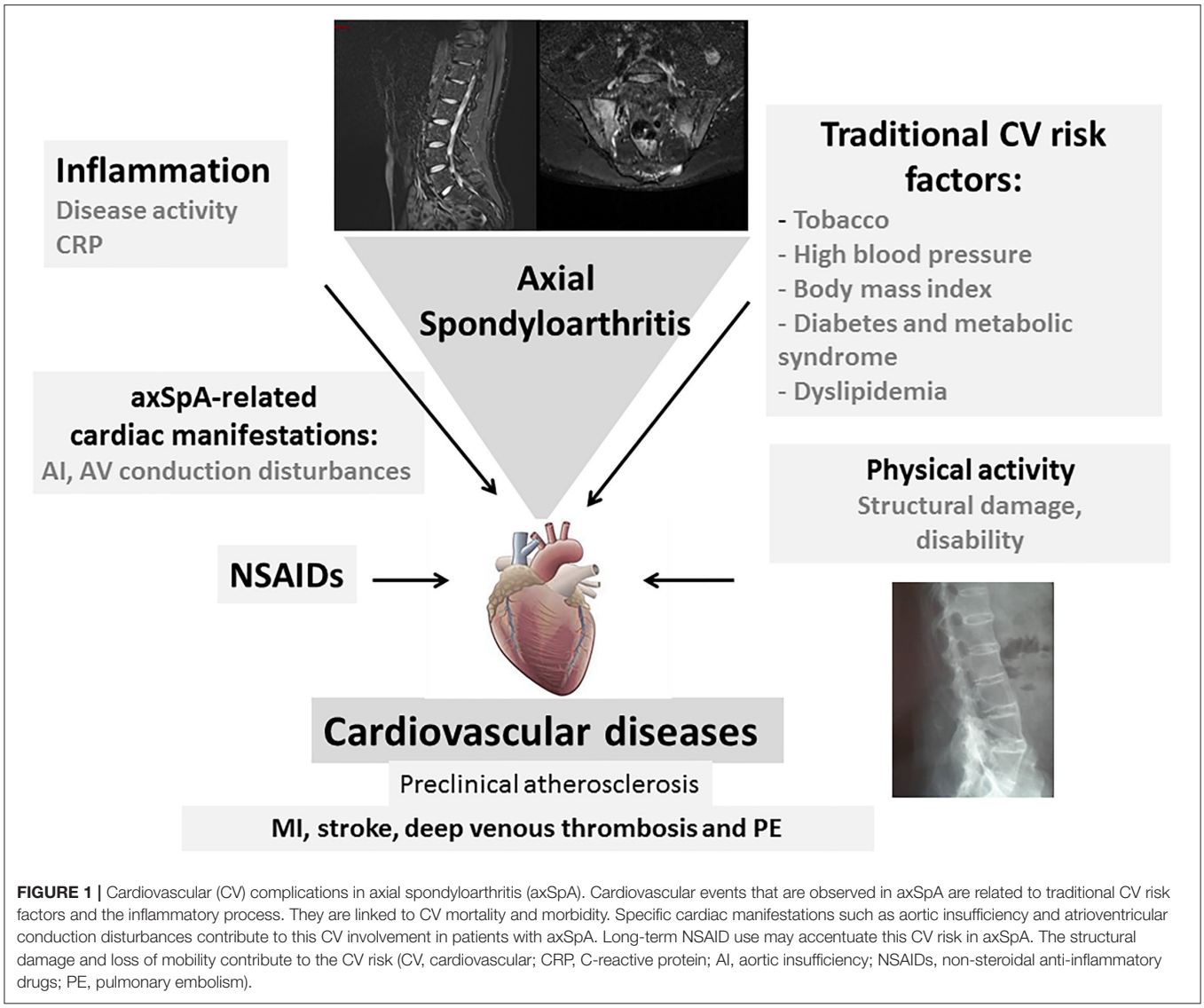

FIGURE 1 | Cardiovascular (CV) complications in axial spondyloarthritis (axSpA). Cardiovascular events that are observed in axSpA are related to traditional CV risk factors and the inflammatory process. They are linked to CV mortality and morbidity. Specific cardiac manifestations such as aortic insufficiency and atrioventricular conduction disturbances contribute to this CV involvement in patients with axSpA. Long-term NSAID use may accentuate this CV risk in axSpA. The structural damage and loss of mobility contribute to the CV risk (CV, cardiovascular; CRP, C-reactive protein; AI, aortic insufficiency; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism).

associated with the higher risk of major vascular events while this risk was less with naproxen (46). NSAIDs are used as first line of treatment in axSpA, but not continuously, according to different recommendations. However, the CV risk induced by NSAIDs in axSpA remains controversial. Indeed, in a Canadian study on the mortality of AS, the lack of NSAID intake was one factor associated with increased CV mortality (47). The same result was found in a Norwegian study showing an excess of death from vascular disease. One of the factors associated with reduced life expectancy was the lack of NSAID use [OR: 4.53; (1.75–10.77)] (14). To explain these results, it was suggested that NSAIDs may partially control inflammation, and thus, in patients not using NSAIDs, atherosclerosis may accelerate. However, these results may reflect a selection bias by proposing NSAIDs only to patients without CV risk factors.

Conventional Synthetic DMARDs

Sulfasalazine (SLZ) is used in selective cases of SpA, with limited efficacy in the peripheral form. Since SLZ has an aspirin moiety, it has been suggested that this drug may have a protective CV effect. In a Taiwanese population-based retrospective study, the use of SLZ provided a protective effect against CV diseases in patients with AS [HR: 0.65 (0.43–0.99)] (48).

Biological DMARDs

In RA, TNFi result in a 20–50% reduction in CV risk (49). There are numerous studies demonstrating that TNFi may reduce subclinical inflammation in axSpA. Results are not universally concordant, but overall, TNFi may favorably impact IMT and endothelial dysfunction, with a stabilizing effect on the atheromatous plaque (50–52). In the systematic review by Tam et al. it was concluded that TNFi are effective in AS in preventing or even reversing the progression of IMT in patients responding to treatment. Pulse wave velocity was reduced or unchanged under TNFi treatment, while aortic augmentation index was also largely unchanged (53). Lipid parameters may fluctuate under TNFi. In axSpA, the atherogenic index did not change under infliximab, while it improved under etanercept (54, 55). In a

prospective study of patients with AS receiving a TNFi, we did not observe significant changes in insulin parameters (HOMA-IR index) (56).

The experience with IL-17 inhibitors (IL-17i) in axSpA is shorter compared to the use of TNFi, with no specific study examining the CV risk. It is considered that IL-17A may have deleterious effect on the arterial wall and cardiac cells, with potentially pro-atherogenic properties (57). In the secukinumab and ixekizumab development programs, there were no reports of increased CV events (58, 59). Similarly, the long term follow-up of patients with psoriasis under secukinumab did not reveal a specific CV signal or an increase in major adverse CV events (MACE) or CV mortality (60, 61). Major CV events were not increased with long term use of ixekizumab in a pooled analysis from 21 clinical trials in patients with psoriasis, psoriatic arthritis (PsA) and axSpA (62).

Targeted Synthetic DMARDs

Janus kinase inhibitors (JAKi) (tofacitinib, upadacitinib, filgotinib) are currently in development in axSpA, but upadacitinib has recently been approved for the treatment of axSpA. During the phase 3 clinical trials, there was no safety signal regarding CV events with JAKi in patients with axSpA (63). In a systematic review and meta-analysis of the CV effects of JAKi in patients with RA in randomized controlled trials, there was no evidence of a significant change in CV risk in the short term (64). In a *post hoc* analysis from the RA, psoriasis and PsA development programs and observational studies, the incidence rates for deep vein thrombosis (DVT), pulmonary embolism (PE) and venous thromboembolism (VTE) were similar between tofacitinib doses (5 vs. 10 mg twice daily) but generally higher in patients with CV or VTE risk factors (65). However, concerns have recently emerged regarding the risk of thrombosis under tofacitinib, leading to warnings by competent authorities. The ORAL surveillance trial analyzed the safety of tofacitinib (5 mg and 10 mg twice daily) vs. a TNFi in subjects with RA aged 50 years or older and with at least one additional CV risk factor. The primary endpoints in this trial were non-inferiority of tofacitinib compared to TNFi in regard to MACE and malignancies (excluding non-melanoma skin cancer). Final analysis of ORAL surveillance showed that the non-inferiority criteria were not met for the primary comparison of the combined tofacitinib doses vs. TNFi [HR for MACE: 1.33 (0.91–1.94); HR for malignancies: 1.48 (1.04–2.09)] [1]. The conclusion is that there was a higher risk of MACE and malignancies (excluding non-melanoma skin cancer) with tofacitinib as compared to TNFi in patients with RA. Following these results, healthcare professionals were advised to keep considering the benefits and risks of tofacitinib when deciding to prescribe and continue patients on the drug [2].

DISCUSSION

There is compelling evidence that there is an increased CV risk in axSpA, and that it represents a major comorbidity deserving specific attention. In a Swedish study comparing the CV events between AS, RA and the general population, the adjusted RR for stroke was equivalent between AS and RA [1.5 (1.1–2.0) and 1.5 (1.2–1.8), respectively] while there was a smaller increase for acute coronary syndrome in RA than in AS [1.7 (1.4–2.0) and 1.3 (1.0–1.7), respectively]. For thromboembolic events, the risk was also less in AS compared to RA (66). Similar to RA, the increased CV risk in axSpA may be detected at a preclinical stage using non-invasive techniques (43) (**Figure 1**). It is well known that inflammation is a major determinant of atheroma development, from plaque initiation to thrombosis. It has been established from epidemiological studies that high sensitivity CRP levels predict CV events in the general population, leading to a higher CV risk to that induced by LDL cholesterol during atheroma formation (67). Inflammation in axSpA may be noticed by elevated circulating high sensitivity CRP, interleukin-6 or homocysteine (68). The EULAR recommendations for the management of patients with axSpA include the "abrogation of inflammation," highlighting the need to control inflammation to reach this goal (69). The parameters evaluating arterial wall dysfunction in axSpA correlated with disease activity or severity measurements. In addition, it should be stressed that CV risk has mainly been evaluated in the radiographic form of axSpA, whereas limited data exist in nr-axSpA. Recommendations for the CV risk management in RA have been elaborated by the EULAR group and expanded to axSpA and PsA (70). General principles for the detection and management of CV diseases in axSpA are outlined, including the correct use of NSAIDs. The identification and subsequent management of traditional CV risk factors is also important. The guidelines recommend the use of risk prediction algorithms, such as SCORE to determine which patients require lipid-lowering and anti-hypertensive therapies. For RA, it is recommended to adjust available prediction scores such as SCORE, by a multiplication factor of 1.5 in order to appropriately evaluate the 10 year CV risk. However, in axSpA, this adjustment is not validated. Lifestyle recommendations include the benefits of a healthy diet, regular exercise and smoking cessation. Physical activity may benefit patients with axSpA, reducing not only CV risk factors, but also disease activity (71).

CONCLUSION

Similarly to RA, CV risk is increased in axSpA. This comorbidity is a reality for patients with axSpA and must be adequately evaluated. It is highly probable that the use of bDMARDs (TNFi and probably IL-17i) and specific treatment strategies, such as the treat-to-target paradigm should have a favorable impact on CV risk, and thus, disease prognosis. However, specific clinical studies examining this question are required. Overall, CV risk detection and management is an important aspect for patients with axSpA that deserves specific attention from physicians.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

[1]https://clinicaltrials.gov: NCT02092467.

[2]https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing.

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MINI REVIEW
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The Effect of Ketogenic Diet on Inflammatory Arthritis and Cardiovascular Health in Rheumatic Conditions: A Mini Review

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The principle of ketogenic diet (KD) is restriction of carbohydrates to a maximum of 5–10% of the total daily caloric intake, aiming at shifting body metabolism toward ketone bodies. Different studies suggested promising results of KD to help patients to lose weight, to reduce insulin requirements in diabetes, to supplement cancer protocols, to treat neurological conditions and to optimize control of metabolic and cardiovascular diseases. However, literature about the anti-inflammatory properties of KD in rheumatic diseases is still limited. The beneficial effects of weight loss in patients with inflammatory arthritis can be explained by biomechanical and biochemical factors. Obesity is associated with macrophage activation and production of pro-inflammatory cytokines including TNF-α, IL-1b, and IL-6. The clinical effect of KD may be primarily attributed to improvement of insulin sensitivity. Insulin resistance is associated with an increase of TNF-α, IL-1α, IL-1β, IL-6, and leptin. Moreover, reduction of body's adipose tissue and weight loss account for part of the anti-inflammatory effects and for the impact of KD on cardiovascular health. In rheumatoid arthritis, fasting was shown to be effective in reducing disease symptoms, possibly through the production of β-hydroxybutyrate (BHB), the main ketone body. BHB may exert inhibitory effects also on IL-17 and intermittent fasting improved the clinical manifestations of psoriatic arthritis. In ankylosing spondylitis, current literature doesn't allow to draw conclusion about the effects of KD. Future prospective studies will be needed to elucidate the potential beneficial effects of KD on specific domains and clinical outcomes in patients with inflammatory arthritis.

Keywords: ketogenic, diet, inflammatory, arthritis, rheumatoid, psoriatic, ankylosing spondylitis, cardiovascular

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INTRODUCTION

Ketogenic diet (KD) is characterized by marked carbohydrate restriction, usually to <50 grams a day, and not in a single meal. In a standard KD, carbohydrates should represent about 5–10% of the total daily caloric intake, while the rest of macronutrients consists of proteins (20%) and fats (70–75%) (1). The concept of KD was proposed for the first time in 1921 as a substitute for

fasting (2). In the early 20th century, before the introduction of anti-epileptic drugs, fasting was the method of choice to manage epilepsy (3). But fasting, although efficient, cannot be maintained for a long period of time. Therefore, in 1921, Dr. Wilder proposed KD as a suitable method to induce a metabolic state similar to fasting, through the production of ketone bodies, but without caloric restriction. This method was widely used as a treatment for epilepsy during the fourth and fifth decade of 20th century but then dramatically decreased when new anti-epileptic drugs were introduced. KD experienced a reemergence in recent years as a means for weight loss and the physiological concepts behind the dietary regimen gained new scientific interest (3). In the present mini review, we summarize available literature regarding the potential role, pathophysiology and clinical implications of KD in inflammatory arthritis.

Literature review was limited to published primary research, including basic science, cohort studies, intervention and observational trials, and review articles indexed in PubMed.

The following search terms were used: "ketogenic diet" AND "arthritis" OR "rheumatoid arthritis" OR "psoriatic arthritis" OR "ankylosing spondylitis." As the intent of the review was narrative, inclusion was based on relevance, as deemed so by the authors, to one of the three subcategories of interest: (1) ketogenic diet in rheumatoid arthritis (RA); (2) ketogenic diet in psoriatic arthritis (PsA); (3) ketogenic diet in ankylosing spondylitis (AS). Additionally, articles reporting the effects of KD on cardiovascular health in patients with rheumatic diseases were considered relevant.

Physiological Effects of Ketogenic Diet

The balance between formation (ketogenesis) and degradation (ketolysis) controls circulating levels of ketone bodies, in a process mainly regulated by the secretion of insulin and glucagon (4). Among the important physiological changes induced by KD there is insulin reduction (5) and the hormonal changes caused by KD, with decreased insulin and increased glucagon levels, favor gluconeogenesis. Under conditions of marked carbohydrate restriction, the body primary energy source switches from glucose toward ketones and fatty acids which are obtained from dietary fat and proteins but also from endogenous sources such as glycogen and adipose stores through lipolysis (6). The accelerated mobilization rate of fatty acids from adipose tissue leads to conversion of acetyl-CoA into ketone bodies, in a process known as ketogenesis (7). Ketogenesis takes place primarily in the liver, which can produce ketone bodies in two ways (8). The first way is the oxidation of fatty acids to acetyl-CoA, which are the building blocks of the ketone bodies, or by conversion of amino acids directly into ketone bodies (9). This results in the synthesis of β-hydroxybutyrate (BHB), acetoacetate and acetone. BHB is the primary and most abundant ketone body found in bloodstream. However, the liver cannot use ketone bodies due to the lack of the enzyme succinyl CoA:3-ketoacid CoA transferase. Therefore, ketone bodies are utilized as a fuel by extra-hepatic tissues, thus sparing glucose metabolism. In these circumstances, ketone bodies replace most of the glucose required by the brain, while liver gluconeogenesis provides the limited amount of energy needed by glucose-dependent tissues such as red blood cells, retina and renal medulla (7).

The mean time for achieving nutritional ketosis is generally 3 days, although longer periods up to 10 days have been documented (10). During the first 3 days, the ketosis induction phase, the patient may experience adverse effects including headache, nausea, asthenia, fatigue, constipation. These effects tend to disappear at the end of the induction phase (10). A different type of adverse effects may be seen in long-duration KD, including gastroesophageal reflux disease, uric acid increase, electrolyte imbalance and hyperlipidemia (11).

Clinical Effects of the Ketogenic Diet

Insulin reduction and improvement of insulin sensitivity contribute to the clinical effects of KD. Insulin resistance is an impaired response to insulin stimulation of target tissues, primarily liver, muscle and adipose tissue (12). Insulin signal is conducted through complex intracellular mechanisms regulated by multiple kinase enzymes (13). One of the most prominent applications of KD is for the purpose of weight loss (14, 15) and a meta-analysis of 60 dietary trials of weight loss suggested insulin reduction as a *primum movens* of weight loss (16). Another clinical manifestation of KD related to glucose metabolism and insulin regulation can be observed in patients diagnosed with glucose transporter 1 (GLUT1) mutation, which have impaired absorption of glucose from the blood, leading to a reduced supply of nutrients to the brain that manifests as epilepsy. In these patients, KD caused a significant improvement of seizure frequency (17). Furthermore, KD has been evaluated as part of cancer treatment protocols in brain, colon, breast, and lung tumors. These studies resulted in beneficial effects when used alongside chemotherapy, radiotherapy, or both (9). Additionally, KD can be used in the setting of Alzheimer's disease, with an increase in cognitive function (18), and therapeutic effects have been proposed also for neurologic conditions characterized by substantial motor dysfunction (19).

Ketogenic Diet and Systemic Inflammation

Systemic inflammation is regulated by the production of pro- and anti-inflammatory cytokines. Alterations in the balance of these mediators results in reduction or increase in systemic inflammation (20). The effects of KD on systemic inflammation are related to three main drivers: (1) insulin reduction, (2) BHB synthesis, (3) glucagon increase (21). Additionally, since insulin reduction leads to weight loss, all the anti-inflammatory effects of weight loss should be taken into account as well (**Figure 1**).

Insulin

Insulin and chronic hyperinsulinemia are associated with an increase of the pro-inflammatory cytokines TNF-α, IL-1α, IL-1β, IL-6, and leptin (22). Leptin is a unique cytokine due to its adipose-derived origin. Adipose tissue is considered not only as the body's energy reservoir, but also as an endocrine tissue that can produce proinflammatory cytokines (23). Furthermore, weight loss is a relevant part of the anti-inflammatory effects of KD and reduction of body's adipose tissue has an influence on the secretion of hormones such as leptin (24).

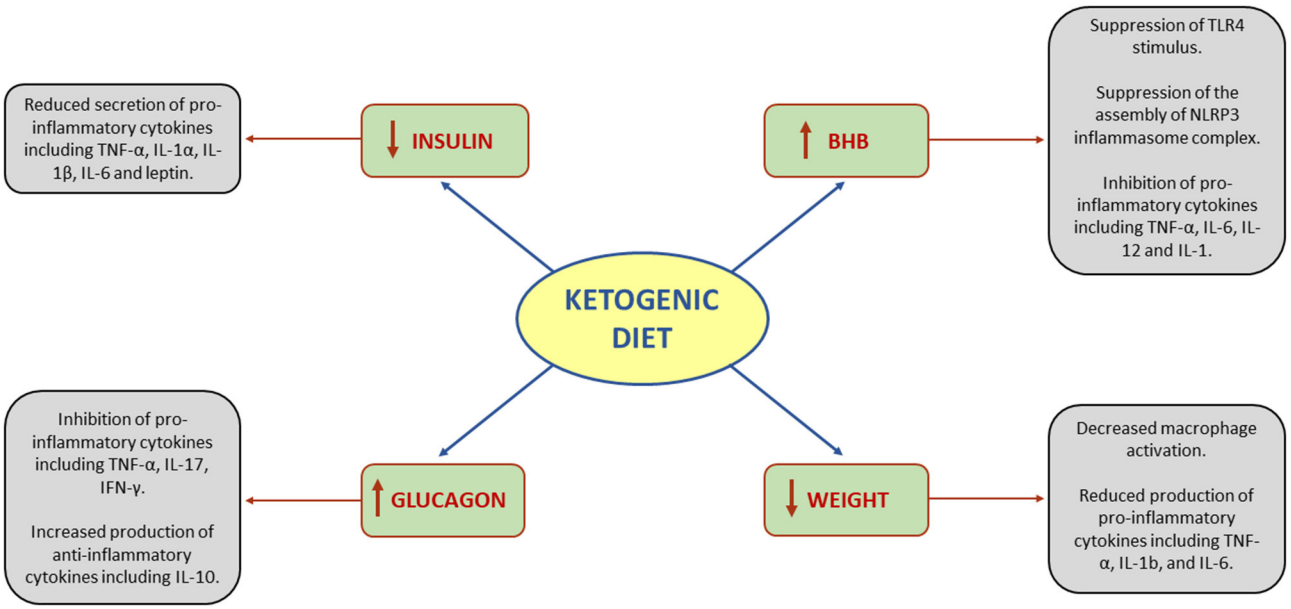

FIGURE 1 | Effects of ketogenic diet on systemic inflammation. BHB, beta-hydroxybutyrate; IFN-γ, interferon gamma; IL, interleukin; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha.

β-Hydroxybutyrate

BHB has a double effect on NLRP3 inflammasome complex (NIC). NIC is a protein complex involved in monocyte-induced inflammation (25). When activated, NIC functions as an inducer of caspase 1, which cleaves pro-IL-1β. After being cleaved, pro-IL1β becomes functional IL-1β (26). The activation of NIC requires two steps: first the stimulus from Toll-like receptor 4 (TLR4) that promotes the synthesis of NIC proteins, and then a second step which is their assembly. BHB suppresses TLR4 stimulus and the assembly of NIC individual proteins (27). Furthermore, BHB functions as a ligand to hydroxycarboxylic acid receptors (HCAr). HCAr, also known as GPR109a, is a G protein-coupled receptor predominantly expressed in adipose and immune cells (28). Activation of HCAr suppresses pro-inflammatory cytokine production, including TNF-α, IL-6, IL-12, and IL-1 (29).

Glucagon

The increase in glucagon is a direct effect of the decrease in insulin. Nevertheless, glucagon is also a potent hormone that affects many systems, including the immune system (30). Glucagon exerts its effect by activating the cyclic adenosine monophosphate (cAMP) pathway. The effects of cAMP activation vary between tissues and even between cells of the same tissue. In dendritic cells, the increase in cAMP suppresses the release of pro-inflammatory mediators including TNF-α, IL-17, IFN-γ, and promotes anti-inflammatory cytokine production such as IL-10 (31). T cells have shown to reduce proliferation and production of IL-2 (31) and to increase production of IL-4 and IL-5, both interleukins that promote Th2 differentiation (32). In smooth muscle cells, cAMP inhibits proliferation and suppresses the release of cytokines such as IL-1ß and IL-8 (30).

Weight Loss

The beneficial effects of weight reduction can be explained by biomechanical and biochemical issues. Weight loss reduces the load exerted on joints (33). Increased adipose tissue has been associated with local and systemic inflammation (23). Obesity is implicated in macrophage activation and production of pro-inflammatory cytokines including TNF-α, IL-1b, and IL-6 (34). As mentioned previously, insulin reduction precedes weight loss (16). Therefore, insulin reduction can be considered a benefit of weight loss. Part of insulin pro-inflammatory effect is exerted through inhibition of anti-inflammatory cytokines production (35). KD, besides the potential anti-inflammatory properties, is also the best non-surgical treatment for weight reduction. A meta-analysis of 53 studies including 68.128 participants suggested that higher-fat, low-carbohydrate diet, was the best intervention to achieve the weight loss and weight maintenance targets (36). In RA, it is important to distinguish between intentional and unintentional weight loss. Intentional weight loss is beneficial in improving the clinical aspects of RA, while unintentional weight loss can worsen the manifestation of RA (37). A retrospective analysis of electronic medical records of 178 patients diagnosed with RA demonstrated obese and overweight patients who achieved weight reduction exceeding 5 Kg had a three-fold higher probability to experience improvement in RA symptoms in comparison with patients who did not succeed in losing weight (38). Similar results were observed in PsA, where several disease activity parameters improved after weight

loss treatment with very low energy diet, in a dose responder manner (39).

KETOGENIC DIET IN RHEUMATOID ARTHRITIS

Several studies have been conducted to investigate the role of dietary interventions in RA (40–44). Available evidence suggests the potentially beneficial effects of anti-inflammatory diets on disease activity (45). Products such as red meat, salt or high-fat diet may trigger inflammation, while fruit, vegetables and fish may exert an anti-inflammatory action (46, 47). Nevertheless, there is no specific dietary recommendation in RA.

A systematic review of 70 dietary studies revealed that fasting, omega 3 and vitamin D3 significantly reduced RA symptoms (48). Fasting and calorie restriction, in particular, were associated with improvement of RA activity, with stronger effects on subjective symptoms (49).

During Ramadan, Muslims refrain from eating and drinking from dawn to sunset. It results in a month of intermittent fasting. Studying the effects of fasting during Ramadan, Su et al. (50) observed non-significantly higher DAS-28 scores before than during Ramadan and significant improvement in morning stiffness and functional disability. Current literature suggests the benefit of fasting in treatment of RA (49–52) and, as previously mentioned, the metabolic state induced by fasting can be considered similar to KD. On this basis, it is conceivable a role for KD in RA but the available knowledge outlines little efficacy (53, 54). Fraser et al. (54) found that fasting, but not KD, significantly decreased serum IL-6 levels and improved disease activity in RA patients. However, in these studies KD was protracted only for 7 days, in order to reproduce the effects of fasting. It has been demonstrated that longer periods are needed to have a response on pain control (55) and to negatively affect oxidative stress (56). It is possible that the tested period of treatment was too short to obtain significant results in RA.

KD may affect RA in several different ways. First, BHB suppresses macrophages and neutrophils' synthesis of IL-1 by inhibiting NIC and thus reducing TNF-α (24, 57). Secondly, BHB has been shown to suppress proinflammatory interleukins including IL-1, IL-12, and IL-6 by activation of HCAr (29). Furthermore, BHB may inhibit the release of IL-1β and IL-18 mediated by NLRP3, contributing to the anti-inflammatory role of KD (58).

KETOGENIC DIET IN PSORIATIC ARTHRITIS

PsA is associated with several metabolic abnormalities. Insulin resistance, hypertension, diabetes, and hyperuricemia are common comorbidities defining the spectrum of the systemic psoriatic disease (59). Literature about the effects of nutritional interventions in PsA is limited (60, 61), with no specific dietary indication for PsA patients. In psoriasis, it has been shown that a ketogenic nutritional regimen led to significant improvement in disease activity indices (62). Through the assessment of nuclear magnetic medicine metabolomic profile, it was also possible to demonstrate a marked amelioration in biochemical parameters indicative of metabolites related to psoriasis (62). It has been suggested that, in psoriatic patients, KD may facilitate weight loss and modulate systemic inflammation resulting in a quick response to systemic therapy (63–65).

We could not retrieve studies about KD in PsA but some information can be derived from a study conducted on PsA patients during the Ramadan fasting (66). Adawi et al. demonstrated that intermittent fasting improved the clinical manifestation of PsA, including PsA disease activity scores, enthesitis and dactylitis. Furthermore, the patients' improvement was independent of changes in the patients' weight (66). PsA has been strongly associated with Th17 and IL-17A increase (67). In addition to the aforementioned KD effects, BHB induces the production of IL-10 *via* dendritic HCAr, resulting in an inhibitory effect on Th17 (68, 69).

KETOGENIC DIET IN ANKYLOSING SPONDYLITIS

Similar to RA and PsA, there is little evidence that specific dietary interventions influence the activity of AS. Macfarlane et al. (70) conducted a systematic review of 16 publications, including 10 full-text articles, to investigate which dietary regimen induced the best clinical results in AS. The authors concluded that reduction in starch intake, exclusion of dairy products, consumption of fish and fish oil or probiotic supplementation did not improve AS symptoms.

Patients affected by AS and, in general, by axial spondyloarthritis (axSpA), are characterized by an increased cardiovascular risk (71–73). Mediterranean diet has been shown to exert a protective role on cardiovascular morbidity (74, 75). When the impact of Mediterranean diet was investigated in axSpA patients, both the subjective perception of pain, acute phase reactants and disease activity improved after 6 months of nutritional intervention (76).

One of the key pathogenetic mechanisms of AS is the impairment of immunomodulatory function of regulatory T cells, resulting in enhanced IL-17 and other pro-inflammatory cytokines production, with proliferation of pro-inflammatory T cell subsets (77). This process leads to inflammation in the enthesis and ileum of patients with active disease (78). Th17 differentiation is facilitated by TGF-β and IL-6, while IL-23 is determinant to stabilize and maintain TH17 activation and secretion of pro-inflammatory cytokines (79).

Interestingly, KD alters the gut microbiome, with ketone bodies directly inhibiting the growth of gut bacteria. Data obtained from mice models suggest that, reducing the colonization levels of gut bacteria, KD may mediate the lack of intestinal Th17 induction (80). KD can thus induce changes in host metabolites. The alteration of gut microbiota may have downstream consequences for immune cells, reducing levels of intestinal TH17 cells (80). Moreover, BHB was shown to affect microbial-mediated

immunomodulation in addition to its ability to inhibit the NLRP3 inflammasome with consequent anti-inflammatory effects (80).

CARDIOVASCULAR RISK IN RHEUMATIC DISEASES AND THE EFFECTS OF KETOGENIC DIET

In RA, the risk of cardiovascular diseases has been reported to be higher than in the general population, in particular for stroke, heart failure, myocardial infarction and atrial fibrillation (81–84). Patients with RA also have increased mortality rate independently from the presence of other cardiovascular risk factors (85). Additionally, high prevalence of cardiovascular comorbidities and increased mortality related to cardiovascular diseases has been demonstrated in patients with PsA and AS (71, 86–90). Robust evidence outlines a pivotal role of inflammation and immune system dysregulation in the pathogenesis of atherosclerosis and endothelial damage (91–93). Biologic and non-biologic anti-rheumatic therapies may exert a protective role on cardiovascular outcomes in patients with rheumatic diseases (94) and optimizing the control of disease activity has been associated with reduction of cardiovascular events in RA, PsA and AS (95–98). Assessment and management of cardiovascular risk factors is therefore essential in the follow-up of patients with rheumatic diseases. Although no study analyzed the effects of KD on cardiovascular health of individuals with inflammatory arthritis, the potential applications of KD in modulating cardiovascular risk factors and outcomes have been extensively investigated in non-rheumatic patients. A systematic review and meta-analysis of clinical trials carried out to study the efficacy of low-carbohydrate diet on major cardiovascular risk factors demonstrated significant reduction in body weight, BMI, abdominal circumference, blood pressure, plasma triglycerides, fasting plasma glucose, glycated hemoglobin, plasma insulin and plasma C-reactive protein, along with an increase in HDL-cholesterol (99). An overall beneficial impact of low-carbohydrate diet on cardiovascular health was therefore observed, although a possible duration effect was suggested, with benefits that decrease over time. However, other reviews found controversial results, with no or little difference in changes of cardiovascular risk factors with KD, rising also questions about prolonged adherence to the dietary regimen (14, 100). In conclusion, current literature suggests that KD might be associated with improvement of cardiovascular risk factors, mainly driven by weight loss possibility but further studies are needed to evaluate the long-term effects of KD on cardiovascular outcomes and also to assess which is the optimal macronutrients composition (101).

DISCUSSION

KD is a well-established treatment option used since the 1920s for drug-resistant epilepsy (102). Emerging evidence suggests an adjuvant role of KD in cancer treatment (9, 103) and a possible applicability also in other conditions such as Alzheimer's disease (18) and Parkinson's disease (104). However, the most significant results of KD have been obtained in treating obesity, with robust evidence showing improvement in body weight and reduction in levels of cholesterol, triglycerides and blood glucose (4, 14, 105). Moreover, a role of KD in the reduction of cardiovascular risk has been proposed (99).

Obesity has been proposed as an environmental factor promoting onset and evolution of autoimmune diseases through a direct involvement of adipokines in their pathogenesis (106). Common mechanistic pathways are shared by obesity and rheumatic conditions (107) and the assessment of obesity status and of possible therapeutic interventions is of relevance when establishing a treatment plan for patients with rheumatic and musculoskeletal diseases (108). Extensive experimental and clinical research suggests that being overweight or obese impacts not only disease activity but also several aspects of the life of patients living with inflammatory arthritis (109). Weight loss improves outcomes in patients with RA (37, 38, 44, 49), PsA (39, 61, 64) and AS (110, 111). Besides inflammatory arthritis, metabolic, and eating disorders were suggested to facilitate the occurrence of early clues of connective tissue disorders (112) and obesity was shown to worsen musculoskeletal symptoms also in patients with fibromyalgia (113). Promoting weight loss strategies may be part of the treatment for overweight and obese patients with fibromyalgia but evidence regarding the efficacy of KD in this setting is lacking. Obesity is also a known risk factor for development and progression of osteoarthritis (114). Weight-loss programs were shown to ameliorate osteoarthritis symptoms (115), with exercise and diet therapy leading to significant improvements (116). Low-carbohydrate diet reduced pain intensity in individuals with knee osteoarthritis (117) but, again, the efficacy of a therapeutic KD on different domains of osteoarthritis such as symptoms, pain relief, physical function and health-related quality of life has not been evaluated.

In conclusion, literature about the effects of KD on disease activity and patient reported outcomes in inflammatory arthritis is extremely limited. Evidence derived from fasting studies suggests a mild beneficial effect. Since fasting and KD induce a similar metabolic state, a potential efficacy of KD could be assumed but the available data do not allow to draw conclusions. Future prospective, population-based and adequately powered studies of dietary intervention are required to determine whether KD plays a role in the treatment strategy of patients with rheumatic musculoskeletal diseases.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Cardiovascular Autonomic Function Changes and Predictors During a 2-Year Physical Activity Program in Rheumatoid Arthritis: A PARA 2010 Substudy

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Background: Chronic inflammation leads to autonomic dysfunction, which may contribute to the increased risk of cardiovascular diseases (CVD) in patients with rheumatoid arthritis (RA). Exercise is known to restore autonomic nervous system (ANS) activity and particularly its parasympathetic component. A practical clinical tool to assess autonomic function, and in particular parasympathetic tone, is heart rate recovery (HRR). The aim of this substudy from the prospective PARA 2010 study was to determine changes in HRR post-maximal exercise electrocardiogram (ECG) after a 2-year physical activity program and to determine the main predictive factors associated with effects on HRR in RA.

Methods: Twenty-five participants performed physiotherapist-guided aerobic and muscle-strengthening exercises for 1 year and were instructed to continue the unsupervised physical activity program autonomously in the next year. All participants were examined at baseline and at years 1 and 2 with a maximal exercise ECG on a cycle ergometer. HRR was measured at 1, 2, 3, 4, and 5 min following peak heart rate during exercise. Machine-learning algorithms with the elastic net linear regression models were performed to predict changes in HRR1 and HRR2 at 1 year and 2 years of the PARA program.

Results: Mean age was 60 years, range of 41–73 years (88% women). Both HRR1 and HRR2 increased significantly from baseline to year 1 with guided physical activity and decreased significantly from year 1 to year 2 with unsupervised physical activity. Blood pressure response to exercise, low BMI, and muscular strength were the best predictors of HRR1/HRR2 increase during the first year and HRR1/HRR2 decrease during the second year of the PARA program.

Conclusion: ANS activity in RA assessed by HRR was improved by guided physical activity, and machine learning allowed to identify predictors of the HRR response at the different time points. HRR could be a relevant marker of the effectiveness of physical activity recommended in patients with RA at high risk of CVD. Very inactive and/or high CVD risk RA patients may get substantial benefits from a physical activity program.

Keywords: heart rate recovery, autonomic nervous system, physical activity, rheumatoid arthritis, inflammation, cardiovascular disease, blood pressure, muscular strength

BACKGROUND

The autonomic nervous system (ANS) plays a major role in cardiac and vascular adaptations to environmental stress and is thus a major health marker for the effects of aging and cardiovascular diseases (CVD) (1). Autonomic dysfunction, i.e., increased activity of sympathetic tone and/or less parasympathetic tone at rest is associated with chronic inflammation (2). Rheumatoid arthritis (RA) is the most common inflammatory joint disease affecting 1–2% of the population worldwide (3). Patients with RA exhibit signs of autonomic dysfunction (4, 5), which may contribute to the established vascular (6, 7) and myocardial (3, 8, 9) affection and increased risk of CVD in patients with RA (10–12).

Even if little is known yet about the mechanisms that associate (i) autonomic dysfunction, (ii) chronic inflammation, and (iii) CVD risk in patients with RA, regular physical activity counterbalances these three entities (3, 13). Physical activity is known to restore ANS activity, and particularly its parasympathetic component (14). Also, the vagus nerve, which represents parasympathetic activity, plays a key role in inflammation by regulating the production of cytokines and decreasing circulating inflammatory markers (13). Finally, the increase of parasympathetic activity has been shown to be a strong protective factor against cardiovascular events (1).

A practical clinical tool to assess autonomic function, and in particular parasympathetic tone, is heart rate recovery (HRR) (13, 15, 16). The decrease in heart rate (HR) immediately following a maximal exercise electrocardiogram (ECG) represent reactivation of the parasympathetic tone (17). Vagal reactivation plays an integral part in reducing HR after exercise, especially during the first 2 min (18). A reduced HRR (an indicator of autonomic dysfunction) has been associated with increased risks of both cardiac and all-cause mortality, whereas rapid HR recovery immediately after exercise is associated with a lower risk of CVD and CVD events (17, 19).

Even though autonomic activity has been explored in RA (20) and after an exercise ECG (21, 22), to our knowledge, no study has assessed HRR post-maximal exercise ECG following physical activity intervention in RA. Therefore, the aim of this work was to establish the effects of a 2-year physical activity program (23) on autonomic function in RA, assessed by HRR post-maximal exercise ECG, and to determine the main predictive factors associated with HRR in RA using machine learning algorithms.

METHODS

Study Population

This is a substudy from the prospective PARA 2010 study (Trial registration number: ISRCTN255 39102) (23). Inclusion criteria were RA according to the American College of Rheumatology, without a history of CVD. For this substudy, 25 PARA 2010 participants were included. These inactive participants, since they did not meet the WHO guidelines on physical activity (24), benefited from a 2-year real-life intervention program. The study protocol was approved by the Stockholm regional ethics committee (reference number 2012/769-32).

Disease Activity

Disease activity score (DAS28) was measured at baseline from the erythrocyte sedimentation rate (ESR) level, the number of swollen (0–28) and tender joints (0–28), and self-reported general health perception (visual analog scale, VAS 0–10 mm). The DAS28 was scored 0–10 with scores below 3.2 indicating low disease activity and those above 5.1 as high (23). RA activity was also assessed from treatment: disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs, and cortisone. They were recommended to maintain their course of medical treatment during the study.

Physical Activity Support Program

During the first year, each participant was encouraged to take part in at least two weekly 45 min circuit training sessions (aerobic exercise and muscle strength) with a physiotherapy coach and to perform moderate-to-vigorous physical activity (MVPA) at least 30 min on most days of the week (MVPA $\geq$ 240 min/week, i.e., $\geq$12 MET-h/week) using a pedometer for monitoring their number of steps. Physiotherapy coaches initially instructed them on the desired performance of exercises and MVPA and then guided them into support group meetings 1 h every other week to facilitate learning of specific behavioral skills to enable incorporation of physical activity sessions in real life, according to social cognitive theory. Alternative types of physical activity, individually or together with group peers, were encouraged. To prevent relapse during holidays, challenge competitions were organized where participants reported their physical activity and could win simple prizes. Furthermore, they were provided with short message service (SMS) and weekly text messages to monitor and encourage their adherence to the program (23). During the second year, participants were expected to continue the program autonomously. They were encouraged to perform MVPA at least

30 min on most days of the week (MVPA ≥150 min/week, i.e., ≥7.5 MET-h/week) and to report adherence by SMS (23).

Resting ECG

A standard resting 12-lead ECG was performed after 10 min of rest. From this 10 s electrocardiographic recording, the duration of all normal sinus intervals (RR intervals) was measured using a digital compass application (Compass EP, EP studios, USA). ECGs with <10 normal intervals in a row were excluded. Two intervals following abnormal beats and intervals differing more than 20% from the preceding interval were also considered abnormal and were excluded (25).

For the assessment of ultrashort heart rate variability parameters as surrogates of longer recordings, the square root of the mean squared differences of successive RR intervals (RMSSD in ms) was considered reliable down to 10 s ECG recordings (26, 27).

$$\mathrm{RMSSD} = \sqrt{\frac{1}{N}\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2}$$

Exercise ECG

A maximal exercise ECG on the cycle ergometer (Ergomedic, Monark, Sweden) was performed by an experienced operator to rule out cardiac ischemia before starting the program and to assess physical capacity at each visit (baseline, year 1, and year 2). A starting load of 50 W was used with a 20 W/min increase in intensity until exhaustion or any of the relative or absolute contraindications of ACSM's guidelines (28) were met. The results were expressed in "W" and in percent of the predicted value. Continuous ECG was recorded, and blood pressure monitoring was measured throughout the exercise and recovery periods.

Exercise ECG was considered as a maximal cardiac level if participants achieved 90% of their maximal predicted HR (220-age for men and 210-age for women). HR exercise deltas between HR at 2 min from exercise and at rest and between maximal and resting were measured (bpm). The criteria for a positive exercise ECG were previously defined (29, 30).

Systolic Blood Pressure

Resting blood pressure was measured manually by an experienced nurse using a random-zero sphygmomanometer when the participant was sitting on the cycle ergometer immediately before the exercise phase. Systolic blood pressure (SBP) was measured every 2 min during exercise, and at 2 min and 5 min recovery from exercise. Maximal SBP was the highest value achieved during the exercise ECG. SBP exercise deltas between SBP at 2 min from exercise and at rest and between maximal and resting were measured (mmHg). SBP recovery deltas between maximal and at 2- and 5-min recovery from exercise were also measured (mmHg).

Heart rate recovery was measured at 1, 2, 3, 4, and 5 min following peak HR during exercise. Peak HR was identified as the maximum HR during the exercise protocol. HRR 1 min (HRR1) was defined as the absolute change from peak HR to HR 1 min post peak HR (HRR1 = peak HR – HR at 1 min post peak HR) (15, 16, 31). Similarly, HRs of recovery at 2 min (HRR2), 3 min (HRR3), 4 min (HRR4), and 5 min (HRR5) were calculated as the absolute change from peak HR to HRs 2, 3, 4, and 5 min, respectively, post-peak HR (31).

Variables Measurements

The variables measurements were obtained at each visit (baseline, year 1, and year 2).

Anthropometric Measures

Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of body height in meters.

Muscular Strength Performance Tests

Lower limb function was assessed with the timed stands test (TST), measuring the time in seconds required for 10 full stands from a sitting position in an armless chair.

Upper limb function was assessed with the Grippit® (AB Detektor, Göteborg Sweden), measuring the maximum and average (three measures) handgrip strength with an electronic dynamometer in Newton (N).

Cardiovascular Assessment

Resting blood pressure was measured after 5–10 min of rest in a seated position before the bicycle ergometer test with a sphygmomanometer and a stethoscope.

Pulse wave velocity (PWV) and aortic augmentation index (AIx) were measured at a constant room temperature and calculated using an oscillometric arteriograph (TensioMed, Budapest, Hungary). It has been described in detail in previous reports from PARA 2010 (6).

Transthoracic echocardiography examinations were performed using a commercially available ultrasound system (Vivid E9, GE Healthcare, Milwaukee, WI, USA). Standard two-dimensional and Doppler echocardiography was performed in keeping with EACVI/ASE recommendations (32). Digital loops were stored and analyzed offline by an experienced reader. Speckle-tracking echocardiography was used to measure LV global longitudinal strain using the apical four-, three-, and two-chamber views. Left atrial (LA) reservoir strain was used to represent atrial deformation in keeping with expert consensus (33).

Biomarkers

Plasma high-sensitivity C-reactive protein (hs-CRP) concentrations were measured by a particle-enhanced immunoturbidimetric method (Roche, France) with a measuring interval of 0.1–20 mg/ml. ESR was measured at baseline using the Westergren method in mm/h.

Questionnaires

A short version of the International Physical Activity Questionnaire (IPAQ) is a self-administered questionnaire collecting information about (i) MVPA in weekly metabolic equivalent of task-h (MET-h/week) and (ii) sedentary time (ST in h/d), undertaken over the past 7 days before the assessment

(34). It was used to measure the physical activity of participants at baseline and at 1 and 2 years.

Quality of life was assessed with the EuroQol (EQ-5D 3L) visual analog scale (VAS), which measured health state the actual day with a line drawn from a box to the appropriate point on a vertical VAS from "worst imaginable health state" (= 0) to "best imaginable health state" (= 100) (23).

Statistical Analysis

Data were expressed as mean (± SD) and frequencies (%). To determine statistically significant changes during the 2-year study protocol, a repeated-measured ANOVA on ranks was used with follow-up *post-hoc* comparisons. Wilcoxon's paired *t*-test was conducted for MVPA and ST data at years 1 and 2. Spearman rank correlation analyses were used to explore the relationship between HRR1/HRR2 and the different variables measured at baseline (Spearman correlogram). Machine learning models fit by elastic net linear regression provided regularized (shrunken) variable estimates and eliminated some variables from the set of predictors. These models were applied to predict HRR evolutions post-maximal exercise ECG using baseline, year 1, and 2 predictors chosen from significant associations in univariate analyses (Spearman correlograms). Eight-fold repeated crossvalidation was also applied to assess the performance of the model and to build a generalizable model. The predictive factors (magnitude ß-coefficient $\neq$ 0) were selected from each model. Correlations were determined between HRR1 (Models A and C)/HRR2 (Models B, D, and E) and (1) general characteristics of the participants: sex, age, anthropometric measures (BMI); (2) anaerobic and aerobic performances: TST (s), handgrip average and max (N), maximal aerobic power (W) (with % of expected); (3) cardiac parameters from resting and exercise ECG: resting HR (bpm), RMSSD (ms), % of expected maximal HR, HRs from exercise, recovery delta values (bpm), and cardiac parameters from echocardiography: LV strain (%) and LA reservoir strain (%); (4) vascular parameters from physical examination and exercise ECG: resting and mean blood pressures (mmHg), SBPs from exercise and recovery delta values (mmHg) and vascular parameters from arteriograph: PWV ($m.s^{-1}$) and AIx (%); (5) inflammation biomarkers with CRP ($mg.L^{-1}$); and (6) quality of life with EQ5D (/100).

Statistical analyses were performed using R (R Development Core Team, 2020) and SAS JMP Pro (JMP®, Version 16.1.0. SAS Institute Inc., Cary, NC, 1989–2021), where $p < 0.05$ was considered statistically significant. All tests were two-sided.

RESULTS

Participants Characteristics

At baseline, the mean age was 60 ± 9.8 (41–73) years and 22 were women (88%). The mean DAS28 was 3.1 ± 1.2. Eighteen (72%) participants were taking biological RA medications, sixteen (64%) other DMARDs, eight (32%) were using non-steroidal anti-inflammatory drugs, and five (20%) cortisone. The mean values of ESR and LVEF were within normal ranges: 17 ± 11 mm and 59 ± 4% respectively. Out of the 25 participants, 22 (88%, 19 women) took part in the supported physical activity program (mean MVPA = 16.6 ± 5.4 MET-h/week and mean ST = 5.7 ± 2.3 h/d) in the first year; and 20 (80%, 18 women) continued the program autonomously (mean MVPA = 11.63 ± 4.6 MET-h/week and mean ST = 5.5 ± 2.6 h/d) during the second year. Exercise ECGs were all negative. **Table 1** displays the general characteristics of the study population at baseline and at each yearly follow-up.

A statistically significant increase was observed in the first year (compared to baseline), then a statistically significant decrease was observed in the second year (compared to year 1) for HRR1 ($p = 0.02$ and $p = 0.01$), HRR2 ($p = 0.03$) (**Table 2**; **Figure 1**; **Supplementary Figure 1**), RMSSD ($p = 0.03$ and $p = 0.04$), SBP recovery index ($p = 0.01$ for 2- and 5-min recovery from exercise) (**Table 1**; **Supplementary Figure 2**) and MVPA ($p = 0.04$ between years 1 and 2).

A significant improvement in resting mean blood pressure ($p = 0.03$) and TST ($p = 0.04$) was observed over the entire study period. All these associations remained significant even after adjusting for the non-sphericity of the data (**Table 1**).

Predictions

In order to predict (1) the significant increase of HRR1 and HRR2 at 1 year (from baseline) and (2) the significant decrease of HRR1 and HRR2 at 2 years (from year 1) of the PARA program (**Table 2**; **Figure 1**; **Supplementary Figure 1**), the most clinically relevant variables were subsequently entered in elastic net linear regression models (**Table 3**; **Supplementary Figure 3**).

Five models were built for predicting five types of outcomes: (1)- the increase of HRR1 (Model A) and (2)- HRR2 (Model B) during the first year of the program, from predictors obtained at baseline, (3)- the decrease of HRR1 (Model C), and (4)- HRR2 (Model D) during the second year of the program, from predictors obtained at year 1 and year 2 for HRR2 (Model E). These five elastic net regression models were retained in a total of 10 of 24 candidate predictors for HRR changes (**Table 3**; **Figure 2**; **Supplementary Figure 4**).

The SBP response to exercise at baseline was the best predictor for an increase of HRR1 (Model A) and HRR2 (Model B). Indeed, SBP recovery at 2 min was positively correlated with HRR1 (Model A: ß-coefficient = 1.88) and HRR2 (Model B: ß-coefficient = 3.99) increase (**Table 3**; **Figure 2**; **Supplementary Figure 4**).

For the changes at year 1, SBP increase at baseline exercise, lower BMI, and higher TST were the other predictive covariates of HRR1 increase (Model A: ß-coefficient = 1.54, −0.88, and 0.47 respectively) (**Table 3**; **Figure 2**). Hs-CRP and % theoretical max were the other predictive covariates of HRR2 increase (Model B: ß-coefficient = 3.38 and 1.26, respectively) (**Table 3**; **Supplementary Figure 4**).

For the changes at year 2, SBP response to exercise at year 1 was the best predictor of HRR1 (Model C) and HRR2 (Model D) decrease (**Table 3**; **Figure 2**; **Supplementary Figure 4**). Indeed, the SBP exercise delta (at year 1) was negatively correlated with HRR1 (Model C: ß-coefficient = −1.71) and HRR2 (Model D: ß-coefficient = −0.96) decrease (at year 2) (**Table 3**; **Figure 2**; **Supplementary Figure 4**). Handgrip was the only other covariate of HRR1 decrease (Model C: ß-coefficient = 1.34) (**Table 3**;

TABLE 1 | General characteristics, static, and dynamic measures of the study cohort at baseline and yearly follow-ups.

General characteristics	Baseline, mean (±SD) *n* = 25	Y1, mean (±SD) *n* = 22	Y2, mean (±SD) *n* = 20
Age (years)	60 (9.8)	60 (10)	59 (10)
BMI (kg/m^2)	25.70 (4.7)	25.1 (4.5)	25.2 (4.2)
Hs-CRP (mg/l)	2.8 (2.5)	1.6 (1.8)	1.8 (1.4)
EQ5D (0–100)	73 (17)	75 (19)	77 (16)
Static measures			
HR rest (bpm)	70 (9)	67 (8)	67 (7.4)
RMSSD (ms)	**31.4 (13.4)**	**43.9 (16.9)**	**36.9 (15.3)**
Resting SBP (mmHg)	127 (10)	126 (10)	124 (12)
Resting mean blood pressure (mmHg)	**99.9 (13.4)**	**86 (11.5)**	**87.5 (11.2)**
LV global longitudinal strain (%)	20.35 (3)	19.56 (3.1)	20.7 (2.8)
LA reservoir strain (%)	31.5 (8.1)	33.12 (9.7)	34.6 (9.9)
PWV (m/s)	10.8 (2.2)	9.8 (2.4)	11.4 2.7)
Aortic augmentation index	36.1 (10.9)	35.8 (10.2)	38 (10.8)
Dynamic measures			
Handgrip average (N)	196 (119)	200 (115)	217 (114)
Handgrip max (N)	239 (136)	235 (131)	257 (132)
TST (s)	**19 (6)**	**16 (6)**	**14 (3)**
MAP (W)	168 (48)	181 (46)	176 (45)
Theoretical % max HR	100 (7)	102 (7)	99 (7)
Theoretical % MAP	134 (23)	145 (24)	144 (12)
HR exercise delta (2 min-rest) (bpm)	46 (14)	38 (11)	45 (11)
HR increase (max-rest) (bpm)	84.4 (13.7)	89 (13)	86 (12)
SBP exercise delta (2 min-rest) (mmHg)	26.4 (14)	26.5 (16.6)	28.8 (15.5)
SBP exercise delta (max-rest) (mmHg)	56.3 (11.1)	56.7 (12.7)	52.3 (18)
SBP recovery delta (max-2 min) (mmHg)	**28.9 (11.8)**	**32.4 (15.1)**	**21.5 (9.2)**
SBP recovery delta (max-5 min) (mmHg)	**47.6 (14)**	**49.7 (18)**	**42 (13.3)**

ANOVA on ranks analysis was conducted to determine statistically significant changes during the 2-year study protocol. Bold font style indicates a statistically significant relationship between column and row parameters ($p < 0.05$). SD, standard deviation; BMI, body max index; Hs-CRP, Plasma high-sensitivity C-reactive protein; EQ5D, EuroQol 5-dimensions; HR, Heart rate; RMSSD, Root mean square of the successive differences; SBP, Systolic blood pressure; LV, Left ventricular; LA, Left atrial; PWV, Pulse wave velocity; TST, Timed stands test; MAP, Maximal aerobic power.

Figure 2). TST and LV strain were the predictors at year 2 of HRR2 decrease during the second part of the program (Model E: ß-coefficient = −3.1 and 1.39, respectively) (**Table 3**; **Supplementary Figure 4**).

TABLE 2 | Heart rate recovery (HRR) measures of the study cohort at baseline and yearly follow-ups.

Heart rate recovery, HRR (bpm)	Baseline, mean (±SD) *n* = 25	Y1, mean (±SD) *n* = 22	Y2, mean (±SD) *n* = 20
HRR1	**25 (8)**	**28 (10)**	**24 (9)**
HRR2	**42 (9)**	**47 (14)**	**43 (11)**
HRR3	55 (11)	57 (13)	55 (12)
HRR4	60 (11)	63 (11)	61 (12)
HRR5	62 (12)	66 (12)	64 (11)

ANOVA on ranks analysis was conducted to determine statistically significant changes during the 2-year study protocol. Bold font style indicates a statistically significant relationship between column and row parameters ($p > 0.05$).

DISCUSSION

The results of this study identified a parallel relation between the changes in levels of physical activity with ANS activity in RA. In particular, a significant improvement after 1 year of supervised physical activity and a decrease toward baseline during the following year with less intense physical activity is noted, as illustrated in **Supplementary Figure 5**. Integrating all plausible factors affecting ANS activity, the present machine learning elastic net regression models identified BMI, CRP, and TST as well as HR and SBP responses to exercise as baseline predictors of the exercise associated ANS improvement in RA (**Supplementary Figure 5**). Taken together, these findings extend the well-established positive effects of exercise in RA to measures and predictors of ANS, with potential clinical implications for CVD risk.

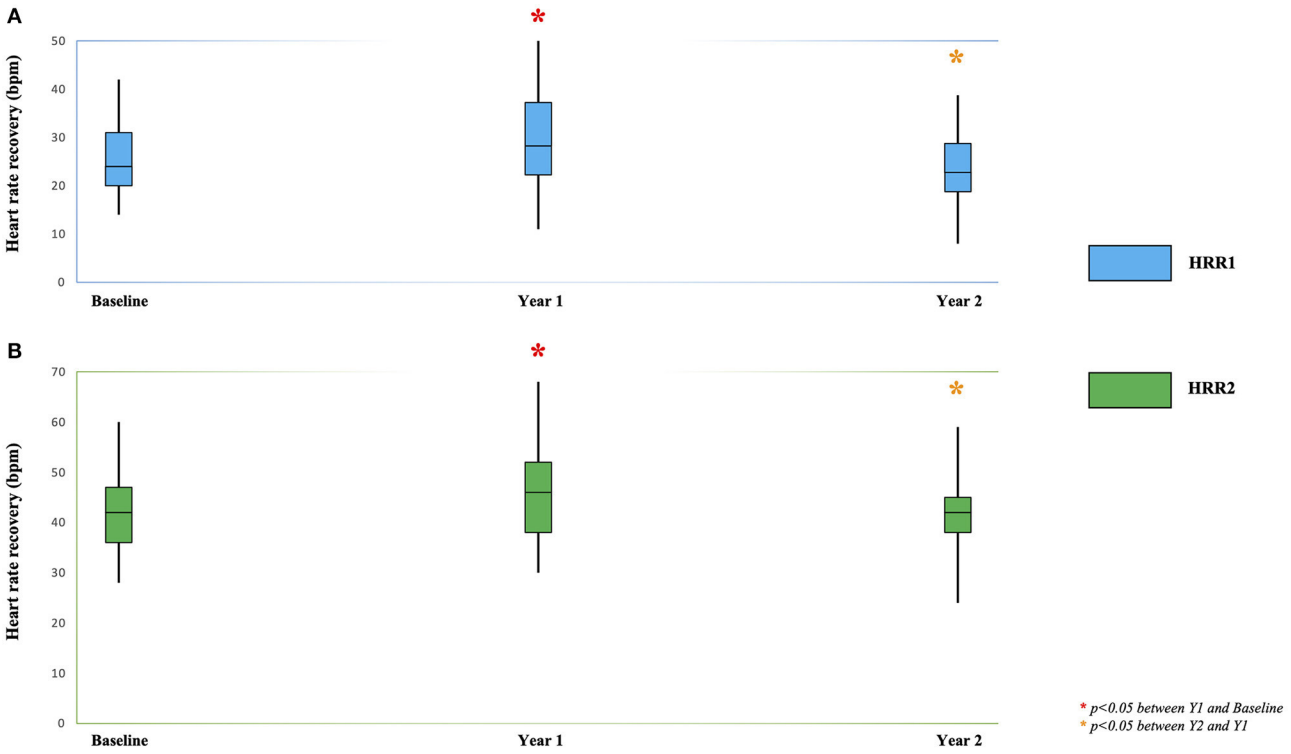

FIGURE 1 | Heart rate recovery at 1 min: HRR1 **(A)** and 2 min: HRR2 **(B)** during the 2-year physical activity program in participants with RA. ANOVA on ranks analysis was conducted to determine statistically significant changes during the 2-year study protocol. *$p < 0.05$ between Y1 and Baseline. *$p < 0.05$ between Y2 and Y1.

The first 2 min of HRR is validated and commonly used ANS measures (31). A slow decrease of HRR after exercise indicates autonomic dysfunction or at least a non-optimal ANS and is an independent predictor of CVD and all-cause mortality (18). Also, an impaired HRR from the first minute after exercise ECG is a predictor of overall mortality (19, 35). In this study, the HRRs 1–5 were largely above the normal cut-off of 12 beats per minute (17), but lower than the HRR observed in larger population-based cohorts (36). The absolute HRR 1 and 2 in this work were similar to previous work in patients with RA after maximal treadmill testing (20) supporting an autonomic dysfunction in RA. Cardiac rehabilitation increases HRR, which is associated with improved outcomes (37). The reversibility of the autonomic dysfunction in RA has *hitherto* remained unexplored. Therefore, we next assessed HRR after a 2-year physical activity program in RA participants (20) to establish the possibility to improve HRR and to determine the main predictive factors associated with HRR in RA.

Importantly, an improved ANS function in RA after the first year of supervised physical activity was demonstrated in this study by significant increases of HRR at 1 and 2 min after maximal exercise. Beneficial cardiovascular effects of exercise interventions in RA are well-established (6, 8–11, 20), and our results extend these findings to a potential link *via* the enhancement of parasympathetic modulation, which was further supported by the significant increase in RMSSD in the present study.

Elastic regression modeling with eight-fold cross validation allowed us to identify blood pressure response to exercise, lower BMI, and higher muscular strength at baseline as predictors of HRR increase during the first year of the PARA 2010 physical activity program. These findings point to the possibility to identify responders and non-responders to physical activity intervention programs in RA.

Both the SBP increase at exercise and the decrease at recovery predicted the HRR increase in response to the PARA2010 intervention in RA. Previous studies have established a relationship between HRR and SBP, but provided contradictory conclusions if SBP changes during exercise are a consequence or cause of the observed HRR (38–42). In this study, SBP recovery followed the pattern of HRR and increased in the first year. The rise and recovery of SBP with exercise is predominantly caused by an increase in cardiac output, being dependent on HR and systolic function (28, 42), which was normal in this study. In RA, increased arterial stiffness (7, 43), diastolic dysfunction (9), and a non-optimal ventricular-arterial coupling (6) may affect the SBP increase and recovery after exercise (28, 44). In addition to SBP responses, positive predictive factors for improved HRR by exercise intervention identified by elastic net regression analysis included also strength and a low BMI at baseline. These observations indicate conditions giving the optimal conditions for improving ANS function by exercise. In contrast, higher CRP predicted an increase in HRR. Exposure to inflammation affects the cardiovascular system, as demonstrated by the disease

TABLE 3 | The results of five elastic net linear regression models applied to predict heart rate recovery (HRR) 1 and 2 increases (Models A and B) and decreases (Models C, D, and E) post-maximal exercise ECG using the baseline, year 1, and year 2 predictors as independent variables.

Parameters	Model A	Model B	Model C	Model D	Model E
General characteristics	**Beta coefficient (*standard error*)**				
Age (years)	-	-	-	-	-
BMI (kg/m^2)	−0.88 (*3.46*)	-	-	-	-
Hs-CRP (mg/l)	-	3.38 (*9.32*)	-	-	-
EQ5D (0–100)	-	-	-	-	-
Static measures	-	-	-	-	-
HR rest (bpm)	-	-	-	-	-
RMSSD (ms)	-	-	-	-	-
Resting SBP (mmHg)	-	-	-	-	-
Resting mean blood pressure (mmHg)	-	-	-	-	-
LV global longitudinal strain (%)	-	-	-	-	1.39 (*113.15*)
LA reservoir strain (%)	-	-	-	-	-
PWV (m/s)	-	-	-	-	-
Aortic augmentation index	-	-	-	-	-
Dynamic measures	-	-	-	-	-
Handgrip average (N)	-	-	1.34 (*4.77*)	-	-
Handgrip max (N)	-	-	-	-	-
TST (s)	0.47 (*5.99*)	-	-	-	−3.10 (*173.45*)
MAP (W)	-	-	-	-	-
Theoretical % max HR	-	1.26 (*10.48*)	-	-	-
Theoretical % MAP	-	-	-	-	-
HR exercise delta (2 min-rest) (bpm)	-	-	-	-	-
HR increase (max-rest) (bpm)	-	-	-	-	-
SBP exercise delta (2 min-rest) (mmHg)	1.54 (*5.81*)	-	−1.71 (*4.93*)	−0.97 (*2.99*)	-
SBP exercise delta (max-rest) (mmHg)	0.07 (*4.92*)	-	-	-	-
SBP recovery delta (max-2 min) (mmHg)	1.88 (*4.11*)	3.99 (*5.68*)	-	-	-
SBP recovery delta (max-5 min) (mmHg)	0.19 (*6.91*)	-	-	-	-

The predictors with a non-zero beta coefficient are represented in each model. The dashes correspond to zero beta predictors. The predictive factors set was chosen based on the eight-fold cross-validation approach.

BMI, body max index; Hs-CRP, Plasma high-sensitivity C-reactive protein; EQ5D, EuroQol 5-dimensions; HR, Heart rate; RMSSD, Root mean square of the successive differences; SBP, Systolic blood pressure; LV, Left ventricular; LA, Left atrial; PWV, Pulse wave velocity; TST, Timed stands test; MAP, Maximal aerobic power.

duration as a major determinant of vascular function in RA (7). There is, in addition, a close relation and possible interregulation between inflammation and ANS activity. The observation that participants with higher CRP exhibited a larger improvement in HRR supports that inflammatory conditions indicate a larger beneficial potential of physical activity.

The observed ANS improvement at year 1 was not preserved over time since HRR was significantly decreased at year 2 compared with year 1 in this study, despite a level of physical activity that continued to overreach the WHO recommendations (>2x in the first year and 1.5x in the second year) (24). These results suggested a high efficient threshold of exercise training to obtain an adapted autonomic response, potentially optimizing the cardiovascular response and improving cardiovascular outcomes. The slightest decrease in physical activity (even over physical activity recommendations) leads to a sympathovagal balance shifting toward less parasympathetic activity. Finally, assessment of the last available cardiovascular characteristics identified a negative association of HRR increase with TST decrease and a positive association with normal-to-high values of LV strain at year 2. Thus, a substantial gain of muscular strength (lower limb with TST and upper limb with handgrip) and a normal LV systolic deformation (absence of subclinical cardiac dysfunction) predicted a better response to exercise after the 2-year physical activity program. Both are strong cardiovascular prognostic factors (9, 45–47), associated with a reduction in resting blood pressure (48, 49). In addition to being significantly correlated at baseline, the significant correlations between autonomic and vascular functions at 1 and 2 years indicate that these two variables are closely related to each other and maybe part of the indirect effects of physical activity increase during the first year and physical activity decrease in the second year.

The bidirectional changes in HRR over increasing and decreasing physical activity may be used to follow a physical activity intervention in RA to identify non-responder and non-adherent participants with potential hypertension risk, despite normal resting blood pressure and normal exercise ECG findings. From a practical standpoint, exercising ECG and extending it for only several minutes into exercise recovery provides a unique,

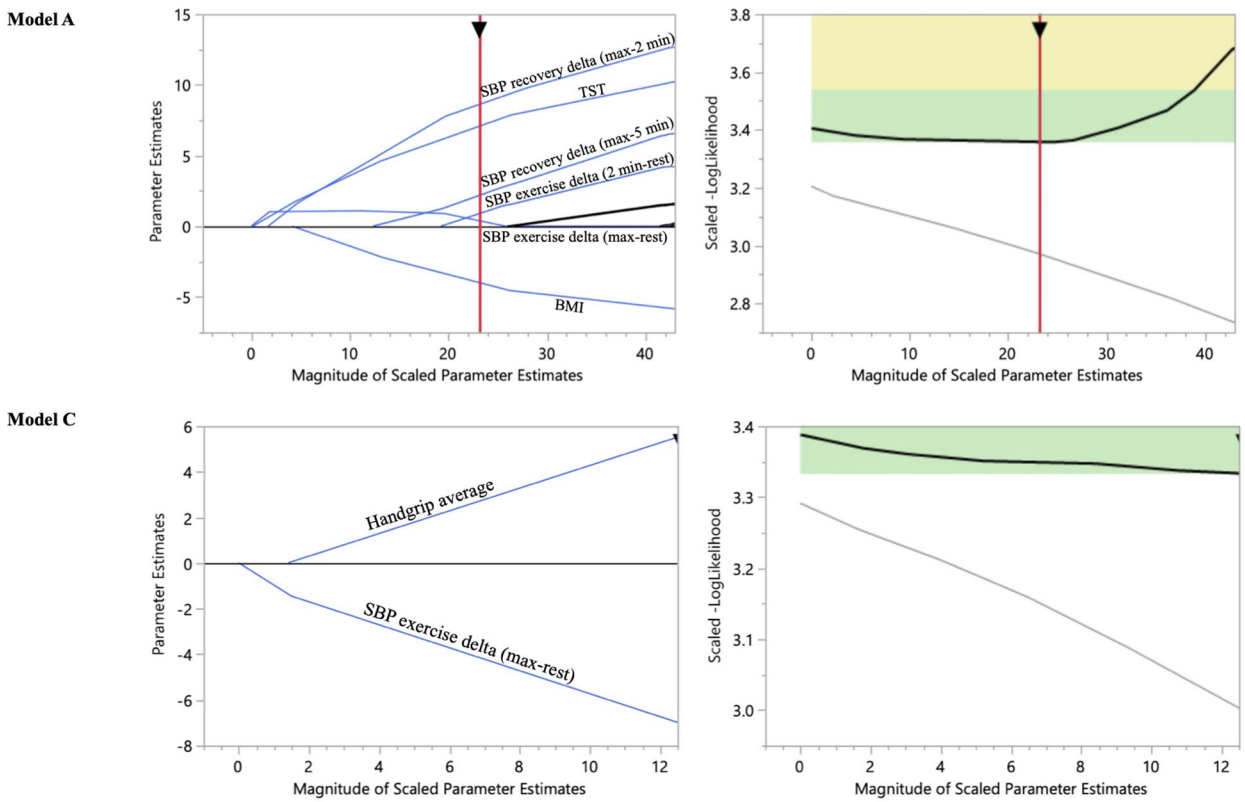

FIGURE 2 | Solution path trace plot applied to predict HRR1 increase and decrease post-maximal exercise ECG using the baseline and year 1 predictors as independent variables: Models A and C. Each line corresponds to a predictor variable. As regularization is applied to the model (from right to left in the trace plot), less important coefficients get smaller, and some are completely removed from the model (the ones that have a beta coefficient of 0 and where the line for the predictor intersects with the x-axis before the optimal solution is reached). A generalizable model was built with an eight-fold cross validation to determine the model which provides a global minimum (within the green rectangle) for the scaled-log likelihood value among the validation folds.

minimally invasive means to assess HR and blood pressure responses to exercise to indirectly determine participant's response or adherence to physical activity and to predict the CVD risk (28, 50), and also mainly to detect hypertension early (39, 42, 51). It was already reported in the literature that a delayed SBP decrease post-exercise was more accurate than ST segment depression for the diagnosis of coronary artery disease (CAD) (39, 52, 53). Early identification of high cardiovascular risk could improve the effectiveness of prevention in RA by targeting patients who will benefit the most from lifestyle interventions (exercise, diet, and antihypertensive drugs). The present results suggest that ANS upregulation by a high (≥7.5 MET-h/week) and regular (≥5 days/7) MVPA training level may be key for successful aging. Obviously, the support group sessions according to social cognitive theory improved adherence of RA participants in the first year (supervised physical activity). The outcomes of this study could provide new insight into the relationship between SBP response to exercise and ANS modulation.

Major strengths of this study include the prospective longitudinal design with close follow-up of the participant's adherence to the physical activity program and with the repeated physiological parameter assessments (23). The longitudinal follow-up allowed to assess causality between physiological parameters according to the steps of the PARA cohort study, which are 0–1 year: whole program of physical activity; and 1–2 years: autonomously physical activity (23). No subject of the study had medication that could affect autonomic function (anticholinergics, cholinesterase antagonists, adrenoreceptor agonists, and adrenoreceptor antagonists). Most of the participants were able to perform the exercise ECG to their maximum cardiorespiratory ability, i.e., until exhaustion (the mean theoretical % of MAP was exceeded by 34–45% each time), despite problems with their joints, which could have influenced their HRR.

Certain limitations should also be acknowledged. First, the relatively small sample size is mainly made up of Swedish women (88%). It is the same population described in the two previous studies from the team, but four participants were excluded due to incomplete data concerning exercise ECG (6, 9). However, the use of a machine-learning algorithm with the elastic net linear regression models permits the identification of predictive factors among an important number of parameters (p) in relation to a small sample (n) of participants ($p > n$). Nested repeated crossvalidation was used for the models

in the study, which provides an unbiased estimation of the performance of the prediction model (54). Compared with a classical linear regression method, the elastic net linear regression model increases the robustness, simplicity, and accuracy of such results in this context (55, 56). However, standard errors are large with the small sample. Second, the study did not have a comparison group, but the aim of the work was to examine the effects of a physical activity intervention on HRR in this population. Third, difficulties, even with experience, to define the values of diastolic blood pressure when it comes to defining or recognizing the fifth Korotkoff sound during exercise ECG (57). Also, a common measure of SBP recovery is defined in the literature as the ratio of the SBP obtained in the third minute of the recovery period to either the peak-exercise SBP or the SBP in the first minute of the recovery period after exercise ECG (39, 42, 58). Unfortunately, SBP was measured at 2 and 5 min recovery from exercise in the PARA study, which is generally performed in clinical research in practice (51, 57). Finally, as participants were tasked to report their level of physical activity, the reporting bias should be acknowledged even if it was the most validated physical activity questionnaire (59). Future studies should be to use objective methods such as accelerometry to assess physical activity, mainly when this activity is practiced in autonomy. A more precise evaluation of physical activity and biological data could determine if exercise leads to a sympathovagal balance shifting toward a more parasympathetic activity or less sympathetic activity (60).

CONCLUSION

Autonomic nervous system activity *via* HRR measurement can be a relevant marker of the effectiveness of physical activity recommended in patients with RA at high risk of CVD. Exercise ECG can serve as a simple minimally invasive means to assess blood pressure responses to exercise and recovery, which are the main predictive factors of HRR evolutions during a physical activity program. HRR and SBP recovery, associated with muscular strength performance tests, can mainly be used to assess sympathovagal balance and to quantify the degree of autonomic dysfunction in order to detect CVD risk early. These results can guide future recommendations for RA patients and may improve adherence to regular physical activity programs and thus their cardiovascular health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Stockholm Regional Ethics Committee (Reference Number 2012/769-32). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DH, PS, CO, IL, and MB: conception and design of the work, interpretation, and draft of the manuscript and substantial revision. DH, AV, CF, BN, and MB: acquisition. DH, PS, and MB: analysis. All authors have approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.788243/full#supplementary-material

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BRIEF RESEARCH REPORT
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Sonographic Tophi and Inflammation Are Associated With Carotid Atheroma Plaques in Gout

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Objective: Gout and cardiovascular disease are closely related, but the mechanism connecting them remains unknown. This study aims to explore whether urate crystal deposits and inflammation (assessed by ultrasound) are associated with carotid atherosclerosis.

Methods: We included consecutive patients with crystal-proven gout newly presenting to a tertiary rheumatology unit. Patients under urate-lowering treatment were excluded. Ultrasound assessment was performed during intercritical periods. Musculoskeletal scans evaluated six joints and four tendons for urate crystal deposits (double contour, aggregates, and tophi), and power Doppler (PD) signal (graded 0–3) as a marker of local inflammation. The sum of locations showing deposits or a positive PD signal (≥1) was registered. Carotids were scanned for increased intima-media thickness (IMT) and atheroma plaques, according to the Mannheim consensus. Associations were analyzed using logistic regression.

Results: The study included 103 patients showing sonographic crystal deposits at the examined locations (mean sum 9.9, minimum 2); tophi were the most frequent. Two-thirds of participants presented a positive PD signal (30.1% grade 2–3). In the carotid scans, 59.2% of participants showed atheroma plaques, and 33.0% increased IMT. Tophi (odds ratio [OR] 1.24; 95% confidence interval [CI] 1.03–1.50) and a positive PD signal (OR 1.67; 95% CI 1.09–2.56) were significantly associated with atheroma plaques, while an increased IMT showed no sonographic association.

Conclusion: Sonographic crystal deposits and subclinical inflammation were consistently observed in patients with intercritical gout. Tophi and a positive PD signal were linked to carotid atherosclerosis. Our findings may contribute to understanding the complex relationship between gout and atherosclerosis.

Keywords: gout, tophi, inflammation, carotid artery diseases, ultrasonography, power Doppler

HIGHLIGHTS

- All patients with gout showed sonographic crystal deposits in at least two explored locations.
- Subclinical inflammation was also revealed by ultrasound despite performed during the intercritical period.
- A high prevalence of carotid atheroma plaques was confirmed.
- Sonographic tophi and power Doppler signal were associated with carotid atherosclerosis.

INTRODUCTION

Cardiovascular disease (CVD) constitutes the main cause of death worldwide (1) and in patients with inflammatory rheumatic disorders. All-cause mortality is twice as high in people with gout as in the general population (2, 3), mainly due to CVD (4, 5).

For a long time, elevated cardiovascular risk in gout has been attributed to traditional cardiovascular risk factors, which tend to be more prevalent in this group of patients than in the general population (6, 7). However, these risk factors cannot account for all the excess mortality seen, suggesting that gout is associated with additional cardiovascular risk, independent of known determinants of CVD (4, 5, 8, 9). Inflammation from any cause plays a crucial role in the atherogenesis process; not only is it considered an important cardiovascular risk factor by itself (10), it also boosts the effect of other risk factors. In gout, inflammation is stimulated by monosodium urate (MSU) crystals through IL-1β production and neutrophil extracellular traps (NETs) in flares. During intercritical periods, low-grade inflammation persists in peripheral blood (11), synovial fluid (12), and tophi (13), as indicated on ultrasound by a persistent power Doppler (PD) signal and progressive erosions in the absence of flares (14, 15). The formation of NETs (16), along with oxidative stress driven by hyperuricemia (17, 18), damages endothelial cells and leads to endothelial dysfunction, which ultimately results in atherosclerosis.

People with gout show variable levels of cardiovascular risk. Some disease characteristics, such as the presence of tophi, bone erosions, longer duration, oligoarticular or polyarticular presentations, and higher serum urate levels, are predictors of subsequent fatal and non-fatal cardiovascular events (19–21). These are indeed markers of severe disease, with a higher crystal and inflammatory load (11, 22).

Subclinical carotid atherosclerosis, and especially atheroma plaques, entail a very high cardiovascular risk, according to European Society of Cardiology guidelines (23, 24), predicting the development of stroke and coronary heart disease (25, 26). The prevalence of carotid atherosclerosis in people with gout ranges from about 29.1 to 48.9% (27–30) and is likely to be higher than in the non-gouty population. In one study, its identification by ultrasound helped reclassify 27.8% of newly seen gout patients to the very high cardiovascular risk level (30). This reclassification was independent of other cardiovascular risk factors, revealing the poor performance of risk assessment tools such as the Framingham Heart Study (FHS) or the Systematic Coronary Risk Evaluation (SCORE) to predict the presence of carotid atherosclerosis.

Two previous reports failed to demonstrate an association between clinical characteristics of gout and the presence of subclinical atherosclerosis (29, 30). This study aims to explore the association between sonographic signs of MSU crystal deposits and accompanying inflammation, and the presence of carotid atherosclerosis. We hypothesized that a higher sonographic crystal load, depicted as double contour (DC) sign, aggregates, tophi, or higher inflammatory signs, detected by a PD signal, would be associated with the presence of subclinical atherosclerosis in patients with gout.

PATIENTS AND METHODS

Study Design and Population

We designed an observational, prospective study to assess the relationship between carotid atherosclerosis and both sonographic crystal deposits and subclinical articular inflammation, and the impact of a treat-to-crystal dissolution strategy (urate-lowering therapy [ULT], flare prophylaxis) and cardiovascular risk management. Here we present the baseline analysis of the study.

The study took place in a tertiary rheumatology unit of a university hospital, covering a population of 278,095 inhabitants (2019 data). Selection of participants followed a consecutive sampling of incident cases. Consecutive, newly seen patients with crystal-proven gout confirmed in synovial fluid or tophus material and not using ULT at diagnosis were eligible for the study. No exclusion criteria applied; previous use of ULT was accepted. Participants were recruited at the time of a gout flare or after its subsidence, but all cases were scanned during intercritical periods (free of inflammatory signs and symptoms). Flare prophylaxis with low-dose colchicine or other agents such as non-steroidal anti-inflammatory drugs was permitted.

Prior to data collection, investigators explained the aim of the study to eligible patients. According to the Declaration of Helsinki, all participants read the study information sheet and signed informed consent. The local Ethics Committee approved the protocol [PI2018/027].

This article was written in accordance with the STROBE statement (31) and EULAR recommendations for reporting ultrasound studies in rheumatic and musculoskeletal diseases (32).

Variables

Outcome variables were (a) increased intima-media thickness (IMT, $>$ 0.9 mm, measured by automatic measurement system), and (b) the presence of atheroma plaques. Both variables were assessed following bilateral carotid artery ultrasound, performed according to the Mannheim consensus (33).

The primary explanatory variables were the presence of a DC sign, aggregates, tophi, and PD signal in the ultrasound evaluating MSU crystal deposits (according to OMERACT definitions for MSU crystal deposits and articular inflammation) (34, 35).

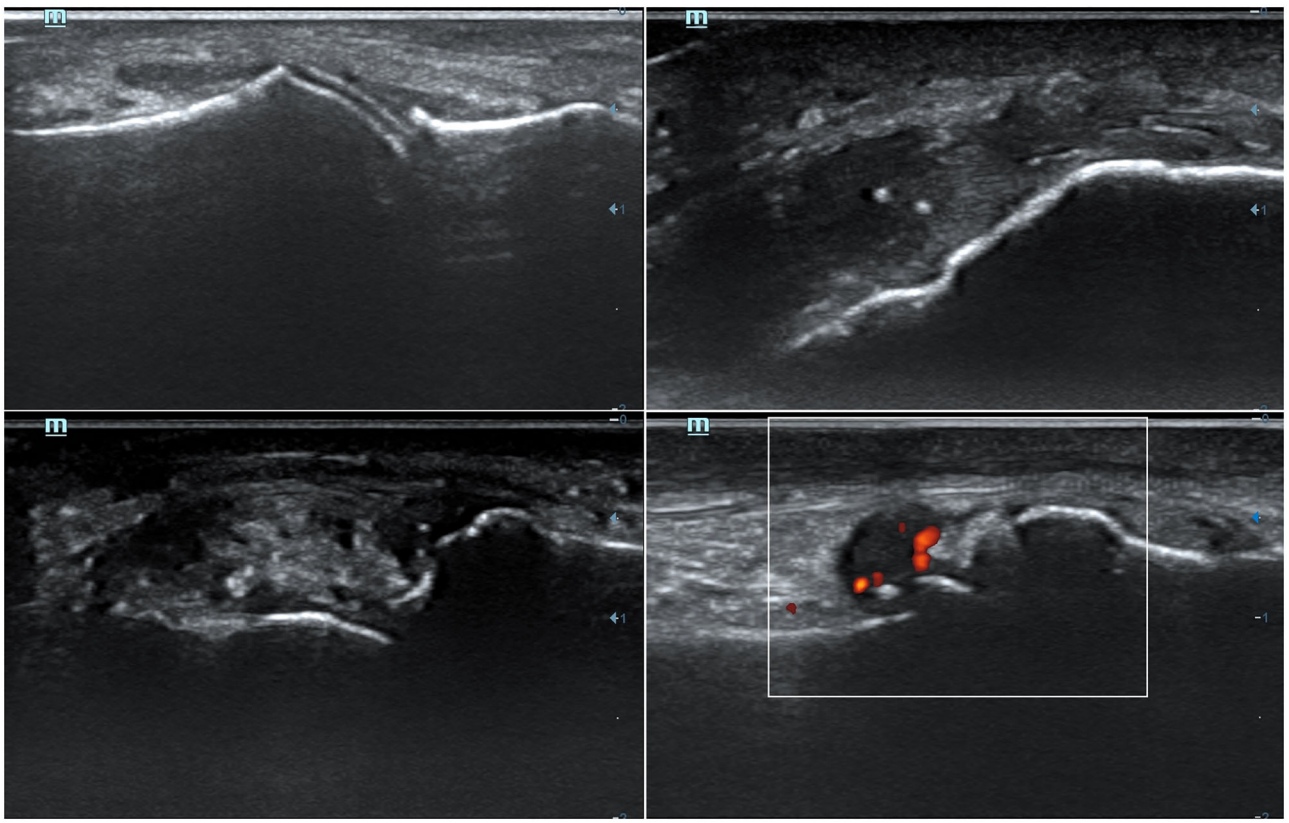

FIGURE 1 | Representative ultrasound features of monosodium urate crystal deposits and associated inflammation. (Up-left) A double contour sign at the cartilage of the 1st metatarsal bone. (Up-right) Two aggregates inside distal patellar tendon. (Bottom-left) A tophus seen at the radial aspect of the 2nd metacarpophalangeal joint. (Bottom-right) A positive (grade 2) power-Doppler signal at 1st metatarsophalangeal joint, indicative of synovitis.

Secondary explanatory variables included demographic and clinical characteristics, including cardiovascular risk factors, history of CVD, cardiovascular risk categories, and others involving gout disease and therapeutics (full list of secondary explanatory variables provided in the **Supplementary Data 1**). These were collected at clinics by attending physicians.

Ultrasound Assessment

Participants were referred for a musculoskeletal and carotid ultrasound assessment. The two sonographers (AMS and MA) who performed the study had accredited experience in vascular and musculoskeletal ultrasound (AMS: 20 years of experience, level 2 European Federation of Societies for Ultrasound in Medicine and Biology competency, a teacher at the Ultrasound School of the Spanish Society of Rheumatology; MA: 10 years of experience, certified by the Ultrasound School of the Spanish Society of Rheumatology). They were blinded to clinical and laboratory data, and patients were asked not to talk about their disease and treatments. Immediately after ultrasound evaluation, sonographers reported their findings, which were available to the patient and the attending rheumatologist.

The ultrasound system used was the Mindray DC-70 device (Mindray Medical International Ltd, Shenzhen, PRC), with a high frequency (6–14 MHz) linear probe (L14-6NE model) and greyscale and Doppler modalities. Frequencies of at least 12 MHz were used to scan for elementary lesions; PD signal assessment was optimized by adjusting gain, reducing pulse repetition frequency, and placing the scanning box to the region of interest.

For the musculoskeletal assessment, we followed a binary (presence/absence) scoring system at the anatomical region level, as suggested by Naredo et al. (36). The domains were (a) elementary lesions of MSU crystal deposits (DC sign, aggregates, and tophi), following OMERACT definitions (34) (**Figure 1**); and (b) inflammation, assessed by the presence of a local PD signal and graded in a semiquantitative score as 0–3 (35) (**Figure 1**). The evaluated regions, adapted from Naredo et al. (36), were wrists (radiocarpal and midcarpal), second metacarpophalangeal (MCPs) and first metatarsophalangeal (MTPs) joints, and triceps and patellar tendons and their entheses. For upper limb scans, patients remained seated, with their hands over a flat surface for hand scans and with an elbow flexion of 90 degrees for triceps tendon scans. For lower limb scans, patients laid in a supine position, with knee flexion of 90 degrees for patellar tendon and feet scans. All regions were examined longitudinally for the whole width of their dorsal aspects; for second MCPs and first MTPs, medial aspects were also examined.

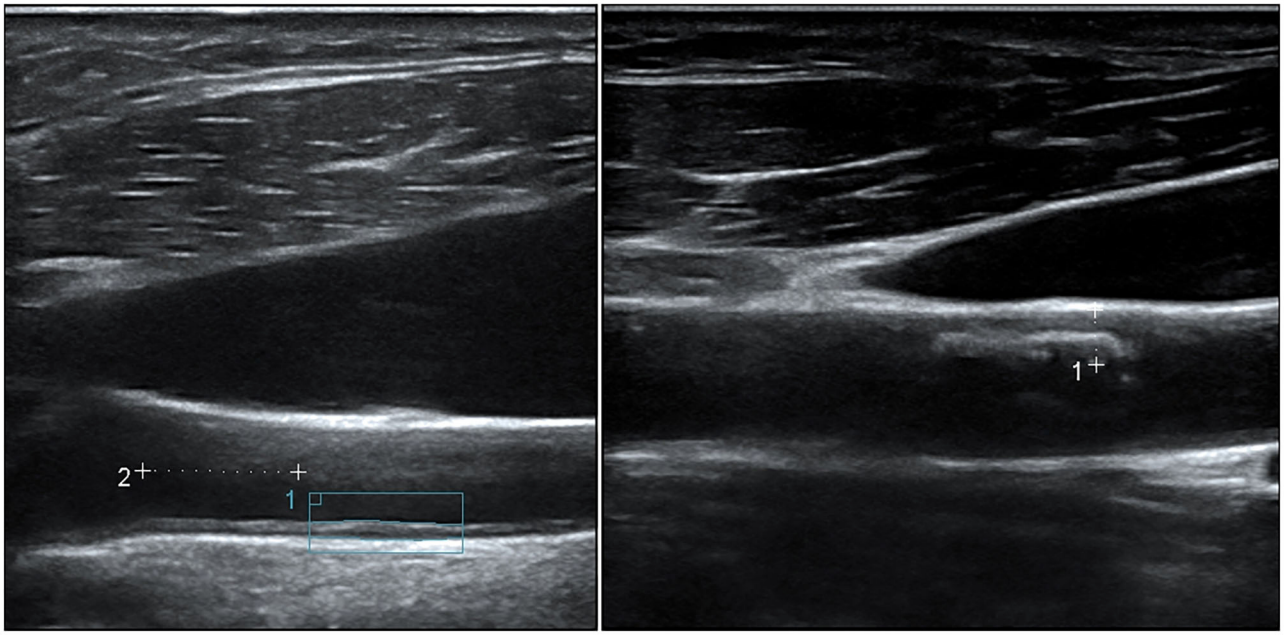

FIGURE 2 | Representative ultrasound features of carotid atherosclerosis. (Left) An increased intima-media thickness (1.048 mm), measured 1 cm proximal to the carotid bulb according to the Mannheim consensus. (Right) A partially calcified atheroma plaque (maximal thickness 3.1 mm) at the anterior wall of the common carotid artery.

Carotid arteries were bilaterally scanned for increased IMT and presence of atheroma plaques, according to the Mannheim consensus (33) (**Figure 2**). Participants laid in a supine position with a mild hyperextension of the neck. Common carotids and their branches were scanned longitudinally and transversally for plaques, while IMT was measured longitudinally at common carotids.

Statistical Analysis

Sample Size

The prevalence of carotid atheroma plaques ranges between 29.1 and 48.9% (27–30). Assuming a prevalence of 40%, with 80% power, a significance level of 95%, and an estimated rate of refusal to participate of 10%, the estimated sample size was a minimum of 86 patients.

Statistical Analysis

Descriptive statistics are presented as frequencies (n) and percentages (%) for qualitative variables and as mean (standard deviation) or median (interquartile range) for parametric or non-parametric quantitative variables, respectively. Three quantitative variables were categorized by standard definitions: obesity (body mass index $\geq$30 kg/m^2), chronic kidney disease (glomerular filtration rate $<$ 60 mL/min/1.73 m^2, according to the CKD-EPI equation) and severe chronic kidney disease, stage 4–5 (glomerular filtration rate $<$ 30 mL/min/1.73 m^2, according to the CKD-EPI equation).

To ensure intra- and interobserver reliability, both sonographers performed the aforementioned musculoskeletal and carotid ultrasound assessment in three patients on the same day and repeated the examination 2 weeks later. Reliability was evaluated by Cohen's κ. The κ for intra-observer agreement ranged from 0.65 to 0.75 ($p < 0.001$); for inter-observer concordance, κ was 0.66 ($p = 0.001$). These results indicate a good level of agreement, similar to the work by Naredo et al. (36).

The sum of locations showing elementary lesions of MSU crystal deposits or positive PD signal ($\geq$1) was estimated to assess crystal and inflammatory burden, respectively. Sum scores for DC sign, aggregates and tophi were given for locations with deposits or a positive PD signal, and individually for each elementary lesion.

The association analysis employed simple logistic regression, considering increased IMT or atheroma plaques as the dependent variables.

A sensitivity analysis was planned, limiting a positive PD signal to scores of 2 or 3, which represent a significant inflammatory burden; a grade 1 PD signal may sometimes be found in healthy individuals (37).

No specific approaches were followed to deal with missing data.

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for the analyses.

RESULTS

Clinical, Demographic, and Gout Characteristics

A total of 103 patients with crystal-proven gout were included in the study between December 2017 and June 2020; no patients

TABLE 1 | Participants' characteristics and comparisons according to carotid ultrasound findings.

Variables	Total ($n = 103$)	Increased IMT			Atheroma plaque		
		Yes ($n = 33$)	No ($n = 67$)	*p*	Yes ($n = 61$)	No ($n = 42$)	*p*
Demographic characteristics							
Age in years, mean (SD)	62.3 (14.1)	70.1 (10.2)	58.3 (14.2)	**<0.001**	68.1 (10.8)	53.9 (14.3)	**<0.001**
Men, *n* (%)	94 (91.3)	31 (93.9)	60 (89.6)	0.471	55 (90.2)	39 (92.9)	0.634
White, *n* (%)	92 (89.3)*	31 (93.9)	58 (86.6)	0.268	55 (90.2)	37 (88.1)	0.738
Clinical characteristics							
Serum urate (mg/dL), mean (*SD*) [*n = 101*]	8.2 (1.5)	8.1 (1.8)	8.3 (1.3)	0.606	8.2 (1.6)	8.3 (1.4)	0.805
GFR (CKD-EPI, mL/min/1.73 m^2), mean (*SD*)	75.2 (22.4)	69.5 (18.7)	78.1 (23.5)	0.067	70.6 (22.6)	81.8 (20.7)	**0.012**
CKD (GFR < 60 mL/min/1.73 m^2), *n* (%)	26 (25.2)	11 (33.3)	14 (20.9)	0.177	19 (31.1)	7 (16.7)	0.096
CKD stage 4–5 (GFR < 30 mL/min/1.73 m^2), *n* (%)	3 (2.9)	0 (0.0)	3 (4.5)	0.549	3 (4.9)	0 (0.0)	0.145
LDL-cholesterol (mg/dL), mean (SD)	112.8 (43.4)	111.4 (46.7)	113.6 (49.2)	0.813	110.4 (46.6)	116.3 (38.5)	0.946
BMI (kg/m^2), mean (SD) [*n = 98*]	30.3 (4.5)	30.4 (4.3)	30.4 (4.7)	0.988	30.4 (4.6)	30.2 (4.5)	0.819
Obesity (BMI ≥ 30), *n* (%) [*n = 98*]	47 (48.0)	16 (53.3)	31 (47.7)	0.609	27 (47.4)	20 (48.8)	0.890
Tobacco consumption, *n* (%) [*n = 101*]	22 (21.8)	7 (21.9)	13 (19.7)	0.802	14 (23.3)	8 (19.5)	0.648
Hypertension, *n* (%)	62 (60.2)	22 (66.7)	38 (56.7)	0.340	41 (67.2)	21 (50.0)	0.079
Diabetes, *n* (%)	23 (22.3)	10 (30.3)	13 (19.4)	0.223	21 (34.4)	2 (4.8)	**<0.001**
Dyslipidemia, *n* (%)	57 (55.3)	21 (63.6)	35 (52.2)	0.280	44 (72.1)	13 (31.8)	**<0.001**
Use of diuretics, *n* (%)	40 (38.8)	17 (51.5)	21 (31.3)	0.051	30 (49.2)	10 (23.8)	**0.009**
Use of lipid-lowering drugs, *n* (%)	37 (35.9)†	14 (42.4)	23 (34.3)	0.430	30 (49.2)	7 (16.7)	**0.001**
History of CVD, *n* (%)	23 (22.3)	11 (33.3)	10 (14.9)	**0.034**	19 (31.1)	4 (9.5)	**0.010**
SCORE, mean (*SD*) [*n = 99*]	4.8 (3.9)	7.2 (4.9)	3.6 (2.8)	**<0.001**	6.2 (4.3)	2.8 (2.1)	**<0.001**
FHS, mean (*SD*) [*n = 99*]	6.4 (3.9)	8.6 (4.7)	5.4 (3.0)	**<0.001**	7.8 (3.9)	4.5 (2.9)	**<0.001**
Gout-related variables							
Years since the first flare, median (IQR) [*n = 100*]	4.0 (0.0–10.0)	4.0 (0.0–10.0)	4.0 (0.0–10.0)	0.909	5.0 (0.0–11.8)	1.0 (0.0–6.5)	**0.004**
Number of flares, median (IQR) [*N = 100*]	3.0 (1.0–10.0)	2.0 (1.0–5.0)	3.5 (1.0–12.8)	0.054	4.0 (2.0–13.5)	2.0 (1.0–5.0)	**0.009**
Number of involved joints, median (IQR)	2.0 (1.0–5.0)	2.0 (1.0–3.0)	2.0 (1.0–6.0)	0.193	2.5 (1.0–6.0)	2.0 (1.0–3.0)	**0.007**
Presence of tophi, *n* (%) [*N = 102*]	17 (16.7)	5 (15.6)	11 (16.4)	0.920	14 (23.3)	3 (7.1)	**0.031**
Pattern of last flare							
Monoarticular, *n* (%)	58 (56.3)	13 (39.4)	42 (62.7)	0.083	29 (47.5)	29 (69.0)	0.094
Oligoarticular, *n* (%)	37 (35.9)	16 (48.5)	21 (31.3)	-	26 (42.6)	11 (26.2)	-
Polyarticular, *n* (%)	8 (7.8)	4 (12.1)	4 (6.0)	-	6 (9.8)	2 (4.8)	-
Prophylaxis at the time of ultrasound, *n* (%)	91 (88.3)‡	29 (87.9)	60 (89.6)	0.801	53 (86.9)	38 (90.5)	0.577

P values were considered significant below 0.050 (bold).

**Ancestries other than white European: Latin American, n = 4 (3.9%); Arabic, n = 4 (3.9%); Roma, n = 2 (1.9%); Asian, n = 1 (1.0%).*

†Lipid-lowering drugs: statins, n = 34 (2 in combination with fibrates and 1 with ezetimibe); fibrates in monotherapy, n = 3.

‡Prophylactic agents: colchicine, n = 90 (87.4%); prednisone, n = 1 (1.0%).

IMT, intima-media thickness; SD, standard deviation; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD, Chronic Kidney Disease; LDL, low-density lipoprotein; BMI, body mass index; CVD, cardiovascular disease; SCORE, Systematic Coronary Risk Evaluation; FHS, Framingham Heart Study; IQR, interquartile range.

were excluded. **Table 1** presents the characteristics of the enrolled participants. Patients were mostly white men, with a mean age of 62 years. At diagnosis, 91 (90.1%) had hyperuricemia (serum urate level ≥ 6.8 mg/dL), and 26 (25.2%) had chronic kidney disease. Twenty-three (22.3%) had established CVD. According to the cardiovascular risk categories, 33% were at moderate risk, 29% at high risk and 38% at very high risk, while none showed a low risk. Regarding gout characteristics, time from the first flare to diagnosis was long (median 4 years), tophi were present in 17 (16.7%), and almost half the patients presented with an oligo- or poly-articular flare, all features indicating a high MSU crystal burden. Ninety patients were taking colchicine at the time of the ultrasound (mode dose of 0.5 mg/day, 17.8% received 1 mg/day).

Ultrasound Assessment

All participants underwent ultrasound assessment, performed a mean of 28.9 days (SD 22.6) after diagnosis. **Table 2** shows the extent of the signs of MSU crystal deposit and inflammation. All participants showed sonographic signs of crystal deposits at the examined locations, with a mean sum of 9.9 and a minimum of 2, with tophi standing out as the most frequent. The mean sum of locations with positive PD signal was 1. The rate of patients presenting positive PD signal was 67.0% (grade 2–3 in 30.1%). Positive PD signal significantly correlated with deposits ($r = +0.37$, $p < 0.001$), mainly due to tophi ($r = +0.37$, $p < 0.001$), and aggregates ($r = +0.20$, $p = 0.040$), but not to the DC sign ($r = +0.12$, $p = 0.232$).

TABLE 2 | Musculoskeletal ultrasound findings and their association with carotid atherosclerosis.

			Increased IMT ($n = 33$)		Atheroma plaque ($n = 61$)	
Sum of locations with	**Mean (SD)**	**Range**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Deposits	9.9 (4.1)	2–21	1.06 (0.95–1.17)	0.290	1.07 (0.97–1.19)	0.162
Double contour sign	0.9 (1.0)	0–5	1.05 (0.68–1.61)	0.830	1.03 (0.69–1.56)	0.878
Aggregates	4.1 (2.8)	0–10	1.01 (0.87–1.18)	0.895	1.01 (0.88–1.17)	0.856
Tophi	4.9 (2.3)	0–10	1.19 (0.98–1.44)	0.088	1.24 (1.03–1.50)	**0.026**
Positive PD signal (≥1)	1.1 (1.1)	0–5	0.79 (0.53–1.20)	0.272	1.67 (1.09–2.56)	**0.019**
PD signal 2–3	0.4 (0.7)	0–3	0.85 (0.44–1.64)	0.621	1.70 (0.87–3.33)	0.122

P values were considered significant below 0.050 (bold).
IMT, intima-media thickness; SD, standard deviation; OR, odds ratio; CI, confidence interval; PD, power Doppler.

Regarding the carotid scans, atheroma plaques were present in 61 individuals (59.2%) and were found bilaterally in 33 (32.0%). IMT measurement was not possible in three patients due to extensive calcified atherosclerosis. Thirty-three participants showed increased IMT, which was bilateral in 13.

The distribution of musculoskeletal and carotid ultrasound findings across secondary explanatory variables is shown in **Table 1** and **Supplementary Tables 1, 2**.

Association Analysis

Table 2 presents the results of the logistic regression, assessing the association between carotid ultrasound findings and signs of MSU crystal deposits and inflammation. The extent of tophi and positive PD signal were significantly associated with the presence of atheroma plaques. No association was found with increased IMT.

An analysis of bilateral carotid ultrasound findings (**Supplementary Table 3**) showed that bilateral atheroma plaques were linked to the extent of locations with deposits, tophi, and positive PD signal. As above, no associations were found with a bilateral increased IMT.

DISCUSSION

The relationship between gout and CVD has been amply documented, with some studies supporting a causative role for gout. Nonetheless, the mechanism by which these entities are connected is still unknown. In this study, we discovered that MSU crystal deposits and consequent intercritical inflammation are linked with the presence of subclinical carotid atherosclerosis. We found that the extent of sonographic MSU crystal load (mainly by tophi) and inflammatory load expressed as a positive PD signal, were associated with the presence of carotid atheroma plaques. This finding may represent a paradigm shift for gout management. All patients with gout, even those with infrequent flares, showed sonographic signs of MSU crystals, especially tophi. The consistent presence of deposits, along with the deleterious association identified in our study, would merit an early initiation of ULT, even after the first flare, once the disease is definitively diagnosed. An early treatment of gout has indeed demonstrated a reduction of flares and inflammation by imaging (38); this approach would hypothetically reduce the ultimate risk of developing CVD. However, experts still recommend delaying the initiation of ULT until the disease has reached a certain severity (39).

Doppler techniques show the degree of vascularization or blood flow at the examined locations. A positive PD signal translates to inflammation in chronic inflammatory arthritis, and it correlates with the cytokine profile (40) and histopathological synovitis (41). In gout flares, the PD signal is markedly increased; it can persist at lower levels during intercritical periods (14, 42, 43) and decrease during ULT (43). In our series, where two out of three patients showed a positive PD signal (a surrogate marker of crystal-led inflammation), an association was observed with atheroma plaques. Our data thus suggest that the PD signal might be an indicator of cardiovascular risk and a potential target for preventing CVD. In line with our clinical practice, 87% of participants were on prophylactic colchicine initiated after proving the diagnosis of gout, which might have influenced the results due to its anti-inflammatory effect (44). In the study by Peiteado et al. (43), a positive PD signal was found in 96% of patients, with a smaller proportion taking prophylactic colchicine (71%). Thus, our findings should be replicated in a population not under prophylactic agents. Still, the 67% rate of positive PD signal is significant, considering the anti-inflammatory therapeutic background and the intercritical situation of the patients.

Ultrasound in gout has mainly been advocated for diagnosis (45), though some recent papers have proven an interesting role in monitoring the disease, such as checking the reduction of deposits during ULT (46), and predicting the occurrence of flares after discontinuation of colchicine (47) or the achievement of remission criteria in the following 12 months (48). Furthermore, ultrasound could also be of interest for establishing cardiovascular risk. Our results on the extent of tophi and joint inflammation strengthen the value of crystal burden assessment to predict cardiovascular outcomes in patients newly diagnosed with gout. A recent paper from France (49) sustains this point of view. The volume of MSU crystals measured by dual-energy computed tomography predicted subsequent cardiovascular events and mortality in the follow-up. Accordingly, the estimated crystal burden by imaging may even be used, like subcutaneous tophi, to individualize the proper serum urate target for the patient (39).

Our findings support a close relationship between MSU crystals and inflammation, on the one hand, and atherosclerosis on the other. However, the cross-sectional design impedes establishing causality. In addition, all the analyzed variables related to CVD and gout are closely intertwined, as shown in **Table 1** and **Supplementary Tables 1, 2**. Potentially, these issues could have introduced some bias into the association analysis. Larger prospective studies would be desirable, but including groups without ULT is unethical. Nonetheless, the MSU crystal–inflammation–atherosclerosis relationship is supported by the current knowledge available for the atherosclerotic process (10).

This study carries a risk of selection bias, as participants were patients with gout who attended our rheumatology clinic, but not those who are monitored in primary care or those who self-managed their flares. This may have led to a higher rate of comorbidities, cardiovascular risk, crystal burden or a more inflammatory disease.

Women were also underrepresented in our study. Although gout is more prevalent in men, the percentage of female participants (8.7%) is too low. A lower suspicion of gout in women, and accordingly a lower referral to the rheumatology unit, could explain this fact.

CONCLUSION

Sonographic deposits of MSU crystals were consistently observed in newly seen patients with gout, and two out of three had inflammation in the intercritical period despite a month on colchicine as average. Crystal and inflammatory load, here shown as tophi and positive PD signal, were found to be associated with carotid atherosclerosis. This new finding may contribute to understanding the complex relationship between gout and atherosclerosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Alicante General University Hospital, Institute of Sanitary and Biomedical Research (ref. PI2018/027). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IC: data curation, investigation, project administration, visualization, writing—original draft, and writing—review and editing. AM-S: funding acquisition, investigation, and writing—review and editing. MA: conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, visualization, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.795984/full#supplementary-material

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The Diagnostic Performance of an Extended Ultrasound Protocol in Patients With Clinically Suspected Giant Cell Arteritis

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Objective: To evaluate the diagnostic performance of an extended ultrasound protocol in patients referred under the suspicion of giant cell arteritis (GCA).

Methods: Consecutive patients with suspected GCA were examined with an extended color duplex ultrasound (CDU) protocol during a period of 2 years. The extended CDU protocol included temporal, axillary, subclavian, brachiocephalic, and carotid arteries. The reference was clinically diagnosed GCA, confirmed after ≥6-month follow-up. Hypo- or medium-echogenic, circumferential, homogenous wall thickening, and/or a positive compression sign in temporal arteries, were regarded as typical signs of arteritis.

Results: Of the eligible 201 patients, 83 (41%) received a clinical GCA diagnosis at follow-up ≥6 months post CDU examination. Among these cases, 48 (58%) demonstrated inflammation solely in temporal arteries, 8 (10%) showed abnormalities restricted to extra-cranial vessels, and 23 (28%) patients displayed inflammatory changes in both temporal and extra-cranial arteries. Color duplex ultrasound of temporal arteries yielded a diagnostic sensitivity and specificity [95% confidence intervals (CI)] of 86% (76–92%) and 99% (95–99%), respectively. By adding axillary artery examination, the sensitivity increased to 92% (83–97%) while the specificity remained unchanged. Further, inclusion of subclavian artery marginally increased the sensitivity by 1%. Finally, by also including brachiocephalic and common carotid arteries resulted in a sensitivity of 95% (88–99%) and a specificity of 98% (94–99%).

Conclusions: Color duplex ultrasound examination demonstrated a high accuracy in diagnosing patients both with cranial and extra-cranial GCA. Further examination of brachiocephalic and common carotid arteries can increase the sensitivity without affecting the specificity when temporal and axillary findings are indecisive. Finally, the extended CDU protocol allows measurement of the general burden of inflammation, which could be relevant for future monitoring purposes.

Keywords: giant cell (temporal) arteritis, color duplex ultrasound, large vessel vasculitis, diagnostic imaging, IMT (intimal medial thickness)

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INTRODUCTION

Giant cell arteritis (GCA) is a systemic inflammatory disease targeting mainly large-sized arteries (1). The classical form of GCA is characterized by headache, scalp tenderness, jaw claudication, and visual loss which all manifests cranial symptoms of GCA (2). However, it is not uncommon that patients with GCA demonstrates extra-cranial vessel inflammation accompanied by diffuse inflammatory symptoms in the absence of headache, visual symptoms, or jaw claudication. Vascular imaging has shown involvement of the aorta and its major branches in up to 83% of such cases (3). Rapid diagnosis and treatment are important to reduce the risk of complications (4, 5). Temporal artery biopsy (TAB) has been considered the gold standard test for the diagnosis of GCA but newer recommendations support that color duplex ultrasound (CDU), if available, should serve as the first diagnostic tool in patients presenting with predominantly cranial GCA (6, 7). EULAR recommends ultrasound of temporal and axillary arteries as the primary imaging test, as examination of axillary arteries may be helpful in patients with suspected GCA who display negative or indecisive temporal artery ultrasound (6). However, it has been suggested that inclusion of axillary arteries only slightly increase the diagnostic sensitivity (8), whereas this examination may fail to identify large-vessel GCA. It has therefore been proposed that additional examination of the subclavian artery may facilitate the diagnosis (9). Nevertheless, the diagnostic benefit of evaluating different vascular beds with CDU in addition to cranial arteries remains largely unknown (10). We have previously developed an extended ultrasound protocol for detection of vessel wall inflammation (11). The aim of this study was to evaluate the diagnostic performance of an extended CDU examination, which in addition to temporal and axillary arteries, also includes subclavian, brachiocephalic and carotid arteries. This was performed as the first-line investigation in patients with suspected GCA as compared to current recommendations of temporal and axillar ultrasound alone. It was hypothesized that our extended ultrasound protocol would increase the diagnostic sensitivity for GCA without substantially affecting the specificity.

TABLE 1 | Patients' characteristics and comparison between patients with and without giant cell arteritis (GCA).

Patients' characteristics	Patients with GCA ($n = 83$)	Patients without GCA ($n = 118$)	*p*-Values
Age, median (range) years	76 (51–94)	71 (37–98)	0.0001
Female, *n* (%)	60 (72)	78 (66)	0.44
Smoking, *n* (%)	10 (12)	4 (3)	0.024
Clinical characteristics, *n* (%)			
New headache	60 (72)	69 (58)	0.052
Jaw claudication	29 (35)	15 (13)	0.0002
Reduced or lost vision	16 (19)	11 (9)	0.058
Double vision	5 (6)	1 (1)	0.084
Temporal artery abnormalities[a]	46 (58)	29 (25)	<0.0001
Myalgia, upper extremity	27 (33)	45 (38)	0.46
Myalgia, lower extremity	15 (18)	41 (35)	0.011
Joint pain	18 (22)	36 (31)	0.20
Joint swelling	4 (5)	19 (16)	0.014
Morning stiffness	13 (16)	35 (30)	0.029
Fatigue	77 (93)	96 (81)	0.023
Loss of appetite	22 (27)	24 (20)	0.31
Weight loss >2 kg	17 (21)	17 (14)	0.34
Temp >38.5°C	5 (6)	15 (13)	0.15
Laboratory findings			
ESR, mm/h, median (range)	75 (6–119)	64 (1–115)	0.024
CRP, mg/L, median (range)	53 (5–338)	35 (2–335)	0.004
Comorbidity, *n* (%)			
Hypertension	48 (58)	69 (59)	1.0
Diabetes mellitus	11 (13)	21 (18)	0.44
Dyslipidemia	27 (33)	37 (31)	0.88
Myocardial infarction	5 (6)	12 (10)	0.44
Cerebrovascular disease	6 (7)	18 (15)	0.12
Peripheral artery disease	2 (2)	3 (3)	1.0
Polymyalgia rheumatica	12 (15)	26 (22)	0.20

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured before initiation of high-dose glucocorticoid treatment.
[a] *Tenderness, pain, swelling, or decreased pulsations.*

MATERIALS AND METHODS

Study Population

This retrospective study comprised all patients examined with CDU at the Department of Clinical Physiology, Linköping, Sweden, between January 2018 and December 2019 due to clinically suspected GCA. Practically all patients examined with CDU presented with elevated levels of C-reactive protein (CRP) combined with unspecific inflammatory symptoms where arteritis not could be excluded. Some patients had fever, weight loss, morning stiffness, and tiredness, whereas others presented symptoms more specific for cranial arteritis, such as headache, jaw claudication, amaurosis fugax, or proximal extremity pain suggestive of polymyalgia rheumatica (PMR) (**Table 1**).

The diagnosis of GCA was based on a model proposed by Czihal et al. using both CDU and clinical parameters (12). Patients were classified as GCA if the 1990 American College of Rheumatology (ACR) criteria were satisfied (13), and/or if patients had the typical ultrasound picture of arteritis characterized by hypo- or medium echogenic, homogenous, circumferential wall thickening combined with increased levels of CRP and/or erythrocyte sedimentation rate (ESR), and good clinical response to corticosteroids.

At least 6 months after the CDU examination, two experienced rheumatologists (PE and CSj), not responsible for clinical care of the patients, reevaluated all data, judged the final clinical diagnosis of arteritis, and excluded other diagnoses explaining inflammatory disease. In order to achieve this, data were collected from a digital medical record system including all parts of the health care system from the catchment area. The use of a 6-month clinical follow-up as the reference is commonplace for studies of GCA (10, 14).

Patients with (1) GCA diagnosis prior to the CDU examination; (2) follow-up CDU; (3) deceased or migrated

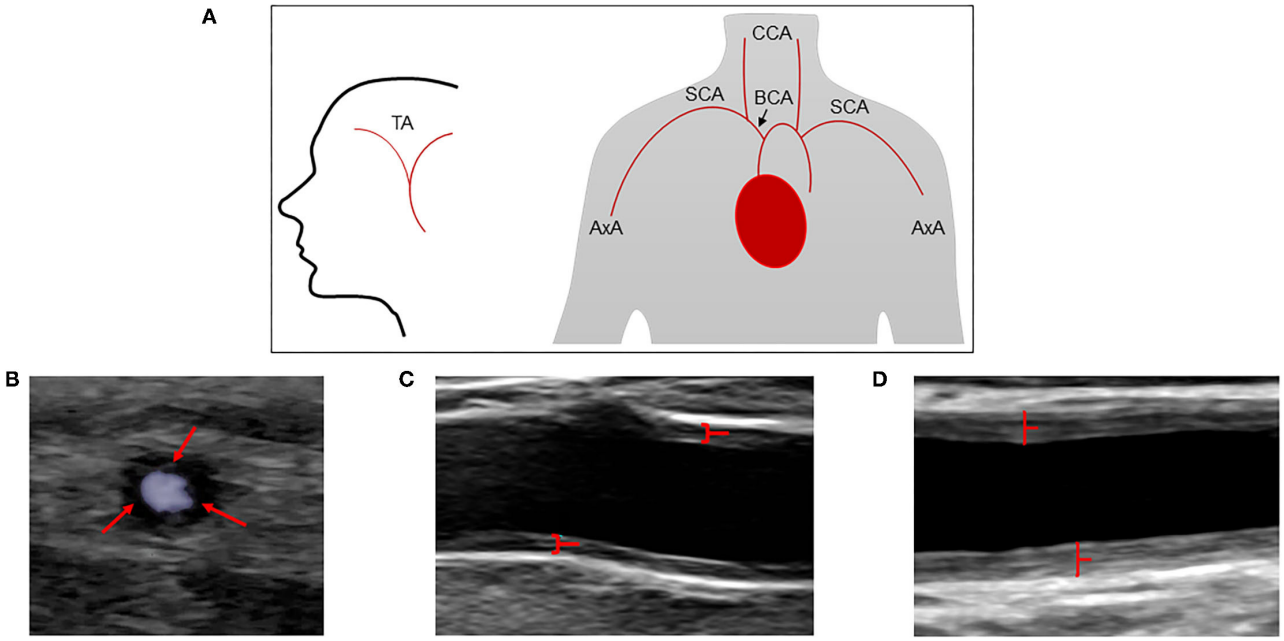

FIGURE 1 | Extended CDU protocol and assessment of cranial and extra cranial vessels by CDU. **(A)** Schematic illustration of the extended CDU protocol. **(B)** Increased circumferential low echogenicity vessel wall thickness in the common temporal artery, often described as halo sign (red arrows). **(C)** Increased circumferential vessel wall thickness (medium echogenicity) in near and far wall of the axillary artery (red marked). **(D)** Marked increased circumferential vessel wall thickness (medium echogenicity) in near and far wall of the common carotid artery (red marked). TA, temporal artery; AxA, axillary artery; SCA, subclavian artery; BCA, brachiocephalic artery; CCA, common carotid artery.

within 6 months after the CDU; (4) high doses steroids >2 month preceding CDU, were excluded.

CDU Assessment

A GE Logic E9 and E10 US system (LOGIQ E9 and E10 XDclear 2.0 General Electric Medical Systems US, Wauwatosa, WI, USA) with linear transducer L2-9 MHz and high frequency hockey stick transducer L8-18i were used for ultrasound measurements. The three branches of the temporal artery (common superficial artery, parietal, and frontal branches) were examined, as well as axillary, subclavian, brachiocephalic, common carotid, internal, and external carotid artery. Both sides were investigated, and the CDU protocol as well as measuring principles are shown in **Figures 1A–D**. The protocol has previously been described in detail (11, 15, 16). Color duplex ultrasound examinations were classified as positive if signs of inflammation were observed in at least one vessel. Hypo or medium echogenic, circumferential, homogenous wall thickening, and/or a positive compression sign of temporal arteries, were regarded as typical signs of arteritis (17–19). The intima-media thickness (IMT) was measured in all investigated vessels, with the exception of temporal arteries. Plaques were defined as focal areas in the vessel wall where IMT showed increase of either 0.5 mm or 50% compared to the IMT in the adjacent wall. Four experienced vascular technologists performed the CDU examinations as part of a standardized routine examination. One vascular technologist and three physicians performed the final interpretation of the CDU examinations. Complicated CDU images were reviewed according to clinical routine.

TAB

The local pathologists reported TAB positive or negative for GCA as part of standard practice. Temporal artery biopsy was defined positive if the sample showed vasculitis characterized by a high proportion of mononuclear cell infiltration or granulomatous inflammation, typically with multinucleated giant cells (13).

Statistical Evaluation

Data are presented as numbers and percentages or median with min and max value or the 25^{th} and 75^{th} percentile. Differences between patients with or without GCA were evaluated with the Mann–Whitney *U*-test. Categorical variables were tested with Fisher's exact test. The sensitivity and specificity (95% CI) of CDU were calculated using the clinical GCA diagnosis after 6 months as reference. Further, positive and negative prediction values as well as accuracy were calculated for the extended CDU protocol. Statistical analyses were carried out using SPSS 27.0 for windows (IBM, Armonk, NY, USA). p-Values < 0.05 were considered significant.

Ethical Considerations

The study was performed according to the declaration of Helsinki, and the study protocol was approved by the Regional Ethical Board in Linköping (ref. 2013/33-31).

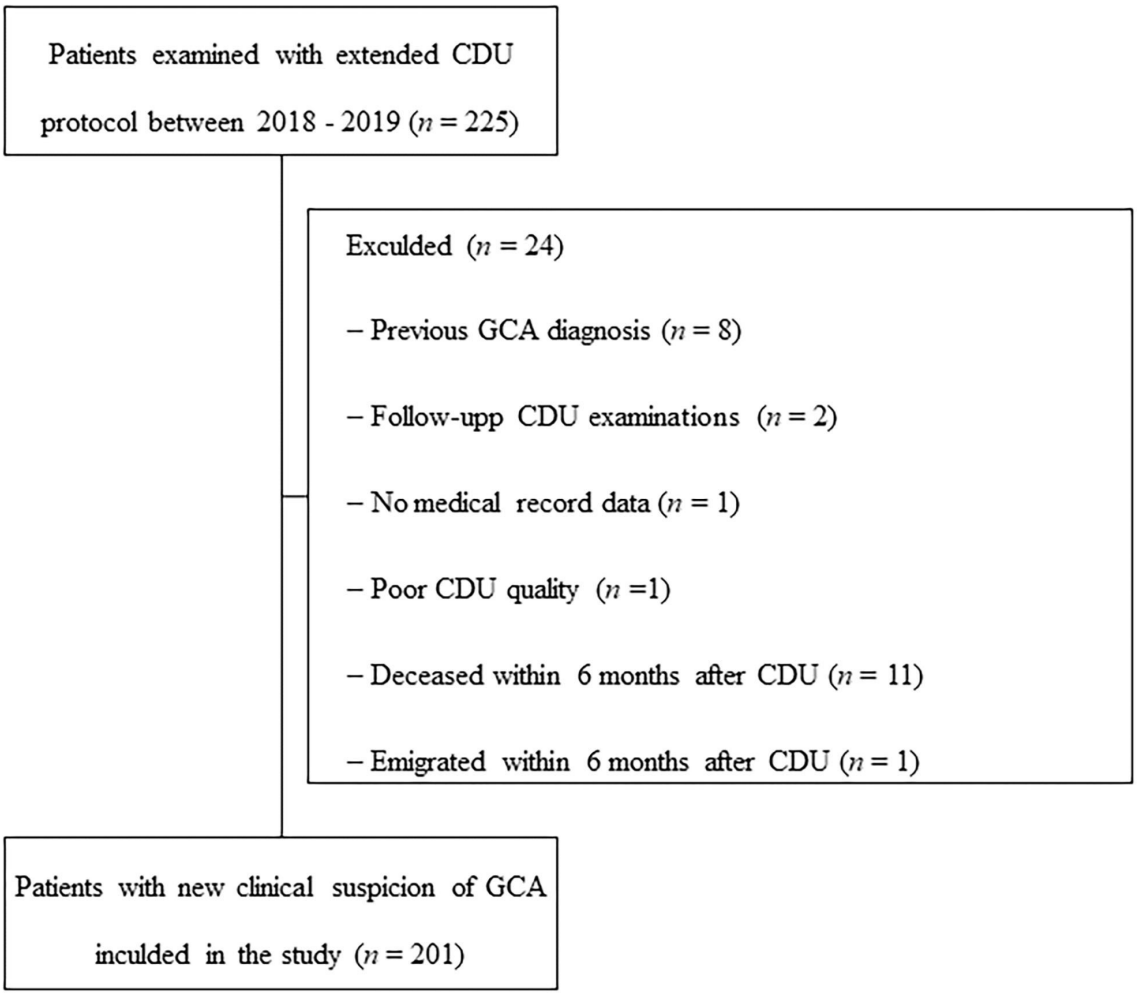

FIGURE 2 | Flowchart of patient inclusion.

RESULTS

Outcomes

In total, 225 cases were examined with an extended ultrasound protocol during 2018–2019, and 201 of these subjects were included in the study (**Figure 2**). Of the included 201 patients with suspected GCA, the median age (range) was 73 years (37–98) and 138 (69%) were females. An evaluation after ≥6 months yielded a clinical diagnosis of GCA in 83 (41%) patients. Sixty-one of the 83 patients diagnosed with GCA fulfilled the ACR criteria (73%). Diagnoses of the non-GCA group are shown **Supplementary Table 1**. Baseline characteristics of those with and without clinical diagnosis of GCA are detailed in **Table 1**. Patients with GCA were more likely to have jaw claudication, temporal artery abnormalities, symptoms of fatigue, and higher levels of CRP and ESR compared to the non-GCA group. TAB was performed in 51 cases (25%), in which 27 (53%) were negative and 24 (47%) were positive. Consistent data from both TAB and CDU, not supporting a diagnosis of GCA, were seen in 14 patients, whereas consistent data compatible with a diagnosis of GCA from both modalities were seen in 20 patients. Thus, 13 patients displayed inflammatory changes during CDU examination but normal TAB, and 4 patients vice versa.

Extended CDU Protocol

Figures 3A,B shows the localization of CDU abnormalities in the 83 patients with GCA. The temporal artery was affected in 71 (86%), axillary artery in 22 (27%), subclavian artery in 13 (16%), brachiocephalic artery in 5 (6%), and common carotid artery in 21 (25%) of the patients (**Figure 3A**). In these patients, 48 (58%), demonstrated signs of vessel wall inflammation only in temporal arteries, 8 (10%) showed abnormalities restricted to extra cranial vessels and 23 (28%) patients displayed inflammatory changes in both temporal and extra cranial arteries (**Figure 3B**). Of the 118 patients not diagnosed with GCA, two patients displayed abnormalities during CDU examination. The temporal artery was affected in one patient, and the other demonstrated atypical inflammatory signs in common carotid artery and brachiocephalic artery, i.e.,

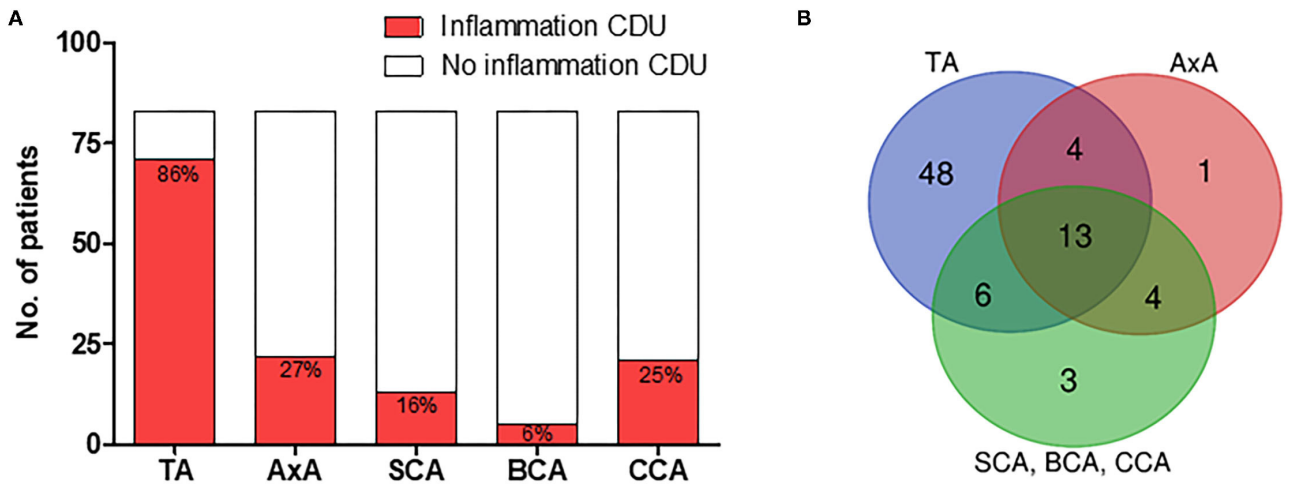

FIGURE 3 | CDU finding in patients with GCA. **(A)** Localization of CDU detected vessel wall inflammation in patients with clinical GCA diagnosis. **(B)** Temporal, extra-cranial, and combined temporal and extra-cranial vessel wall inflammation in patients with clinical GCA diagnosis. TA, temporal artery; AxA, axillary artery; SCA, subclavian artery; BCA, brachiocephalic artery; CCA, common carotid artery.

an asymmetric, hypo to medium echogenic, and homogenous vessel wall thickening of inflammatory type. The former was diagnosed with headache of unknown origin and the latter with chronic myelomonocytic leukemia.

Patients with GCA displayed a significantly higher IMT in large vessels bilaterally compared to the non-GCA group, with the exception of the brachiocephalic artery (**Table 2**). Atherosclerotic plaques in neck arteries were common in both groups and only 13 (16%) in the GCA group and 18 (15%) in the non-GCA group showed no plaques. The most frequent localizations of atherosclerotic plaques were in the carotid bifurcation where 41 (49%) of patients with GCA and 50 (42%) of patients with no GCA had plaque formation. No differences in localization or frequency of plaques were seen between the groups (**Table 2**).

TABLE 2 | IMT and atherosclerotic plaque in patients with and without giant cell arteritis (GCA).

Variable	Patients with GCA ($n = 83$)	Patients without GCA ($n = 118$)	*p*-Values
IMT, right			
AxA, mm median (IQR)	0.70 (0.60–1.00)	0.60 (0.50–0.70)	0.007
SCA, mm median (IQR)	0.70 (0.60–1.00)	0.70 (0.60–0.80)	0.007
BCA, mm median (IQR)	1.00 (1.25–1.45)	1.1 (0.90–1.50)	0.63
CCA, mm median (IQR)	0.80 (0.70–1.00)	0.80 (0.60–0.90)	0.026
IMT, left			
AxA, mm median (IQR)	0.70 (0.60–0.92)	0.60 (0.50–0.70)	0.0001
SCA, mm median (IQR)	0.70 (0.60–1.00)	0.60 (0.50–0.80)	0.003
CCA, mm median (IQR)	0.80 (0.70–1.10)	0.70 (0.60–0.90)	0.003
Atherosclerotic plaque			
No plaque, *n* (%)	13 (16%)	18 (15%)	1.0
AxA, *n* (%)	9 (11%)	7 (6%)	0.29
SCA, *n* (%)	2 (2%)	1 (1%)	0.57
ICA, *n* (%)	2 (2%)	1 (1%)	0.57
ECA, *n* (%)	–	2 (2%)	0.51
Carotid bifurcation, *n* (%)	41 (49%)	50 (42%)	0.39
≥3 vessels, *n* (%)	21 (25%)	36 (31%)	0.43

IQR, interquartile range; GCA, giant cell arteritis; IMT, intima media thickness; AxA, axillary artery; SCA, subclavian artery; BCA, brachiocephalic artery; CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery.

Diagnostic Performance of an Extended CDU Protocol

Figure 4 display the diagnostic accuracy of the extended ultrasound protocol. With the clinical GCA diagnosis at ≥6 months as reference, CDU evaluation of temporal arteries yielded a diagnostic sensitivity and specificity [95% confidence intervals (CI)] of 86% (76–92%) and 99% (95–99%), respectively. By adding CDU examinations of the axillary artery, the sensitivity increased to 92% (83–97%) while the specificity remained at 99% (95–99%). Further incorporation of the subclavian artery in the diagnostic evaluation yielded a sensitivity and specificity of 93% (84–97%) and 99% (95–99%). Finally, by also including the brachiocephalic and common carotid artery in the CDU examination resulted in a sensitivity of 95% (88–99%) and a specificity of 98% (94–99%). Based on a prevalence of 41% in the present study population, our extended CDU protocol demonstrated a positive and negative prediction value of 97% (90–99%) and 97% (92–99%) respectively, and an accuracy of 97% (94–99%).

DISCUSSION

The present study confirmed our hypothesis that a CDU examination including temporal, axillary, subclavian,

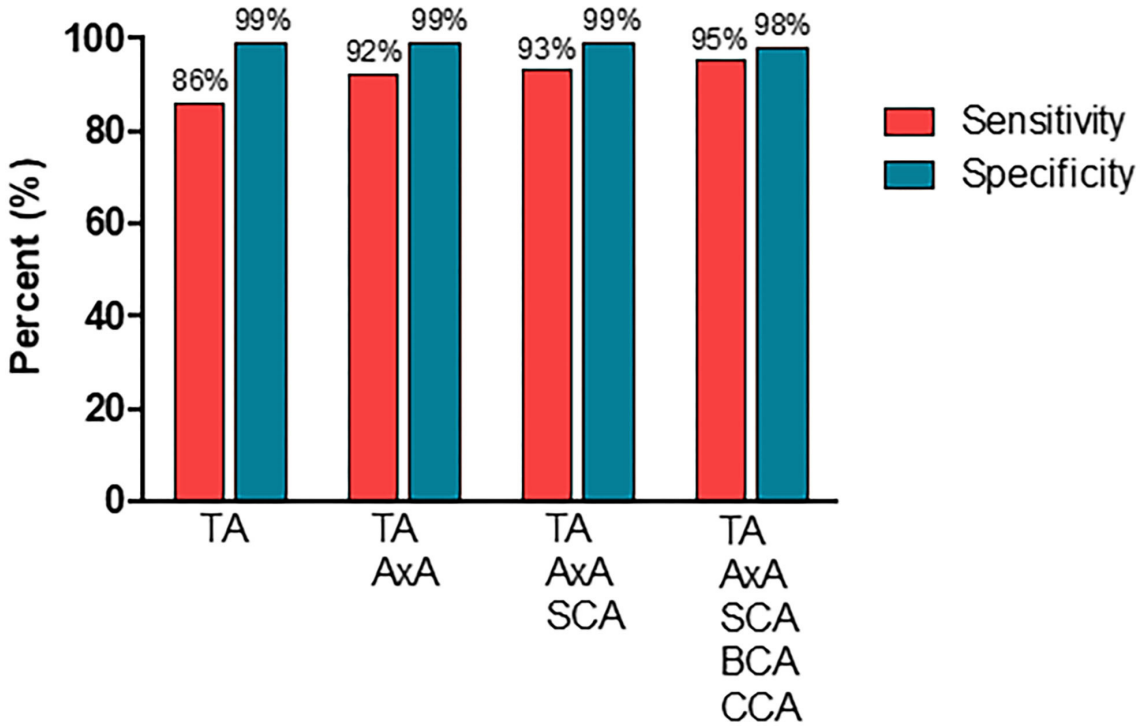

FIGURE 4 | The diagnostic performance of CDU examinations in different vascular segments. TA, temporal artery; AxA, axillary artery; SCA, subclavian artery; BCA, brachiocephalic artery; CCA, common carotid artery.

brachiocephalic, and common carotid arteries increased the diagnostic sensitivity for GCA without substantially affecting the specificity.

EULAR recommends ultrasound of temporal arteries, applied by trained ultrasonographers, as the first imaging modality in patients with suspected cranial GCA (6), and if the examination is negative or indecisive, a further evaluation of axillary arteries is suggested (6). The reason why the examination needs to be expanded in some cases is that some patients do not show any changes in the temporal arteries. However, which vessels to include, and the effects of the additional CDU scanning on the sensitivity and specificity of the examination remains unclear. The present study included 201 patients of which 83 had a confirmed clinical diagnosis of GCA 6 months after the ultrasound examination. Of these 83 patients, 48 (58%) displayed abnormalities solely in temporal arteries, whereas 23 (28%) showed signs of inflammation in both the temporal and extra cranial arteries, and 8 (10%) demonstrated abnormalities restricted to extra cranial vessels. Inflammatory changes were most frequently seen in temporal (86%), axillary (27%) and common carotid arteries (25%). Previous studied have shown somewhat conflicting results regarding the extra diagnostic value of incorporating other vascular territories than temporal arteries in the ultrasound examination. Schmidt et al. found that 20 of 53 patients with extra cranial GCA had no temporal artery abnormalities on ultrasound (20). No sensitivity or specificity calculation was presented since only GCA patients were included. Subsequent reports by Hop et al. demonstrated an increased sensitivity of 19% when adding the axillary to the investigation (21). However, other reports suggest that the increase in sensitivity may be only 2% (8), and the TABUL study found that only 2.4% of suspected GCA cases displays ultrasound abnormalities in axillary arteries (22). The reason for these discrepancies is not obvious, but differences in inclusion criteria between patients with and without cranial symptoms may have contributed. In the present study, all patients with suspected GCA were examined with an extended ultrasound protocol. We found that, by adding the axillary artery, five additional patients (6%) with GCA were identified. This increased the sensitivity with 6%, i.e., from 86% (95% CI, 76–92%) for ultrasound of only temporal arteries to 92% (95% CI, 83–97%) for temporal and axillary arteries. The specificity of CDU examination of only temporal arteries was 99% (95% CI, 95–99%), which is similar to recent a meta-analysis (10). The specificity remained essentially unchanged when adding the axillary artery to the examination.

Recently, a Halo Score have been developed to quantify the extent of inflammation detected with ultrasound (14). This score includes temporal as well as axillary arteries, and a higher score support GCA diagnosis (14). A modified Halo Score, also including subclavian arteries, has been suggested to better cover large vessel GCA, which is otherwise at risk of being missed (9).

We only identified one individual with detectable subclavian inflammation in which no vasculitic changes were observed in temporal or axillary arteries. Thus, by adding subclavian arteries to the ultrasound examination, the sensitivity increased by only one percent and the diagnostic accuracy was not obviously

improved by including the subclavian artery if the axillary artery is incorporated in the examination protocol. It should also be noted that the above-mentioned patient with inflammatory signs in subclavian arteries also demonstrated changes in the brachiocephalic artery and common carotid arteries. These vessels are included in our extended ultrasound protocol (11, 16). Apart from the above-mentioned patient, two additional patients with confirmed GCA 6 month after the CDU examination were found by examining brachiocephalic artery and common carotid arteries. Thus, the sensitivity of diagnosing GCA with our extended protocol was 95% (95% CI, 88–99%).

It is important to note that other pathological conditions, e.g., malignancies, infections, and other rheumatologic diseases, may manifest with signs of inflammation in the vessel wall and thus mimic GCA (11, 23). In the present study, CDU showed an atypical inflammatory appearance in the brachiocephalic artery and common carotid artery in one patient. This patient was later diagnosed with chronic myelomonocytic leukemia. Thus, it must be emphasized that although ultrasound is an important tool in diagnosing GCA, it ought to be used as a complement to clinical history, laboratory results, and physical examination. It should also be underlined that although atherosclerosis can be distinguished from vasculitis it is far less common in temporal and axillary arteries compared to carotid arteries. Thus, atherosclerosis can disturb the sonographic evaluation of arteritis especially in other arteries than temporal and axillary arteries (18, 24). We found that the majority of patients demonstrated plaque in the carotid bifurcation or in three or more vessels. Although patients with GCA displayed higher IMT in large vessels, this was not the case with the brachiocephalic artery. This reinforce the notion that IMT should be interpreted with caution when differentiating between arteritis and atherosclerosis. Intimal medial thickness can be strongly affected by atherosclerosis and it is possible that an IMT above the cut-off is not related to GCA. Likewise, an IMT below the cut-off may be related to GCA (24). It is thus important that IMT and vessel wall appearance are interpreted in relation to each other. Nevertheless, the rather high frequency of atherosclerosis did not seem to affect the specificity for our extended protocol which was 98% (95% CI 94–99%), compared to a specificity of 99% (95% CI 95–99%) for examinations including temporal and axillary arteries.

Immediate treatment is recommended in patients with suspected GCA due to potential irreversible ischemic complications (1, 4, 5). However, as many patients are older and have other co-morbidities it is important to restrict unnecessary use of steroids due to its side effects. The present study demonstrated a good diagnostic accuracy using ultrasound examination of temporal and axillary arteries as recommended by the EULAR guidelines (6). However, if the examination is negative or indecisive, our results suggest that a further evaluation with our extended ultrasound protocol is of value.

A major strength of the study is the Swedish healthcare system, which is public, tax funded, and offers universal access. This significantly reduces the risk of selection bias and ensures a high coverage of cases. Potential drawbacks with this study were the retrospective design and that the examinations were performed as routine health care studies by more than one ultrasonographer. Interobserver variability was not measured. However, the strength of the extended CDU protocol is that it is strictly standardized, and thus, the results mirror real life in the routine health care system. Positron emission tomography/computed tomography (PET/CT) was conducted only in cases where it was clinically indicated. As such, no standardized comparison could be performed between PET/CT and CDU in patients with extra-cranial GCA.

CONCLUSIONS

Ultrasound examination as the initial diagnostic test in patients with suspected GCA demonstrated a high sensitivity and specificity for the final diagnosis of GCA, both for cranial and extra-cranial GCA. The present study suggests that if no decisive abnormalities are detected in temporal or axillary arteries, an extended examination of neck arteries is indicated in order not to miss GCA involving other parts of the vascular tree. Finally, as the extended CDU protocol provides information about the general burden of inflammation it may also have a role in future monitoring of disease activity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethical Board in Linköping (ref. 2013/33-31). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PE and HZ contributed to conception and design of the study. JS, PE, CSj, and HZ organized the database. JS performed the statistical analysis and wrote the first draft of the manuscript. CSv, PE, CSj, and HZ wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.807996/full#supplementary-material

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From Active to Non-active Giant Cell Arteritis: Longitudinal Monitoring of Patients on Glucocorticoid Therapy in Combination With Leflunomide

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In the present study, we longitudinally monitored leukocyte subsets, expression of neutrophil surface adhesion molecules (CD62L and CD11b) and serum analytes in therapy-naïve patients with active giant cell arteritis (GCA). We collected blood samples at the baseline, and at weeks 1, 4, 12, 24, and 48 of follow-up, and evaluated short- and long-term effects of glucocorticoids (GC) vs. GC and leflunomide. Our aim was to identify candidate biomarkers that could be used to monitor disease activity and predict an increased risk of a relapse. Following high doses of GC, the numbers of CD4+ T-lymphocytes and B-lymphocytes transiently increased and then subsided when GC dose tapering started at week 4. In contrast, the numbers of neutrophils significantly increased during the follow-up time of 12 weeks compared to pre-treatment time. Neutrophil CD62L rapidly diminished after initiation of GC therapy, however its expression remained low at week 48, only in patients under combinatorial therapy with leflunomide. Levels of acute phase reactant SAA and IL-6 decreased significantly after treatment with GC and leflunomide, while levels of IL-8, IL-18, and CHI3L1 did not change significantly during the follow-up period. CHI3L1 was associated with signs of transmural inflammation and vessel occlusion and might therefore serve as a marker of fully developed active GCA, and a promising therapeutic target. Patients with relapses had higher levels of IL-23 at presentation than patients without relapses ($p = 0.021$). Additionally, the levels of IL-23 were higher at the time of relapse compared to the last follow-up point before relapse. IL-23 might present a promising biomarker of uncontrolled and active disease and could give early indication of upcoming relapses.

Keywords: giant cell arteritis, glucocorticoids, leflunomide, follow-up, biomarkers, disease monitoring

INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous vasculitis affecting large- and medium-sized arteries (1). In the majority of patients, cranial and extracranial large arteries are involved to different degrees, leading to specific clinical phenotypes (2). Predominant cranial GCA (C-GCA) is characterized by headache, jaw claudication and visual disturbances, while clinical signs and symptoms of extra-cranial [large vessel (LV-GCA)] typically include weight loss, myalgia and fever (3). Erythrocyte sedimentation rate (ESR) and/or levels of C-reactive protein (CRP) are usually increased at presentation in GCA patients, indicating a strong acute inflammatory response (4, 5).

High dose glucocorticoids (GC) represent the first-line treatment for GCA (6). They effectively control systemic inflammation and successfully prevent ischemic complications, such as acute vision loss. Relapses, however, are common when GC tapering regimen is applied, most likely due to ongoing inflammation in the affected vascular tissues, not adequately suppressed by GC (7). In addition, long-term use of GC is associated with various adverse effects, including bone fractures, infections, diabetes mellitus, and hypertension (8). Several other disease modifying anti-rheumatic drugs have subsequently been investigated for their steroid-sparing effect in GCA (9). So far, only tocilizumab showed the efficacy for achieving a sustained remission at week 52 of follow-up compared to placebo (10, 11). However, it was recently discovered by magnetic resonance angiography that signs of vascular inflammation persist in two-thirds of GCA patients treated with tocilizumab, despite clinical remission (12). Other agents, such as methotrexate exhibited limited or no evidence of benefit in the treatment of GCA (13). Leflunomide, on the other hand, has been shown to be effective and safe in reducing the rate of relapses in GCA in a small open-label study (14).

Classical acute phase parameters, such as ESR and CRP are commonly used for monitoring GCA activity (15, 16). However, measuring ESR and CRP to predict relapses has a limited value, since GC strongly suppress the systemic acute phase response, decrease ESR, as well as serum levels of CRP, despite an ongoing local vascular inflammation (17, 18). Subsequently, one cannot determine whether patients in GC-free remission are truly in remission or are still suffering from an ongoing subclinical disease. Therefore, new biomarkers are needed to predict the risk of relapses, and monitor disease activity in patients with GCA.

Van Sleen et al. (19) demonstrated higher numbers of monocytes and neutrophils, and lower numbers of natural killer (NK) and B cells in therapy-naïve GCA patients compared to healthy blood donors (HBDs). During GC treatment, as well as in GC-free remission, myeloid subsets remained elevated, while lymphoid subsets fluctuated substantially (19). Additionally, an altered phenotype of circulating neutrophils was also reported. The neutrophil phenotype changed from activated and highly adhesive, in the early stages of GCA, to a less adhesive after 48 h of GC treatment. However, 24 weeks following GC treatment and therapy tapering, neutrophils with the activated phenotype reappeared exhibiting a high expression of adhesion molecules L-selectin (CD62L) and integrin αM (CD11b) (20). Long-term monitoring of the neutrophil phenotype could point to an incompletely controlled disease process (e.g., relapse) (21).

Previously, our cross-sectional study revealed significantly higher levels of serum amyloid A (SAA), interleukin (IL)-6, IL-8, IL-18, IL-23 and chitinase 3 like protein 1 (CHI3L1) in sera of therapy-naïve GCA patients compared to HBDs, reflecting an active disease (22). SAA has recently gained more attention in GCA (23), since it has been found to be highly elevated in GCA patients with active vs. inactive disease (24), and associated with relapses and visual disturbances (22).

In the current study, we longitudinally monitored the quantitative changes in leukocyte subtypes, neutrophil expression of adhesion molecules (CD62L, CD11b) and serum levels of selected analytes in GCA patients to evaluate the short- and long-term effects of GC vs. GC and leflunomide. Our aim was to identify candidate cellular and molecular biomarkers that could help monitoring disease activity and predicting the risk of a relapse.

METHODS

Patients

Thirty-one consecutive therapy-naïve GCA patients were enrolled in the study between October 2016 and October 2017. The diagnosis was established based on the 1990 ACR classification criteria (25) and a positive temporal artery biopsy (TAB) or positive color Doppler sonography (CDS) of temporal arteries. Blood samples from GCA patients were obtained at baseline visit [before initiation of GC therapy (T_0)], as well as during follow-up at weeks 1, 4, 12, 24 and 48, unless otherwise stated. GC treatment was initiated at the time of diagnosis (**Figure 1**) in accordance with the unified protocol following the EULAR guidelines (26). Tapering of GC started at week 4 after baseline visit. Leflunomide (10 mg/day) was introduced as an adjuvant therapy at the week 12 to 17/31 patients. 2/17 patients experiencing adverse events (e.g., hair loss, diarrhea), discontinued leflunomide therapy and were consequently excluded from the longitudinal analysis. During follow-up and GC tapering, 4/31 patients experienced disease relapse after having already responded to GC therapy. Relapse was defined as the need for treatment intensification following new or increasing clinical symptoms typical of GCA. At the time of relapse, these patients were on GC monotherapy and consequently received leflunomide (10 mg/day), in addition to GC. From 3 relapsing patients, data was collected at the time before relapse (in remission), at the time closest to relapse (active disease) and 12 weeks after relapse (in remission). One patient relapsed in week 57 after diagnosis (after the last study follow-up point) and was excluded from the longitudinal analysis due to missing data (**Figure 1**). Patients and their samples were anonymized, before being used in the analyses. All patients signed informed consent to participate in the study. The study was approved by

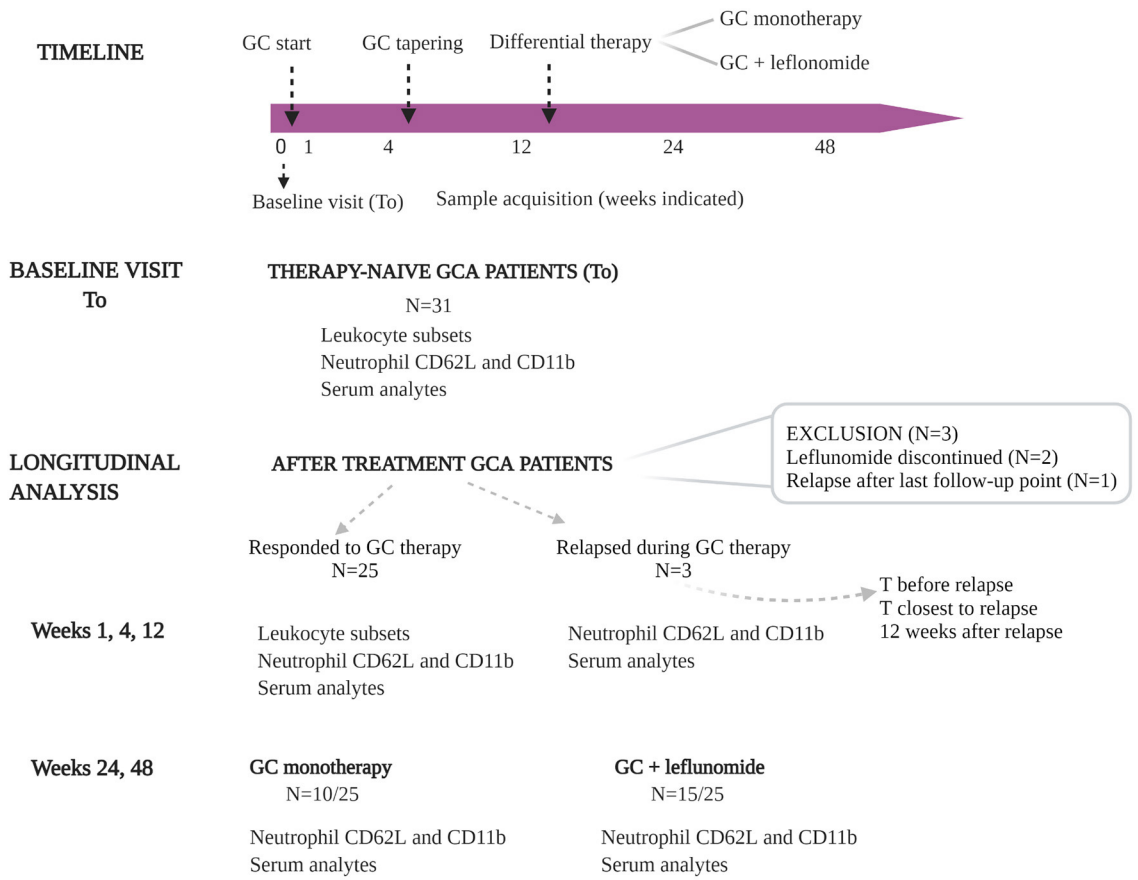

FIGURE 1 | Overview of the study design. Thirty-one consecutive, therapy-naïve GCA patients were included in the study. Blood samples from GCA patients were obtained at baseline visit [before initiation of GC therapy (T_0)], and during follow-up at weeks 1, 4, 12, 24, and 48. GC treatment was initiated at the time of diagnosis. GC tapering started at week 4 after sampling. Leflunomide (10 mg/day) was introduced as an adjuvant therapy at week 12 to 17 GCA patients (two of them experienced therapy-related adverse events and were excluded from longitudinal analysis). During follow-up and GC tapering, three of 25 patients experienced disease relapse after they already responded to GC therapy. At the time of relapse these patients were on GC monotherapy and consequently received leflunomide (10 mg/day), in addition to GC. From 3 relapsing patients, the data was collected before relapse, at the time closest to relapse and 12 weeks after relapse. GC, glucocorticoids; GCA, giant cell arteritis; T, time.

the Slovenian National Medical Ethics Committee (#99/04/15 and #65/01/17).

Histological Examination of Temporal Artery Biopsies and Routine Laboratory Parameters

Histological analyses were performed on formalin-fixed paraffin-embedded sections stained with hematoxylin and eosin. Arterial wall inflammatory infiltrate and arterial occlusion were semiquantitatively scored. Arterial occlusion was considered when luminal stenosis was >75%.

Among laboratory parameters, ESR was measured by the WesternGreen method, CRP using Siemens Advia colorimetric assay, fibrinogen was detected by Siemens BCS XP/modified Clauss method, ferritin using the Advia chemiluminescence assay, SAA and haptoglobin were determined using immunonephelometry from Siemens (BN Prospec System and BN II, respectively).

Flow Cytometry

Venous blood was drawn from GCA patients into heparin-containing tubes. Whole blood immunophenotyping was performed using 7-Color Immunophenotyping kit with the following antibodies (Miltenyi Biotec, catalog #130-098-456): CD14-FITC (clone Tük4), CD56-PE (clone REA196), CD16-PE (clone REA423), CD4-PerCP (clone VIT4), CD19-PE-Vio® 770 (clone LT19), CD3-APC (clone BW264/56), CD8-APC-Vio 770 (clone BW135/80), CD45-VioBlue® (clone 5B1). Briefly, 100 µl of whole blood was incubated with 10 µl immunophenotyping reagent for 10 min in the dark, at 4°C. After incubation, whole blood was lysed using Red Blood Lysing Solution (Miltenyi Biotec, catalog #130-098-456). Neutrophil phenotyping was performed in 50 µl of whole blood, incubated for 30 min at 4°C in the dark, with the following antibodies (eBioscience): CD16-PE (clone eBioCB16; catalog #50-112-4738), CD62L-PE-Cy5 (clone DREG56; catalog #50-140-71) and CD11b-APC (clone ICRF44; catalog #17-0118-42). After incubation, samples

were lysed, using Whole Blood Lysing Reagent Kit (Beckman Coulter; catalog #6602764). All samples were analyzed using flow cytometer MACSQuant Analyzer 10 (Miltenyi Biotec). Analysis of flow cytometry data was performed using MACSQuantify (Analysis Software version 2.8, Miltenyi Biotec) and FlowLogic (Flow Cytometry Analysis Package, version 7.00.0a, Invasion Software Technologies Pvt Ltd).

Biomarker Protein Detection

Serum concentrations of IL-8, IL-18, IL-23, CHI3L1 and soluble CD62L (sCD62L) were measured by MagPix (Luminex xMAP Technology) using human pre-mixed multi-analyte kits (R&D Systems; catalog #LXSAHM) and IL-6 using ELISA (Invitrogen; catalog #KHC0061).

Statistical Analysis

Statistical analysis was performed using SPSS statistical software package version 22.0 and Graph Pad Prism software 9.0. The normality of data distribution was investigated by the Shapiro-Wilk test. Due to the non-normal distribution of the data, summary statistics are expressed as medians and 25–75th percentiles (Q_{25}-Q_{75}). Mann-Whitney U-test was used to compare medians of measured parameters in GCA patients with or without specific clinical signs/symptoms. Statistical analysis of longitudinal data was performed using Kruskal-Wallis test followed by Dunn's multiple comparison test, which calculates adjusted p-values. All tests were two-tailed and p-values of <0.05 were regarded as statistically significant.

RESULTS

Baseline Visit

The median (Q_{25}-Q_{75}) age of the included patients was 74.9 (68.0–76.8) and there were 20 (65%) females. The most frequent clinical symptoms/signs reported were newly formed headache (74%), jaw claudication (65%) and general symptoms (71%). Visual disturbances were present in eight (26%) patients and seven patients (23%) had LV-GCA. The median (Q_{25}-Q_{75}) ESR was 78.0 (48.0–94.5) mm/h and the median CRP value was 71.5 (34.3–128.8) mg/l (**Table 1**).

TABLE 1 | Demographics, clinical and laboratory data of therapy-naïve GCA patients at baseline visit.

Demographic data	
Number of patients	31
Median age in years (Q_{25}-Q_{75})	74.9 (68.0–76.8)
Number of females (%)	20 (65)
Median duration of symptoms (days) (Q_{25}-Q_{75})	30 (30–60)
Median body mass index (kg/m^2) (Q_{25}-Q_{75})	23.8 (21.3–28.7)
Symptoms and signs *n* (%)	
General symptoms	22 (71)
Fever	5 (16)
Weight loss	19 (61)
Headache	23 (74)
Jaw claudication	20 (65)
Scalp tenderness	12 (39)
Visual disturbances	8 (26)
Dry cough	5 (16)
Large vessel involvement	7 (23)
Histological examination of TABs *n* (%)	
TAB performed	23 (74)
Transmural inflammation	18 (78)
Vessel occlusion	8 (34)
Ultrasound examination of temporal arteries *n* (%)	
HALO effect	28 (90)
Median laboratory values (Q_{25}-Q_{75})	
ESR (mm/h)	78.0 (48.0–94.5)
CRP (mg/l)	71.5 (34.3–128.8)
Fibrinogen (g/l)	6.2 (5.7–7.2)
Ferritin (g/l)	258 (161–441)
Haptoglobin (g/l)	4.5 (2.6–5.6)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; TAB, temporal artery biopsy.

Therapy-Naïve GCA Patients With Transmural Inflammation and Occlusion of Temporal Arteries Have Higher Serum Levels of CHI3L1

To reveal if the inflammatory process in TABs of therapy-naïve GCA patients associates with the numbers of leukocyte subsets and serum parameters, we correlated the measured baseline cell and serum parameters with the presence of histological signs of GCA (transmural inflammation, occlusion of temporal arteries), clinical symptoms and signs and development of a future relapse.

Histological examination of TAB was performed in 23 therapy-naïve GCA patients. Signs of transmural inflammation (TAB + GCA) and vessel occlusion were found in 18 (78%) and 8 (26%) of the examined TABs, respectively (**Table 1**). In general, the patients with transmural inflammation had significantly higher ESR ($p = 0.0443$), haptoglobin ($p = 0.0470$) and CHI3L1 ($p = 0.0279$) compared to patients with no signs of inflammation in the TABs (TAB- GCA) (**Figure 2A**). GCA patients with occlusion of the temporal arteries had higher amount of CHI3L1 ($p = 0.0306$) but lower neutrophil expression of CD11b ($p = 0.0017$) compared to GCA patients without vessel occlusion (**Figure 2B**). Other measured parameters (serum analytes, the number of leukocyte subsets, the expression of CD62L) did not associate with temporal artery transmural inflammation or occlusion.

Correlating the clinical signs and symptoms with the measured parameters, we found that therapy-naïve GCA patients with visual disturbances ($n = 8$) had lower median amount of serum IL-23 compared to patients without visual disturbances ($n = 23$; $p = 0.047$, **Figure 2C**). Additionally, the median amount of IL-23 was significantly higher in the serum of therapy-naïve GCA patients (at baseline visit) who developed a future relapse ($n = 4$) compared to patients with no future relapses ($n = 27$; $p = 0.021$) (**Figure 2D**). Other clinical symptoms and signs at baseline visit did not correlate with measured cell and serum parameters.

Longitudinal Follow-Up

The longitudinal analysis included 28 of the initial 31 GCA patients, who received GC immediately after pre-treatment

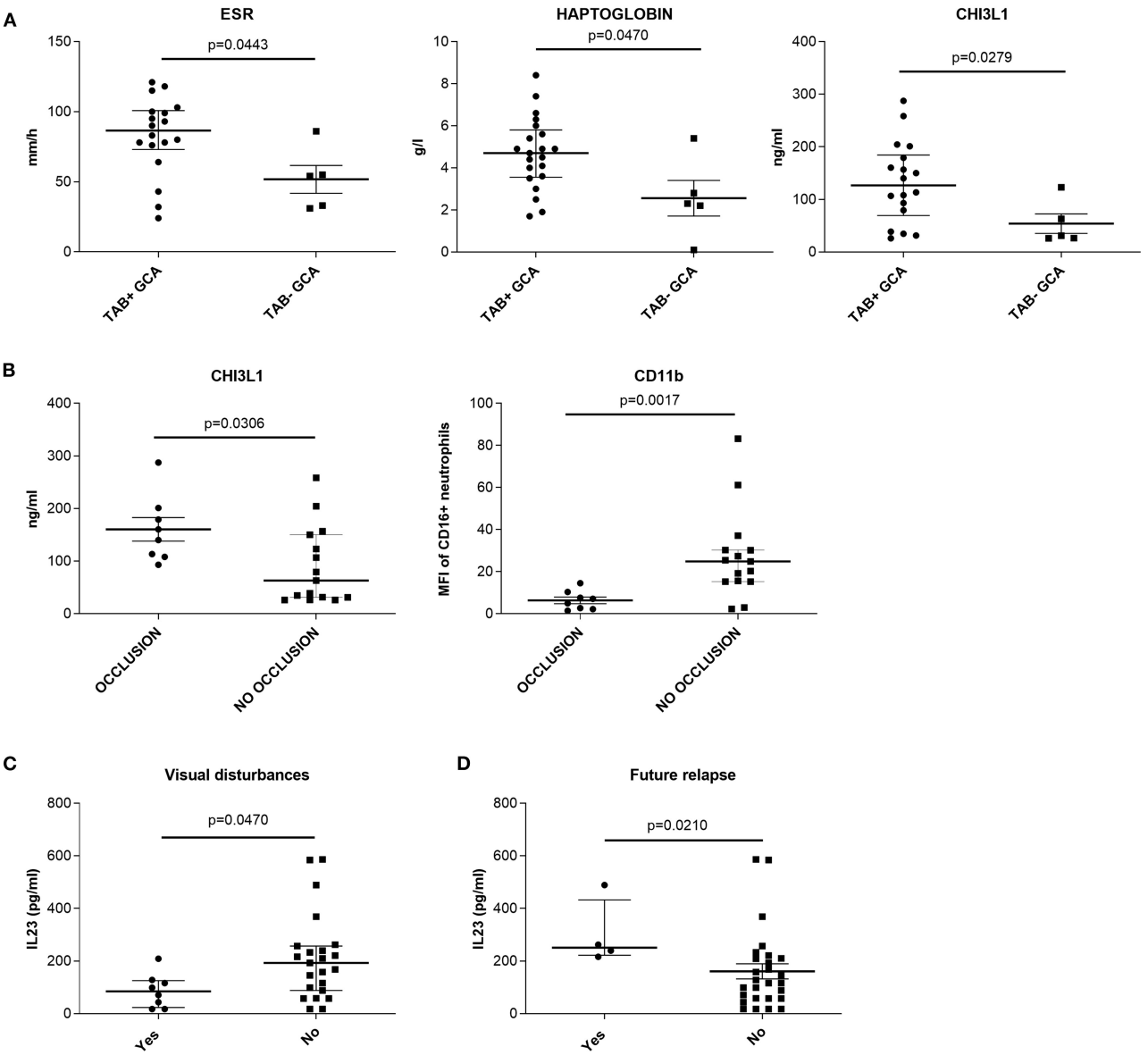

FIGURE 2 | Association between histopathological findings in temporal artery biopsies of therapy-naïve GCA patients and **(A,B)** presence of visual disturbances; **(C)** development of a future relapse and **(D)** measured cell and serum parameters. **(A)** medians, Q_{25} and Q_{75} in patients with (TAB + GCA) or without (TAB− GCA) signs of transmural inflammation in the temporal arteries. **(B)** medians, Q_{25} and Q_{75} in patients with or without occlusion of the temporal arteries. **(C)** medians, Q_{25} and Q_{75} in patients with or without visual disturbances. **(D)** medians, Q_{25} and Q_{75} in patients with or without future relapse. CHI3L1, chitinase 3 like protein 1; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; IL, interleukin; MFI, median fluorescence intensity; TAB, temporal artery biopsy.

(baseline) sampling. Among them, 25 responded to GC at the initial dosage, with prompt improvement of clinical signs and symptoms of GCA, as determined by a rheumatologist during the follow-up visits. These patients were able to continue GC reduction without any deviation from the protocol. Three patients (9.7%) experienced a relapse following a period of remission during the 48 weeks of follow-up. Patient 1 (P1) experienced a relapse at week 24, P2 relapsed at week 48 and P3 relapsed at week 12. All relapsing patients were on GC monotherapy at the time of relapse. P1 and P2 received GC dosage of 4 mg/day, while P3 received 12 mg/day. All three relapses were characterized by new or intensified clinical symptoms considered typical of GCA. P1 and P2 experienced signs of systemic inflammation (fever, weight loss, fatigue, myalgia), while P3 experienced cranial signs (headache, jaw claudication). P1 and P2, but not P3, also had increased ESR and CRP, associated with GCA in the absence of an alternative explanation, compared to the last time point before relapse when they were in remission. All relapsing patients responded to additional therapy with leflunomide

(10 mg/day), and were able to continue with GC tapering as scheduled.

Longitudinal Analysis Shows Fluctuation in Leukocyte Subsets From Active (Pre-treatment) to Non-active (After Treatment) GCA

To get insight into the effects of GC treatment on alterations of leukocyte subset composition during GC therapy, we obtained longitudinal profiling data for immune cells at T_0 and 1, 4, and 12 weeks of follow up for 16 GCA patients. These patients were on GC monotherapy and responded to GC treatment. At week 1 after GC treatment, the number of circulating CD4+ T-lymphocytes ($p = 0.019$) and B-lymphocytes ($p = 0.002$) significantly increased in GCA patients compared to T_0. The number of CD4+ T-lymphocytes then diminished, reaching the pre-treatment (T_0) numbers at weeks 4 ($p = 0.0009$ vs. week 1) and 12 ($p = 0.044$ vs. week 1), while the number of B-lymphocytes only slightly decreased. In contrast, the number of neutrophils progressively increased over the weeks 1 and 4 and was significantly elevated at week 12 compared to T_0 ($p = 0.0003$). No significant differences were observed in the number of monocytes,

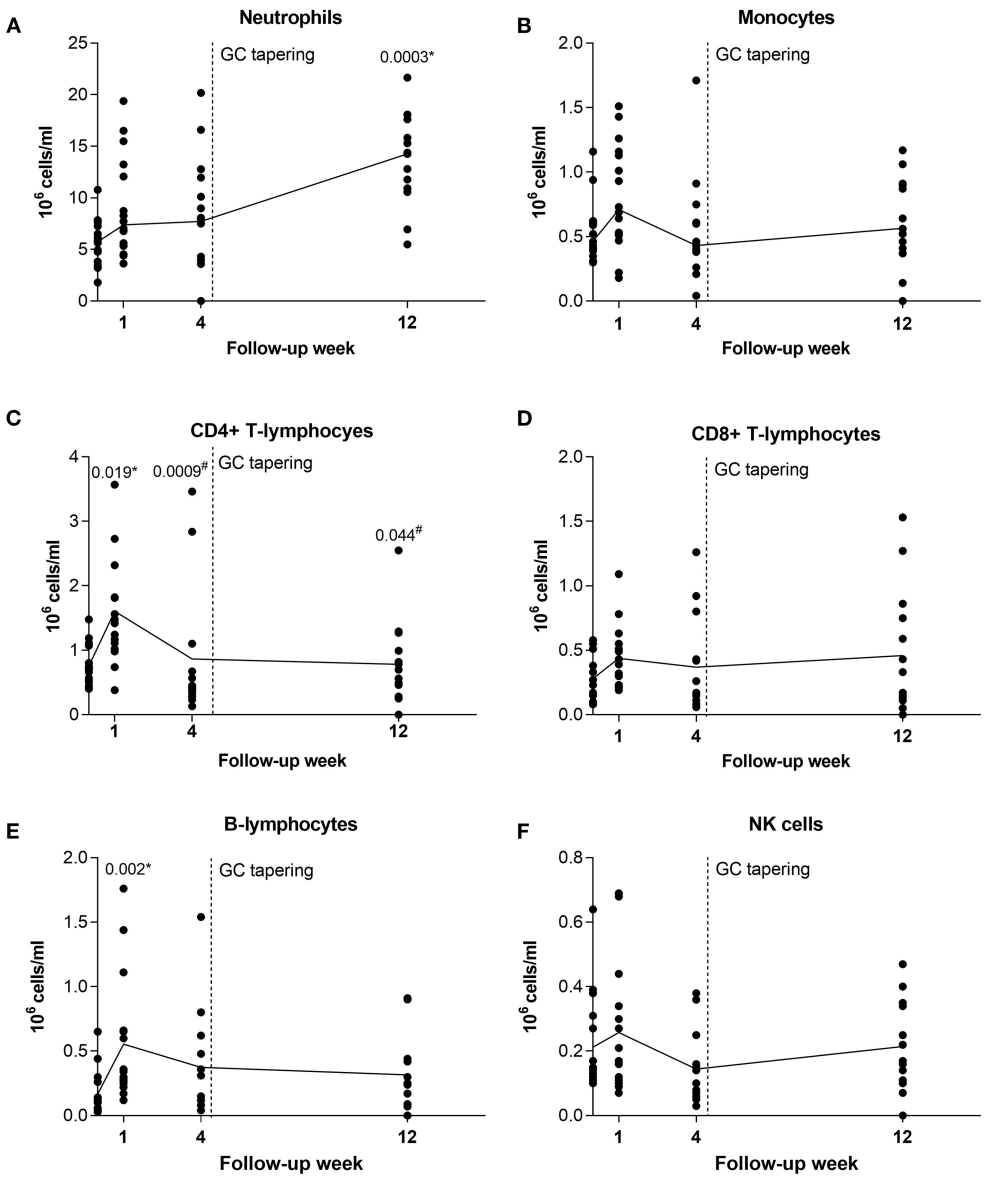

FIGURE 3 | Longitudinal analysis of leukocyte subsets in GCA patients before and during therapy with GC. After pre-treatment sampling, all patients received GC and therapy tapering started after week 4 (indicated with vertical dotted line). Shown are medians from each follow-up time point (black horizontal connecting line) for **(A)** neutrophils; **(B)** monocytes; **(C)** CD4 + T-lymphocytes; **(D)** CD8+ T-lymphocytes; **(E)** B-lymphocytes; and **(F)** NK cells. GC, glucocorticoids; GCA, giant cell arteritis; NK, natural killer. * indicates statistical significance between the corresponding timepoint and T_0; # indicates statistical significance between the corresponding timepoint and week 1.

CD8+ T-lymphocytes and NK cells during the 12 weeks of follow-up (**Figure 3**).

Neutrophil Adhesion Molecules Are Differentially Expressed in Active Compared to Non-active GCA

To confirm the effect of GC and leflunomide on neutrophil phenotype, we measured neutrophil CD62L and CD11b expression in peripheral blood of 25 GCA patients who responded to therapy, at T_0 and at weeks 1, 4, 12, 24, and 48 of follow-up.

No significant differences in the neutrophil CD62L and CD11b expression were observed at T_0 or at week 12, prior to leflunomide addition, between patients receiving GC and patients who later received GC and leflunomide (**Supplementary Table 1**). The median expression of CD62L on neutrophils, decreased in GCA patients, responding to therapy, from T_0 to weeks 1, 4, and 12 after GC treatment (**Figure 4A**). At week 48, there was a distinct elevation in CD62L: patients receiving GC only, showed a marked increase, compared to T_0, while in patients additionally receiving leflunomide, the CD62L expression was consistently low. However, the difference between the two groups was not significant. The median neutrophil expression of CD11b declined from T_0 to week 4, but increased and reached median pre-treatment expression levels at week 12. Patients receiving GC only, showed an increase in CD11b expression at week 24 compared to patients receiving leflunomide in addition to GC, however both treatment groups exhibited similar CD11b expression at week 48 (**Figure 4A**). The differences in CD11b expression between different time points or differential therapy groups were not statistically significant.

Since the activation of neutrophils causes CD62L shedding from the membrane into the bloodstream (23), we also measured serum levels of sCD62L at baseline and during the follow-up of GCA patients. In contrast to the changing expression of neutrophil CD62L, median levels of sCD62L remained constant during the entire follow-up time (**Figure 4B**). No correlation between neutrophil CD62L and sCD62L was determined at T_0 or any of the follow-up points (**Supplementary Figure 1**).

Serum Biomarker Levels Decrease From Active to Non-active GCA Depending on the Type of Treatment

To identify serum biomarkers that can be used to monitor GCA activity and could inform on the ongoing vascular inflammation, we determined serum levels of a predefined set of proteins (SAA, IL-6, IL-8, IL-18, IL-23, CHI3L1) in 25 GCA patients who responded to therapy at T_0 and at weeks 4, 12, 24, and 48 of follow-up.

No significant differences in measured analytes were observed at T_0 or at week 12, prior to leflunomide addition, between patients receiving GC and patients who later received GC and leflunomide (**Supplementary Table 1**). Importantly, the median levels of SAA ($p = 0.0099$) and IL-6 ($p = 0.0001$) decreased significantly at week 4 after GC treatment compared to T_0. Both analytes remained low at weeks 12, 24, and 48 compared to T_0 in both groups of patients although significance was only reached for patients under combinatorial therapy with leflunomide ($p = 0.0001$ for SAA at week 48; $p = 0.0012$ and $p = 0.0054$ for IL-6 at weeks 24 and 48, respectively). Median levels of serum IL-8, IL-18 and CHI3L1 remained stable during the entire follow-up, regardless of therapy used. Median IL-23 decreased from T_0 to week 48 in patients receiving GC monotherapy, while in patients under combinatorial therapy there was an increase at weeks 24 and 48 compared to week 12, although this was not significant (**Figure 4B**).

IL-23 Is Increased in Relapsing Patients

The expression of neutrophil CD62L and CD11b, as well as the levels of sCD62L in the group of relapsing patients varied greatly between the three patients (**Figures 5A,B**). This variation might also be attributed to the different time points when the patients relapsed and different GC dosages.

Acute phase reactants IL-6 and SAA showed different fluctuations in relapsing patients (**Figure 5B**). At the time of relapse (active disease) strong increase of IL-6 as compared to the last follow-up point before relapse (inactive disease) was observed for P1 and P2, while the increase in P3 who relapsed early in the course of the disease (week 12), while still on a high GC dose (48 mg/day) was very low. A small increase in the level of SAA was observed in just one patient at the time of relapse, compared to the time point before relapse (**Figure 5B**). Since elevated levels of IL-6 at the time of relapse could indicate the reactivation of GCA, we next determined how many patients in the responder group had elevated levels of IL-6 without disease flare during the follow-up period. We defined the number of patients with elevated levels of IL-6 on two consecutive visits at weeks 12, 24 or 48 [similar to Stone et al. (17)] compared to the week 4 when patients were on high GC dose (48 mg/day) for the longest period of time (4 weeks). 15/25 (60%) patients from the responder group (10/10 from GC only group and 6/15 from GC plus leflunomide group) exhibited elevated levels of IL-6 (at two consecutive visits at weeks 12, 24 or 48 vs. week 4), despite disease inactivity and no subsequent relapse. We therefore next looked for other biomarkers that were elevated in all three relapsing patients with active (at the time of relapse) compared to non-active (before relapse, in remission) disease. We identified three serum markers which met our criteria: IL-18, IL-23 and CHI3L1 (**Figure 5B**). Subsequently, we analyzed how many patients from the responder group had elevated levels of the three identified parameters during the follow-up without a subsequent relapse (the same as previously described for IL-6). 13 out of 25 (52%) patients in the responder group had elevated IL-18, 9/25 (36%) patients had elevated CHI3L1 and 6/25 (24%) had elevated IL-23 during the course of the disease in the absence of clinical manifestations indicating a relapse.

DISCUSSION

The current longitudinal study provides data on the effects of short- and long-term use of GC or GC, in combination with leflunomide on leukocyte subtype dynamics, neutrophil phenotype and serum analytes in GCA patients. The steroid-sparing effect of leflunomide in GCA has been shown in an open-label study by Hočevar et al. (14). During the first 48 weeks of follow-up, 13.3% of GCA patients who received GC

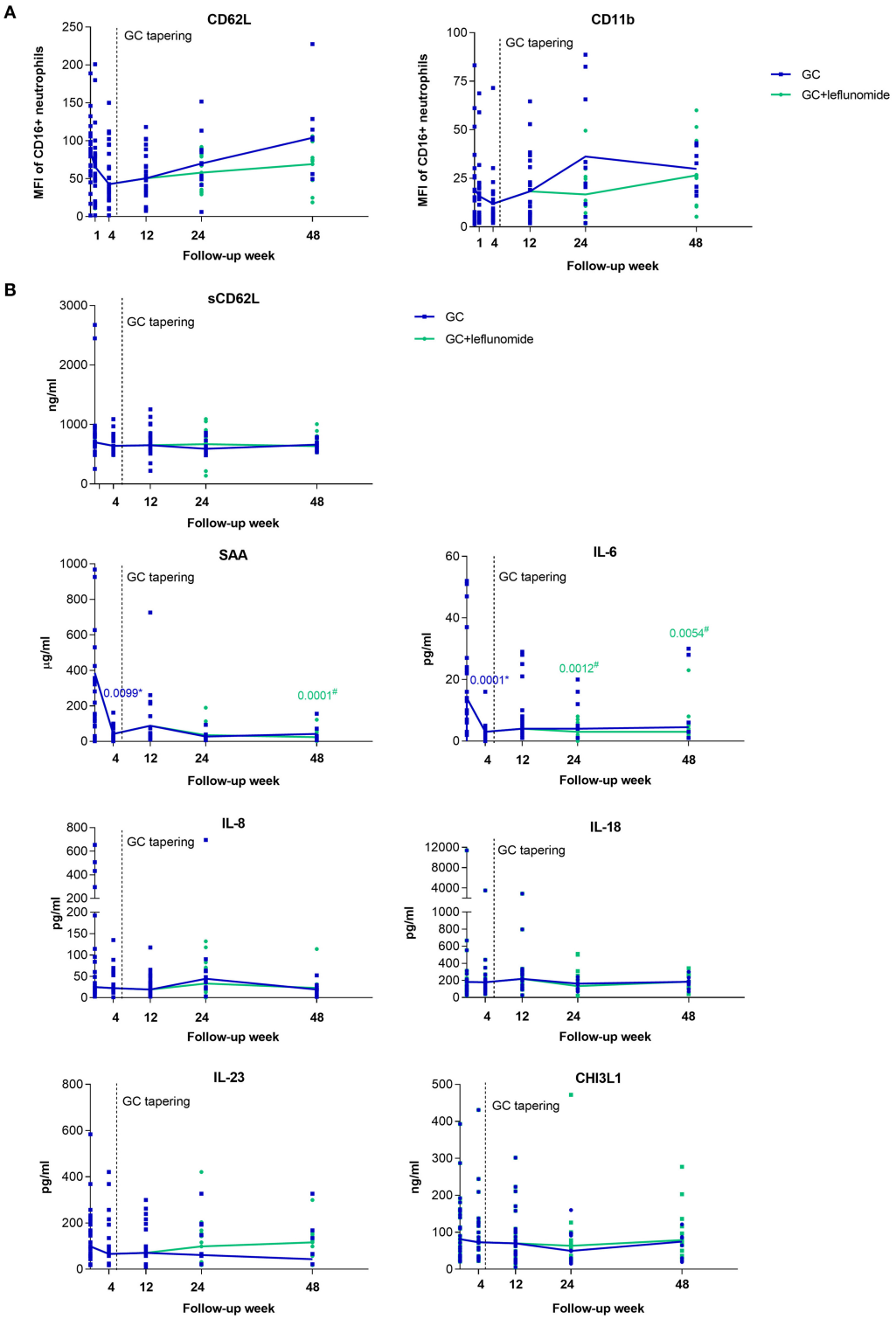

FIGURE 4 | Surface expression of CD62L and CD11b on neutrophils **(A)** and serum levels of selected analytes **(B)** from GCA patients who responded to therapy ($n = 25$), at baseline visit (To) and 1, 4, 12, 24, and 48 weeks of follow-up. After pre-treatment sampling (time point 0), all patients received GC and therapy tapering started after week 4 (indicated with vertical dotted line). After week 12 some of the patients (15/25) received leflunomide, in addition to GC therapy (green). The horizontal lines connect the medians from each follow-up time point. GCA, giant cell arteritis; MFI; median fluorescence intensity. * indicates statistical significance between the corresponding timepoint and T_0 in patients receiving GC monotherapy (blue); # indicates statistical significance between the corresponding timepoint and T_0 in patients receiving GC in combination with leflunomide (green).

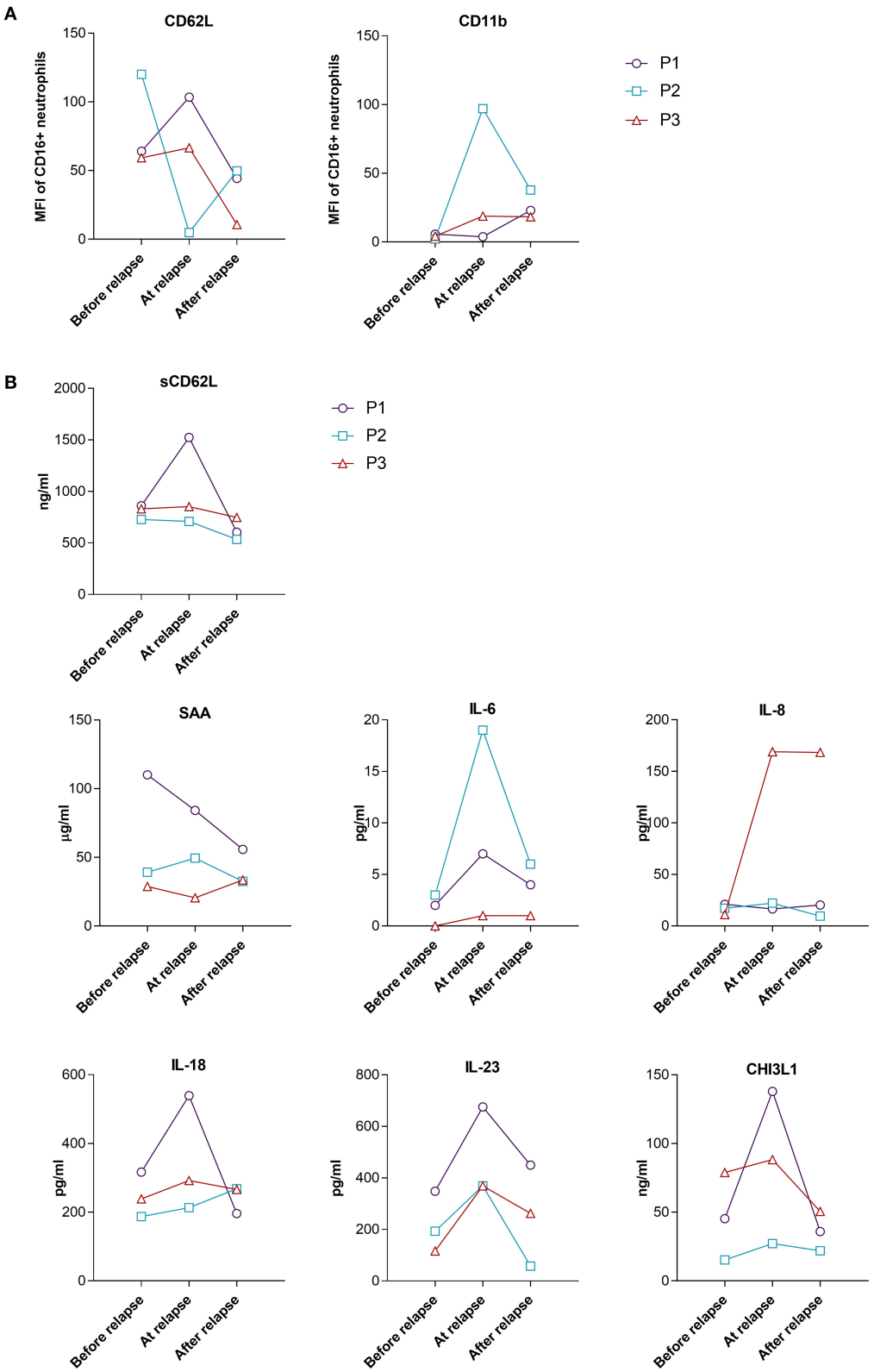

FIGURE 5 | Surface expression of CD62L and CD11b on neutrophils **(A)** and serum levels of selected analytes **(B)** from relapsing GCA patients during the 48 weeks of follow-up. Shown are levels/MFI at the last follow-up time point before relapse, at the time point closest to relapse and 12 weeks after relapse. P1 relapsed at week 24, P2 relapsed at week 48 and P3 relapsed at week 12. MFI, median fluorescence intensity, P, patient.

in combination with leflunomide relapsed compared to 39.1% relapsing patients receiving GC monotherapy (14). We observed similar findings in the present study, where all three relapsing patients were receiving GC monotherapy and there were no relapses observed in patients under combinatorial therapy with leflunomide during the 48 weeks of follow-up. Furthermore, the relapsing patients received leflunomide at the time of relapse in addition to GC and they all entered into remission 12 weeks after relapse. Subsequently, they were able to adhere to GC tapering as initially scheduled.

We observed an immediate short-term effect of high dose GC on increasing the numbers of $CD4^+$ T- and B-lymphocytes after 1 week, while long-term GC treatment (12 weeks) resulted in decreased numbers of CD4+ T- and B-lymphocytes, with increased numbers of neutrophils compared to the pre-treatment time. Similar findings were reported previously by other studies (19, 27). Van der Geest et al. observed the same increase in B cell count 2 weeks after GC treatment, however did not find any evidence of either B cell replenishment from the bone marrow or compensatory hyperproliferation of circulating B cells (27). An increase in B cell counts as a result of early GC treatment might reflect a redistribution or intravascular marginalization of B cells during active disease. Neutrophilia caused by GC is a known effect resulting from increased polymorphonuclear cell release from the bone marrow to the circulation and their increased survival. On the other hand, GC can reduce the migration of neutrophils into inflammatory sites by decreasing the surface expression of CD62L, thus preventing the adhesion of neutrophils and their tissue accumulation (28). The same was observed in the present study, in which the expression of CD62L rapidly decreased after initiation of GC treatment and began to increase progressively to week 48, when patients received lower doses of GC monotherapy. The expression of CD62L was higher at week 48 compared to the pre-treatment timepoint. The activated $CD62L^{hi}CD11b^{hi}$ neutrophil profile in GCA patients at baseline has been reported in a previous study (20). Within 1 week of GC treatment, this phenotype was brought under control, as demonstrated by switching to $CD62L^{lo}CD11b^{lo}$ phenotype with reduced endothelial adhesion. However, 24 weeks after initiation of GC therapy and tapering, an escaped pro-inflammatory phenotype ($CD62L^{hi}CD11b^{hi}$), with elevated endothelial adhesion was reported (20). The progressive increase of CD62L was not observed in our study in patients under combinatorial therapy with leflunomide. In contrast, the expression of CD62L decreased in these patients compared to the pre-treatment time. Leflunomide is a selective inhibitor of *de novo* pyrimidine synthesis (limiting proliferation of lymphocytes) and lowers the production of IL-6, TNF-α, IL-12 and IL-17. Moreover, leflunomide can affect the expression of adhesion molecules and reduces leukocyte adhesion to endothelial cells (29), which could explain the downregulation of CD62L neutrophil expression observed in our study. The addition of leflunomide might have a beneficial long-term effect on the control of neutrophil adhesion. However, no significant differences in the expression of CD62L were observed between relapsing patients and responders.

We and others have previously already determined higher serum levels of CHI3L1 in therapy-naïve GCA patients compared to HBDs (22, 30), while in the present study, we additionally found that the levels of CHI3L1 were associated with signs of transmural inflammation and vessel occlusion in temporal arteries. The source of CHI3L1 in serum of GCA patients might stem from monocytes, macrophages and giant cells (30). Additionally, CHI3L1 is highly expressed in TABs of GCA patients, predominantly in the intima-media border region (30, 31). CHI3L1 is involved in tissue remodeling and angiogenesis (32), and deregulation of these processes in GCA TABs might contribute to increased amounts of CHI3L1 in occluded temporal arteries. Our finding suggests that CHI3L1 is mainly released in fully developed GCA with transmural inflammation and lumen occlusion. Although *in vitro* production of CHI3L1 by macrophages has been shown to be sensitive to GC (33), we observed only a slight reduction in serum CHI3L1 levels between baseline and follow-up visits, indicating that cells producing CHI3L1 may be GC resistant. In line with these observations, GCA patients with extensive transmural inflammation and remodeling of temporal arteries had higher levels of CHI3L1 that might require a therapeutic approach different from the currently established GC. Targeting CHI3L1 in GCA may inhibit macrophages that might currently be insufficiently suppressed by GC (34).

Traditional inflammatory parameters, such as ESR and CRP have been described as insufficient markers for monitoring disease activity in GCA (17). In the current study, increased ESR and CRP were observed in only two out of three relapsing patients at the time of relapse when the disease clinically reactivated. Tocilizumab additionally suppresses these markers (17, 35), indicating the need for new inflammatory markers to aid in monitoring GCA activity during treatment. Our results demonstrated the suppressive effect of GC on systemic levels of additional acute phase reactants, such as SAA and IL-6 which limits their use as markers of disease activity during therapy. Similar to our results, Dartevel et al. showed significantly higher SAA levels in patients with active (newly diagnosed and relapsing) compared to inactive GCA (responding to therapy). However, the authors did not compare the difference in SAA levels in relapsing patients at the time before, at and after relapse (24). In contrast to SAA, levels of IL-6 increased in all three relapsing patients, in our study, when the disease reactivated, but also in 60% of the responder patients at two consecutive visits at weeks 12, 24 or 48 compared to week 4. All 10 patients in the responder group that received GC monotherapy had increased levels of IL-6, while this was observed in only 5/15 patients under combinatorial therapy with leflunomide. Since increasing the doses of GC to completely suppress serum IL-6 would lead to the higher rate of treatment related adverse effects, the addition of leflunomide could be a better option. As seen in the present study, leflunomide may have a beneficial effect on reducing both systemic and vascular inflammation. CHI3L1, on the other hand, was increased in all three relapsing patients at the time of relapse and was elevated in only 36% of the patients who responded to therapy with GC or GC and leflunomide. This might indicate an incompletely controlled disease process in these patients that may

lead to a future relapse, but needs to be confirmed on a larger cohort of patients after a longer follow-up period.

Prior to treatment, relapsing patients had significantly elevated levels of IL-23 compared to patients without relapses. The levels of IL23 were also higher in all three relapsing patients, at the time closest to relapse, compared to the last time point before relapse. Levels of IL-23 decreased again after patients entered into remission and concurrently received leflunomide. Conway et al. similarly found significantly increased expression of IL-23 in the TABs of GCA patients with two or more relapses compared to patients without or with only one relapse (36). IL-23 is pivotal in differentiation of Th17 cells, producing IL-17A with pleiotropic effects on a variety of cells, including macrophages, neutrophils, endothelial cells and fibroblasts, and actively contributes to inflammatory cascades (37). IL-23 seems to be GC-dependent, since in our study, its levels decreased substantially from baseline visit to week 48 of follow-up in patients treated with GC monotherapy, however it remained elevated in GCA patients who experienced a relapse. Higher levels of IL-23 might indicate an ongoing vascular tissue inflammation in relapsing patients, inferring that IL-23 might serve as a marker of persistent, active disease and as a relapse predictor in GCA patients. Although patients receiving GC and leflunomide had slightly higher levels of IL-23 during the 48 weeks follow-up period, none of them developed a relapse. This might be associated with the primary effect of leflunomide inhibiting T-lymphocyte proliferation (29, 38) and thus inhibiting the IL-23-driven polarization toward the Th17 lineage (37, 39). As IL23 is most strongly expressed and produced by macrophages and dendritic cells (40, 41), this (in addition to CHI3L1) might represent another clue for potential therapeutic benefits of suppressing macrophage activation in GCA.

The strengths of our current report are the prospective study design, and the uniform clinical evaluation, with known dates of GC therapy start and tapering at follow-ups. Moreover, GCA patients joined our study when they were therapy-naïve, which allowed us to evaluate the effects of active disease. Previous longitudinal studies often included patients already treated with GC.

The major limitation of our study is a relatively small number of included and longitudinally followed GCA patients ($n = 25$), as well as the small number of relapsing patients ($n = 3$) that explains the lack of statistical significance. The patients were only followed up to 48 weeks when they did not yet achieve GC-free remission and we only assessed their peripheral blood that may not completely reflect the pathological processes at the sites of tissue inflammation. Future longitudinal studies with similar designs could provide further insights by increasing the number of patients, tested parameters and follow-up time, as well as assessing the vascular pathological processes in the temporal arteries in greater detail.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Medical Ethics Committee of Slovenia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TK, KL, SS-Š, and AH designed the experiments. TK, KL, and PŽ performed the flow cytometry analysis and conducted the serum biomarker experiments. AK supported the analysis of flow cytometry study. TK and GT performed the statistical and bioinformatic analyses. AH and MT conducted the clinical evaluation of the patients. SS-Š, SČ, AH, and MT coordinated the study. MF-B provided critical input to data analysis, visualization and interpretation. TK wrote the original draft. All authors reviewed, edited the final draft, authors have seen, approve the manuscript and its contents, and as well as are aware of the responsibilities connected with the authorship.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.827095/full#supplementary-material

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Angiotensin Converting Enzyme Activity in Anti-TNF-Treated Rheumatoid Arthritis and Ankylosing Spondylitis Patients

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Introduction: Angiotensin-converting enzyme (ACE) and ACE2 have been implicated in the regulation of vascular physiology. Elevated synovial and decreased or normal ACE or ACE2 levels have been found in rheumatoid arthritis (RA). Very little is known about the effects of tumor necrosis factor α (TNF-α) inhibition on ACE or ACE2 homeostasis. In this study, we assessed the effects of one-year anti-TNF therapy on ACE and ACE2 production in RA and ankylosing spondylitis (AS) in association with other biomarkers.

Patients and Methods: Forty patients including 24 RA patients treated with either etanercept (ETN) or certolizumab pegol (CZP) and 16 AS patients treated with ETN were included in a 12-month follow-up study. Serum ACE levels were determined by commercial ELISA, while serum ACE2 activity was assessed using a specific quenched fluorescent substrate. Ultrasonography was performed to determine flow-mediated vasodilation (FMD), common carotid intima-media thickness (ccIMT) and arterial pulse-wave velocity (PWV) in all patients. In addition, CRP, rheumatoid factor (RF) and ACPA were also measured. All assessments were performed at baseline and 6 and 12 months after treatment initiation.

Results: Anti-TNF therapy increased ACE levels in the full cohort, as well as in the RA and AS subsets. ACE2 activity increased in the full cohort, while the ACE/ACE2 ratio increased in the full cohort and in the RA subset ($p < 0.05$). Uni- and multivariable regression analyses determined associations between ACE or ACE/ACE2 ratios at different time points and disease duration, CRP, RF, FMD and IMT ($p < 0.05$). ACE2 activity correlated with CRP. The changes of ACE or ACE2 over 12 months were determined by treatment together with either RF or FMD ($p<0.05$).

Conclusions: Anti-TNF treatment may increase ACE and ACE2 in the sera of RA and AS patients. ACE and ACE2 may be associated with disease duration, markers

of inflammation and vascular pathophysiology. The effects of TNF inhibition on ACE and ACE2 may reflect, in part, the effects of these biologics on the cardiovascular system.

Keywords: rheumatoid arthritis, ankylosing spondylitis, angiotensin converting enzyme, vascular disease, biologics, anti-TNF therapy

INTRODUCTION

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) have been associated with increased cardiovascular (CV) morbidity and mortality (1–5). Non-invasive ultrasound-based techniques are suitable to assess preclinical vascular pathophysiology in RA and AS (1, 6). Early endothelial dysfunction of the brachial artery, carotid atherosclerosis and increased arterial stiffness are indicated by abnormal endothelium-dependent, flow-mediated vasodilation (FMD) (4, 6, 7), common carotid intima-media thickness (IMT) and carotid plaques (4–6, 8), as well as arterial pulse-wave velocity (PWV) (5, 6, 9), respectively.

Systemic inflammation and pro-inflammatory cytokines including tumor necrosis factor α (TNF-α) are involved in the pathogenesis of arthritis-associated secondary atherosclerosis and CV disease (10, 11). Anti-TNF agents are effective and safe in the therapy of RA and AS (12–16). TNF inhibitors also suppress synovial angiogenesis and vascular endothelial growth factor (VEGF) production (17, 18). The control of inflammation by targeted therapies including TNF-α inhibitors, may decrease CV morbidity and mortality in arthritides (1, 10, 14, 19), especially in anti-TNF responder patients (14, 20). Anti-TNF biologics may improve or at least stabilize vascular physiology indicated by FMD, IMT and PWV (14, 19, 21–24).

Angiotensin-converting enzyme (ACE) is a member of the renin-angiotensin-aldosterone system (RAAS), which is an important regulator of blood pressure and salt-water homeostasis (25). ACE catalyzes the conversion of angiotensin I to angiotensin II, and the metabolism of bradykinin (25). ACE has been implicated in CV disease, myocardial infarction, hypertension, heart failure and diabetic nephropathy (25, 26). ACE inhibitors are among the most frequently prescribed drugs with antihypertensive and cardioprotective effects (25, 26). ACE2 is an ACE homolog with monocarboxypeptidase activity (27). ACE2 generates angiotensin peptides Ang_{1-9} and Ang_{1-7} from Ang-I and Ang-II, respectively (27, 28). ACE2, through Ang_{1-7}, is capable of reducing myocardial oxidative stress and pathological remodeling (28, 29). TNF-α converting enzyme (TACE/ADAM17) is responsible for ACE2 shedding from cardiomyocytes and endothelial cells (30). Thus, opposite to the Ang-I-ACE-Ang-II pathway, ACE2 exerts vasculoprotective and antihypertensive mechanisms by the counter-regulation of the RAAS system (28, 31). Increased soluble ACE2 activity has been associated with advanced heart failure (32), ventricular arrhythmias (33) and hypertension (28).

ACE and ACE2 concentrations and activity are readily measurable in the serum. ACE activity is affected by the intake of ACE inhibitors while ACE2 activity is not (26, 28). Changes in soluble ACE and ACE2 may reflect redistribution and opposite changes of tissue activity of these enzymes (28, 34).

With respect to ACE and ACE2 in arthritides, *ACE* insertion-deletion (I/D) gene polymorphism has been associated with RA and AS in some populations, primarily in cohort studies carried out in Arabic countries (35–40). When studying DD, ID and II genotypes, the frequency of the D allele was higher in RA compared to healthy controls (35). Moreover, the DD genotype may confer increased susceptibility to RA (35, 38, 40). Results in AS are controversial. In one study, similarly to RA, the DD genotype has been associated with AS including sacroiliac and ocular involvement (39). Moreover, in AS, carrying the D allele was correlated with higher CRP levels (41). In contrast, another study reported association between the I allele and AS (42). The II genotype was also associated with juvenile idiopathic arthritis (37). *ACE* polymorphisms could not be correlated with psoriatic arthritis (PsA) (36).

Regarding serum or plasma ACE and ACE2 levels, the very first study on ACE serum and synovial fluid ACE levels in various arthritides was published as early as in 1986. In this study, serum ACE levels were similar in RA, AS, PsA, osteoarthritis (OA) patients and healthy controls. On the other hand, synovial fluid ACE levels were increased in RA vs. OA (43). More recently, 50 RA compared to 30 healthy women, RA patients had increased Ang-II, Ang_{1-7} and ACE plasma levels, as well as ACE/ACE2 ratios vs. controls. RA was associated with lower Ang-II/Ang_{1-7} ratios. ACE inhibitors did not significantly influence serum Ang-II, Ang_{1-7}, ACE and ACE2 levels in RA patients. ACE2 levels inversely correlated with carotid IMT (44). Decreased ACE2 levels were also found in RA, systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) vs. healthy controls (45). In contrast, other studies found similar serum ACE levels in RA, OA and healthy individuals (46). Increased synovial fluid ACE concentrations have been described in RA compared to OA (46, 47). Within the RA synovial tissue, ACE expression is localized to endothelial cells and synovial macrophages (48).

With respect to the regulation of ACE and ACE2 production in arthritides, in animal models of arthritis, Ang_{1-7} exerted significant anti-inflammatory effects as it attenuated oxidative stress, as well as TNF-α, interleukin 1 (IL-1) and IL-6 production (49). Moreover, IL-6 upregulated ACE2 in synovial tissues (50). Anti-ACE2 antibodies that inhibit the anti-inflammatory and anti-fibrotic effects of ACE2 have been described in connective tissue diseases with constrictive vasculopathies, such as SSc, SLE and mixed connective tissue disease (MCTD) (51, 52).

Therapeutically, both ACE inhibitors and angiotensin receptor blockers (ARB) may exert significant anti-inflammatory effects (53). However, in the multiple regression analysis

TABLE 1 | Patient characteristics.

	RA	AS	Total
n	35	16	51
Female:Male	31:4	2:14	33:18
age (mean ± SD) (range), years	55.7 ± 9.9 (35–83)	41.9 ± 10.3 (24–57)	51.4 ± 11.8 (24–83)
age at diagnosis (mean ± SD) (range), years	46.4 ± 10.3 (11–71)	35.8 ± 8.1 (23–50)	43.1 ± 10.8 (11–71)
disease duration (mean ± SD) (range), years	9.3 ± 8.3 (1–44)	6.1 ± 5.2 (1–18)	8.3 ± 7.6 (1–44)
RF positivity, n (%)	25 (81)	-	-
ACPA positivity, n (%)	20 (57)	-	-
DAS28 (baseline) (mean ± SD)	4.98 ± 0.86	-	-
BASDAI (baseline) (mean ± SD)	-	5.94 ± 1.03	-
BMI (mean ± SD), kg/m^2	29.4 ± 3.7	31.4 ± 3.7	30.0 ± 3.7
Obesity (BMI > 30 kg/m^2), n (%)	17 (49)	11 (69)	28 (55)
Smokers (current), n (%)	16 (46)	8 (50)	24 (47)
Positive CV history, n (%)	21 (60)	3 (2)	24 (47)
Diabetes mellitus history, n	3	1	4
Hypertension history, n (%)	16 (46)	8 (50)	24 (47)
ACE inhibitor treatment, n (%)	11	0	11
Treatment (ETN, CZP)	20 ETN, 15 CZP	16 ETN	36 ETN, 10 CZP
Low-dose corticosteroids (< 6 mg/day methylprednisolone), n (%)	8	1	9

ACE, angiotensin converting enzyme; ACPA, anti-citrullinated protein antibody; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CZP, certolizumab pegol; DAS28, 28-joint disease activity score; ETN, etanercept; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation.

of RA patients receiving ACE inhibitors or ARBs in comparison to those not taking such drugs, the use of either ACE inhibitors or ARBs was not associated with disease activity (54).

There have been very few studies on the possible effects of TNF inhibitors on ACE and ACE2. In a small study, ACE2 plasma levels were significantly lower in RA patients on anti-TNF treatment compared to healthy controls (55). In the study of RA, SSc and SLE patients, most antirheumatic treatments did not affect ACE2 levels (45). We have not found any studies where changes in ACE or ACE2 levels or activity were evaluated upon anti-TNF therapy.

Thus, ACE and ACE2 may be involved in the inflammatory processes underlying RA and AS, as well as in vascular pathology associated with these arthritides. Yet, very little information has become available on the effects of anti-TNF therapy on ACE and ACE2 production and on their correlation with disease activity, markers of inflammation, autoantibodies and vascular pathophysiology. We have recently set up a mixed cohort of RA and AS patients and reported multiple effects of anti-TNF treatment over one year on vascular pathophysiology (19) and various vascular biomarkers (56, 57). We have published data on vascular pathophysiology and bone in the very same cohort before (19, 56, 58–60). As a novelty in comparison to the previous publications of the same cohort, now we wished to study ACE and ACE2 production in context with inflammation, autoantibodies and vascular pathophysiology in the very same cohort in order to obtain more information on the possible effects of biologics on the RAAS.

PATIENTS AND METHODS

Patients

Fifty one patients with inflammatory arthritis (35 RA and 16 axial radiographic AS) selected for the initiation of anti-TNF therapy but unselected for CV disease (any previous CV events) were enrolled in the study as described before (19, 56, 57). These patients were consecutively selected in one tertiary rheumatology center (University of Debrecen). Patient characteristics in the full, RA and AS cohorts are seen in **Table 1**. The full cohort included 33 women and 18 men with mean age of 51.4 ± 11.8 (range: 24–83) years, while mean age at diagnosis was 43.1 ± 10.8 (range: 11–71) years. The mean disease duration was 8.3 ± 7.6 (range: 1–44) years. Exclusion criteria included untreated, unstable hypertension (blood pressure >140/90 mmHg), current inflammatory disease other than RA or AS, infectious disease or renal failure (based on eGFR and hospital records). None of patients received antiplatelet (e.g., aspirin, clopidogrel) or anticoagulant therapy (e.g., heparin, warfarin) at the time of inclusion. As antihypertensive drugs may affect the vascular status, hypertension had been stabilized for at least 6 months before the onset of this study. Moreover, antihypertensive drugs remained unchanged throughout the study. Some patients received ACE inhibitors prior to the study. However, we have previously demonstrated that ACE inhibitor treatment does not have any effects on circulating ACE concentration or ACE2 activity (28).

Patients with active disease were recruited prior to initiating a biological therapy. At baseline RA patients had a mean DAS28 of 4.98 ± 10.86, while AS patients exerted mean BASDAI of 5.94

± 1.03. All patients started on an anti-TNF therapy at baseline and continued the same biological treatment during one year. Among the 35 RA patients, 20 received etanercept (ETN) 50 mg/week subcutaneous (SC) and 15 received certolizumab pegol (CZP) (400 mg at 0, 2 and 4 weeks, and thereafter 200 mg every two weeks SC). Altogether 12 RA patients were treated with ETN and eight with CZP in combination with methotrexate (MTX). The other patients received anti-TNF monotherapy. RA patients did not take DMARDs other than MTX. All 16 AS patients received ETN monotherapy 50 mg/week SC. Altogether eight RA and one AS patients took low-dose (<6 mg/day) methylprednisolone (**Table 1**).

The study was approved by the Hungarian Scientific Research Council Ethical Committee (approval No. 14804-2/2011/EKU). Written informed consent was obtained from each patient and assessments were carried out according to the Declaration of Helsinki.

Clinical Assessment

First, detailed medical history was taken. We inquired for history of CVD, as well as current smoking, experience of chest pain resembling angina pectoris, hypertension and diabetes mellitus during the last 2 years prior to the start of this study by a questionnaire (**Table 1**). We also determined body mass index (BMI) and obesity (**Table 1**). Further clinical assessments including physical examination were performed at baseline (B), and after 6 (6 M) and 12 months (12 M) of therapy. At baseline RA patients had a mean DAS28 of 4.98±0.86, while AS patients exerted mean BASDAI of 5.94 ± 1.03 (**Table 1**).

Laboratory Measurements

Blood samples were collected from patients by using a standard aseptic technique. Native blood was incubated for 60 min at room temperature; serum fractions (separated by centrifugation at 1,500 *g* for 15 min) were stored at −20°C until further use.

Serum high sensitivity C reactive protein (hsCRP; normal: ≤ 5 mg/l) and IgM rheumatoid factor (RF; normal: ≤ 50 IU/ml) were measured by quantitative nephelometry (Cobas Mira Plus-Roche), using CRP and RF reagents (both Dialab). ACPA (anti-CCP; aCCP) autoantibodies were detected in serum samples using a second generation Immunoscan-RA CCP2 ELISA test (Euro Diagnostica; normal: ≤ 25 IU/ml). The assay was performed according to the manufacturer's instructions.

In order to exclude the possible interference effect of RF, we compared ACE concentration and ACE2 activity values in RF positive and negative patients at baseline. We did not find statistically significant differences between positive or negative patients, thus presence of RF in the sample may not interfere with the tests (data not shown in figure).

Measurement of Serum ACE Concentration

Serum ACE concentration was determined by a commercial human ACE ELISA development kit (R&D Systems) according to the manufacturer's instructions, with minor modifications, as described previously (61). Enzyme-linked immunosorbent plates (Greiner Bio-One) were coated with 80 ng/well capture antibody, and the remaining binding sites were then blocked with reagent diluent (10 mg/mL bovine serum albumin [Sigma-Aldrich] in Dulbecco's phosphate buffered saline solution [PBS, Gibco]). Diluted sera (in reagent diluent, 100-fold dilution) were added to the wells, and the antibody-antigen complexes were labeled with a biotinylated detection antibody (20 ng/well). Two hundred-fold-diluted streptavidin-conjugated horseradish-peroxidase (kit component) was added to the wells. Finally, the amounts of complexes were detected with a substrate solution containing 0.3 mg/mL tetramethylbenzidine, 0.1 mM H_2O_2 and 50 mM acetic acid. The reaction was terminated after 20 min by the addition of 0.5 M HCl, and the optical density was measured at 450 nm. Serum ACE concentration rather than activity was measured as 11 RA patients had been receiving ACE inhibitor treatment (**Table 1**). ACE levels are expressed in ng/mL units.

Measurement of Serum ACE2 Activity

Serum ACE2 activity was determined using a specific quenched fluorescent substrate as previously described (28). The reaction mixture (200 μL) contained 20 μl serum, 80 μL buffer and 100 μl (100 μM) ACE2-specific fluorescent substrate (7-methoxycoumarin-4-yl)acetyl-Ala-Pro-Lys(2,4-dinitrophenyl)-OH [Mca-APK(Dnp)] (Peptide 2.0, USA). Serum ACE2 activity was measured by fluorometric assay of the enzymatic cleavage of K(Dnp) from the fluorogenic substrate Mca-APK(Dnp). The reaction mixture contained 500 mM NaCl, 10 μM $ZnCl_2$ and 75 mM TRIS HCl, pH 6.5. All chemicals were from Sigma (St. Louis, MO, USA) if not stated otherwise. The reaction was performed in black 96-well microtiter plates (Greiner Bio-One, Frickenhauser, Germany). The assay was monitored continuously by measuring the increase in fluorescence (excitation wavelength = 340 nm, emission wavelength = 405 nm) upon substrate hydrolysis using a fluorescence microplate reader (NOVOstar; BMG Labtech GmbH, Offenburg, Germany). Initial enzyme activities were determined from the linear rate of fluorescence increase over the 0–120 min time course. The increase in fluorescence was plotted as a function of reaction time and fitted with a linear regression. Serum ACE2 activity was calculated by the equation:

ACE2 activity = (S/k) * D
S: rate of observed increase in fluorescence intensity;
k: change in fluorescence intensity upon the complete cleavage of 0.1 nmol of Mca-APK(Dnp);
D: dilution of the serum sample.

One unit of fluorescence (UF) corresponds to the quantity of enzyme which can degrade 0.1 nmol Mca-APK(Dnp) in one h at 37°C. The specificity of the serum ACE2 enzyme activity assay was tested using the specific human ACE2 inhibitor DX600 before (28). ACE2 activity is expressed in UF/mL units.

ACE inhibitors do not interfere with ACE2 activity.

Assessment of Vascular Physiology by Ultrasound

The FMD, IMT and PWV assessments carried out in the very same cohort were performed and published previously (19).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM) software. Normally distributed data are expressed as the mean ± SD for continuous variables and percentages for categorical variables. Continuous variables were evaluated by paired two-tailed *t*-test and Wilcoxon test. Nominal variables were compared between groups using the chi-squared or Fisher's exact test, as appropriate. Matched data with not normal distribution are expressed in median [interquartile range] and compared with Wilcoxon matched-pairs signed rank tests. Correlations were determined by Pearson's and Spearman's analyses. Univariate and multiple regression analysis using the stepwise method was applied to investigate independent associations between angiogenic biomarkers (dependent variables) and other clinical, laboratory and imaging parameters (independent variables). The β standardized linear coefficients showing linear correlations between two parameters were determined. The B (+95% CI) regression coefficient indicated independent associations between dependent and independent variables during changes. Repeated measures analysis of variance (RM-ANOVA) was performed in order to determine the additional effects of multiple parameters on changes of vascular imaging markers between B and 12 M. The dependent variables were FMD, ccIMT and PWV. Partial η^2 is given as indicator of effect size, with values of 0.01 suggesting small, 0.06 medium and 0.14 large effects. In all analyses, P values < 0.05 were considered significant.

RESULTS

Separate vascular imaging, as well as disease activity, inflammatory and vascular biomarker data obtained in the very same cohort have been published (19, 56, 57). Here we used those data to associate them with the ACE and ACE2 measurements. None of the data presented here have been published elsewhere.

Effects of TNF Inhibition on ACE Concentration and ACE2 Activity

In the mixed cohort of 51 arthritis (RA+AS) patients, serum ACE concentration significantly increased after 6 M (166.7 [124–232] ng/mL; $p = 0.003$) and 12 M of treatment (183.4 [121–222] ng/mL; $p < 0.001$) compared to B (142.7 [88–176] ng/mL).

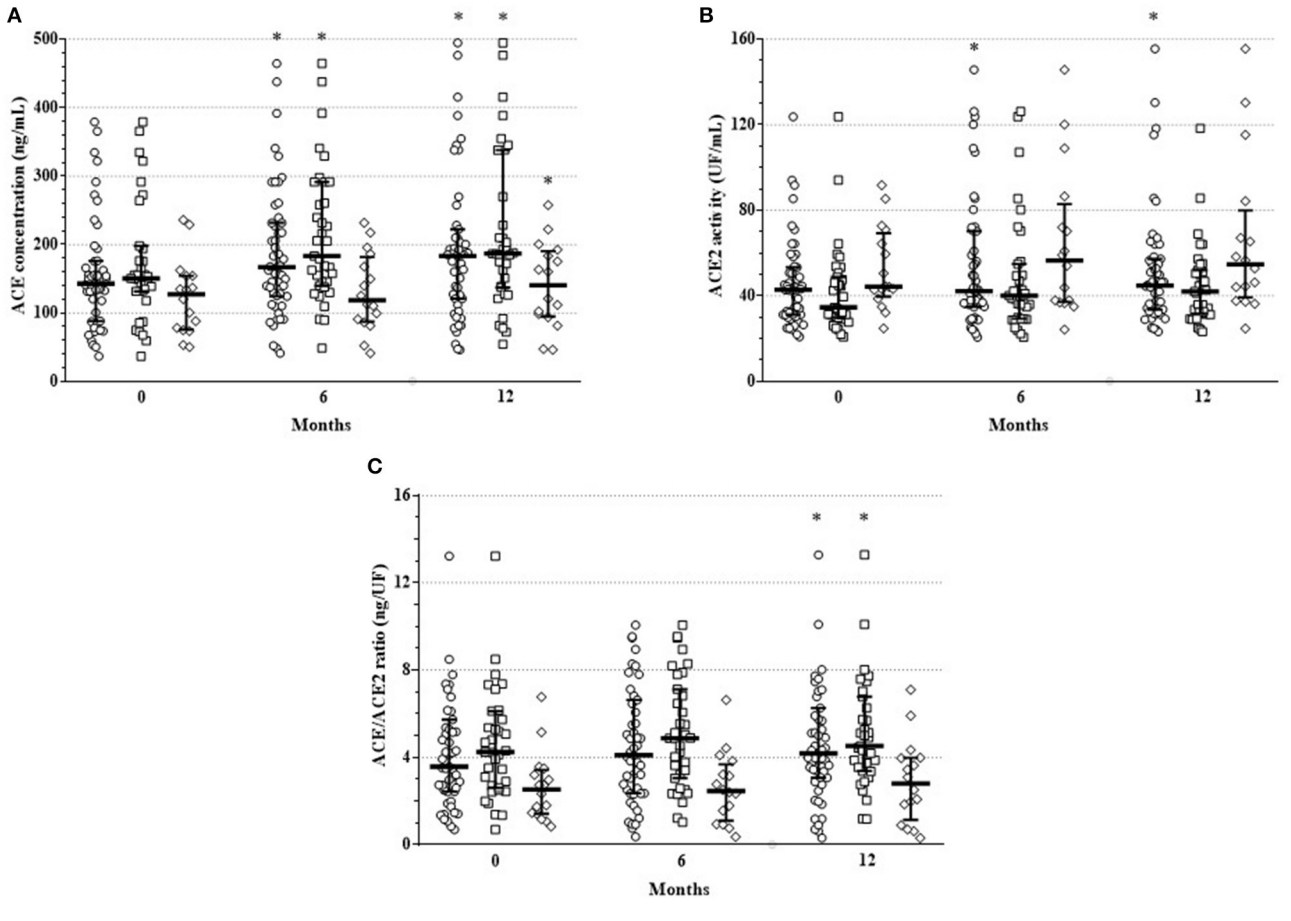

FIGURE 1 | One-year changes of **(A)** ACE concentration, **(B)** ACE2 activity and **(C)** ACE/ACE2 ratio upon TNF inhibition in the full RA + AS cohort (cycle symbol), as well as in the RA (square symbol) and AS subsets (diamond symbol). Median and interquartile range are shown on the figure; each symbol corresponds to an individual value. *indicate significant differences compared to baseline using Wilcoxon matched-pairs signed rank tests ($p < 0.05$).

In the RA subset, ACE concentration also increased after 6 M (183.1 [140–291]; $p = 0.006$) and 12 M (186.6 [137–338] ng/mL; $p = 0.001$) vs. B (150.3 [131–198] ng/mL). Finally, in AS, ACE concentration did not change significantly after 6 M (118.7 [87–182] ng/mL; $p = 0.245$), however, it significantly increased after 12 M (140.5 [95–190] ng/mL; $p = 0.043$) compared to B (127.1 [76–154] ng/mL) (**Figure 1A**). ACE levels in RA and AS did not differ at B ($p = 0.055$). On the other hand, ACE concentration was significantly higher in RA compared to AS after 6 M ($p = 0.004$) and 12 M of treatment ($p = 0.024$) (**Figure 1A**).

In the full RA+AS cohort, ACE2 activity significantly increased after 6 M (41.1 [35–70] UF/mL; $p = 0.044$) and 12 M

TABLE 2 | Univariable and multivariable regression analysis of ACE and ACE2.

Dependent variable	Independent variable	Univariable analysis				Multivariable analysis			
		β	p	B	CI 95%	β	p	B	CI 95%
Full cohort (RA + AS)									
ACE-B	age	0.331	0.018	3.985	0.725–7.245	0.331	0.018	3.985	0.725–7.245
	IMT-B	0.315	0.048	559.8	4.958–1114.6				
ACE-6M	age	0.393	0.004	3.160	1.034–5.285	0.479	0.013	2.403	1.194–3,613
	disease duration	0.336	0.016	4.216	0.821–7.611				
	IMT-B	0.314	0.048	330.4	2.367–658.4	0.629	0.008	433.3	267.4–599.1
	PWV-6M	2.298	0.026	3.285	0.403–6.167				
ACE-12M	CRP-6M	0.310	0.027	9.478	1.127–17.830				
	CRP-12M	0.433	0.001	16.549	6.668–26.429	0.433	0.001	16.549	6.668–26.429
	FMD-B	0.448	0.004	33.557	11.583–55.531				
	FMD-6M	0.552	<0.001	31.987	17.114–46.860				
ACE2-6M	CRP-B	0.330	0.018	0.862	0.154–1.569				
ACE/ACE2-B	age	0.295	0.036	0.084	0.006–0.162	0.295	0.036	0.084	0.006–0.162
	disease duration	0.291	0.038	0.129	0.007–0.251				
	IMT-B	0.329	0.038	13.892	0.784–27.000				
ACE/ACE2-6M	disease duration	0.430	0.002	0.145	0.058–0.232	0.430	0.002	0.145	0.058–0.232
	FMD-6M	0.296	0.048	0.142	0.001–0.282				
	IMT-B	0.318	0.046	9.560	0.185–18.996				
ACE/ACE2-12M	CRP-6M	0.291	0.038	0.253	0.014–0.492				
	CRP-12M	0.373	0.007	0.405	0.116–0.694				
	FMD-B	0.414	0.008	0.887	0.246–1.528				
	FMD-6M	0.519	<0.001	0.860	0.425–1.294	0.519	<0.001	0.860	0.425–1.294
RA patients									
ACE-B	RF-B	0.431	0.010	0.429	0.110–0.748				
ACE-12M	CRP-6M	0.465	0.005	22.649	7.397–37.902				
	CRP-12M	0.455	0.006	19.669	6.049–33.288				
	RF-B	0.335	0.049	0.706	0.002–1.409				
	FMD-B	0.522	0.007	42.925	12.651–73.199				
	FMD-6M	0.598	0.001	37.769	17.786–57.752	0.598	0.001	37.769	17.786–57.752
ACE2-12M	Age	0.336	0.049	0.647	0.004–1.289				
ACE/ACE2-B	RF-B	0.382	0.023	0.009	0.001–0.016				
ACE/ACE2-6M	disease duration	0.360	0.034	0.109	0.009–0.209				
ACE/ACE2-12M	CRP-6M	0.423	0.011	0.585	0.141–1.028				
	CRP-12M	0.378	0.025	0.463	0.061–0.865				
	RF-B	0.343	0.044	0.020	0.001–0.040				
	FMD-6M	0.560	0.002	1.008	0.419–1.598	0.637	<0.001	1.923	1.850–1.996
AS patients									
ACE-6M	BASDAI-6M	0.569	0.021	30.731	5.292–56.170				
ACE-12M	IMT-B	0.549	0.034	454.674	39.429–869.919				
ACE/ACE2-6M	disease duration	0.548	0.028	0.173	0.022–0.325				

Univariate and multiple regression analyses were performed. ACE, ACE2 and ACE/ACE2 ratios are the dependent variables. 6M, 6-month result; 12M, 12-month result; ACE, angiotensin converting enzyme; AS, ankylosing spondylitis; B, baseline; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAS, disease activity score; FMD, flow-mediated vasodilation; IMT, intima-media thickness; RA, rheumatoid arthritis; RF, rheumatoid factor.

(44.7 [34–57] UF/ml; $p = 0.010$) compared to B (42.8 [31–53] UF/mL). In RA, ACE2 activity did not change after 6 M (40.1 [29–55] UF/mL; $p = 0.201$) and after 12 M (42.0 [32–52] UF/mL; $p = 0.080$) vs. B (34.6 [30–49] UF/mL). Similarly, in AS, ACE2 activity remained unchanged after 6 M (56.6 [37–83] UF/mL; $p = 0.088$) and 12 M (54.7 [39–80] UF/mL; $p = 0.063$) compared to B (44.3 [40–69] UF/mL; $p = 0.039$) (**Figure 1B**). ACE2 activity was higher in AS than in RA at B ($p = 0.037$) and after 12 M ($p = 0.019$) (**Figure 1B**).

Finally, in order to reflect the ACE/ACE2 balance, we calculated ratios of ACE concentrations and ACE2 activity (ACE/ACE2 ratios) (**Figure 1C**). In the mixed cohort, ACE/ACE2 ratio did not change after 6 M (4.1 [2.4–6.6] ng/UF; $p = 0.083$) but significantly increased after 12 M (4.2 [3.1–6.3] ng/UF; $p = 0.019$) compared to B (3.6 [2.4–5.7] ng/UF). In RA, ACE/ACE2 ratio did not change after 6 M (4.87 [3.0–7.1] ng/UF; $p = 0.069$) but significantly increased after 12 M (4.52 [3.4–6.8] ng/UF; $p = 0.035$) vs. B (4.24 [2.6–6.1] ng/UF). In AS, ACE/ACE2 ratio remained unchanged after 6 M (2.46 [1.1–3.7] ng/UF; $p = 0.990$) and 12 M (2.8 [1.1–4.0] ng/UF; $p = 0.501$) compared to B (2.53 [1.4–3.4] ng/UF) (**Figure 1C**). ACE/ACE2 ratio was higher in RA than in AS at B ($p = 0.004$), as well as after 6 M ($p = 0.001$) and 12 M ($p = 0.003$) (**Figure 1C**).

Correlations of ACE Concentration and ACE2 Activity With Other Parameters

All results of the simple correlation analysis are seen in **Supplementary Table S1**. This table indicates the full cohort, as well as the RA and AS subsets.

In the univariable regression analysis of the RA+AS cohort, ACE levels at various time points were independently and positively associated with RF and FMD and inversely with age, disease duration, CRP, RF, IMT and FMD ($p < 0.05$) (**Table 2**). ACE2 activity was independently determined by CRP ($P < 0.05$) (**Table 2**). The ACE/ACE2 ratio independently correlated with age, disease duration, CRP, RF, IMT and FMD (**Table 2**). In RA, ACE concentrations were only associated with CRP, RF and FMD, while ACE2 activity did not show any correlations. In RA, ACE/ACE2 ratio correlated with disease duration, CRP, RF and FMD ($p < 0.05$) (**Table 2**). In AS, ACE level was independently associated with BASDAI, while ACE2 activity did not show any correlations. ACE/ACE2 ratio positively associated only with disease duration ($p < 0.05$) (**Table 2**).

The multivariable regression analysis confirmed the positive correlation among ACE levels and age, CRP and IMT in the mixed cohort. Similarly, ACE/ACE2 ratios also correlated with age and disease duration ($p < 0.05$) (**Table 2**). In RA, the only correlation revealed was that between ACE levels and FMD ($p < 0.05$) (**Table 2**). No such correlations were observed in AS (**Table 2**).

Finally, RM-ANOVA analysis was performed in order to assess determinants of ACE or ACE2 changes over time. In the full cohort, one-year change in ACE concentration or in ACE/ACE2 ratio was determined by anti-TNF treatment together with higher RF or FMD at B ($p < 0.05$) (**Table 3**). In RA, ACE level or ACE/ACE2 ratio changes were associated with treatment along with higher RF ($p < 0.005$) (**Table 3**). No such associations were observed in AS (**Table 3**).

TABLE 3 | Significant results of general linear model (GLM) repeated measures analysis of variance (RM-ANOVA) test determining the effects of treatment and other independent variables on ACE and ACE2 as dependent variables.

Dependent variable	Effect	F	p	Partial η^2
Full cohort (RA + AS)				
ACE B-6M-12M	Treatment * RF-B	2.075	0.017	0.224
	Treatment * FMD-B	3.543	0.039	0.161
ACE/ACE2 B-6M-12M	Treatment * RF-B	4.038	0.027	0.202
	Treatment * FMD-B	3.544	0.039	0.161
RA patients				
ACE B-6M-12M	Treatment * RF-B	4.629	0.017	0.224
ACE/ACE2 B-6M-12M	Treatment * RF-B	4.038	0.027	0.202
AS patients				
–				

Repeated measures analysis of variance (RM-ANOVA) was performed in order to determine the additional effects of multiple parameters on changes of vascular imaging markers between B and 12M. 6M, 6-month; 12M, 12-month; ACE, angiotensin converting enzyme; AS, ankylosing spondylitis; B, baseline; GLM, general linear model; FMD, flow-mediated vasodilation; RA, rheumatoid arthritis; RF, rheumatoid factor; RM-ANOVA, repeated measures analysis of variance.

DISCUSSION

To our best knowledge, these may be the first data on the effects of one-year anti-TNF therapy on ACE level and ACE2 activity in arthritis patients. We found that one-year anti-TNF treatment significantly increased ACE concentration in the mixed cohort, as well as in the RA and AS subset. TNF inhibition also stimulated ACE2 activity in the RA+AS cohort but not in RA or AS. ACE/ACE2 ratios significantly increased in the mixed cohort and in RA, but not in AS. Interestingly, ACE levels and ACE/ACE2 ratios were higher in RA vs. AS, while ACE2 activity values were higher in AS vs. RA at most time points. Moreover, baseline, 6- and 12-month ACE levels, as well as ACE/ACE2 ratios variably correlated with disease duration, CRP, RF and various parameters of vascular pathophysiology. ACE2 activity only correlated with CRP.

We assessed ACE levels and ACE2 activity. ACE activity could not be included in this study as some patients received ACE inhibitors (**Table 1**), which could interfere with this parameter (26, 28). ACE2 activity is not affected by the use of ACE inhibitor treatment (28).

Upon TNF-α inhibition, ACE concentration increased in the mixed patient cohort throughout the treatment period. ACE levels also increased in RA and exerted a late, 12 M increase in AS. Similarly, anti-TNF therapy increased ACE2 activity in the mixed cohort, while ACE/ACE2 ratios showed late, 12 M increases in the full cohort and in RA. We could not compare our data from those published by others as, to our best knowledge, there have not been any studies evaluating the longitudinal effects of TNF-α inhibition on ACE or ACE2 levels or activity. In RA, increased synovial fluid ACE concentrations (46, 47) and decreased serum

ACE2 (45) or unchanged serum ACE levels have been reported (46). Thus, in RA, there may be a redistribution of ACE and ACE2 from the serum to the synovium. This may be reversed by anti-TNF treatment, however, this was hypothetical as no prospective studies assessing the effects of TNF inhibition of ACE and ACE2 redistribution have been conducted. Similarly to RA, Potdar et al. (34) reported increased expression of colonic ACE2 in active ulcerative colitis (UC) and low expression of small bowel ACE in Crohn's disease (CD) vs. controls. Anti-TNF therapy restored ACE2 tissue expression by decreasing colonic ACE2 in UC and stimulating small bowel ACE2 in CD (34). The redistribution of ACE and ACE2 between tissue and serum was discussed above (28). Thus, although we did not conduct tissue expression studies, elevated serum ACE concentrations and ACE2 activity upon one-year anti-TNF treatment may reflect redistribution between tissue and serum of ACE and ACE2 (28, 45–47). The pattern of ACE2 changes in our cohort is similar to the UC results reported by Potdar et al., however, they only assessed tissue ACE2 levels and not serum ACE2 activity (34). In addition, increased synovial fluid RA ACE levels were reported in RA compared to controls (43, 46, 47). The synovial fluid compartment reflects the characteristics of the tissue better than the serum. Again, considering the redistribution patterns of ACE and ACE2 between serum and tissue (28), our results indicating increasing ACE levels and ACE2 activity upon treatment may reflect decreasing synovial ACE and ACE2 expression.

When comparing RA and AS, there was no difference in ACE level between the two groups at baseline. On the other hand, after 6 M and 12 M, ACE concentrations were higher in RA compared to AS suggesting that TNF inhibition might have a more pronounced effect on ACE in RA vs. AS. With respect to ACE2 activity, it was higher in AS compared to RA both at B and after 12 M. Yet, the difference was greater between AS and RA after one-year therapy again suggesting a stronger stimulating effect of anti-TNF agents on ACE2 activity in AS vs. RA. Moreover, one-year anti-TNF treatment resulted in the increase of ACE levels in both RA and AS. In contrast, ACE2 activity was only increased in the full cohort, but not in the RA and AS subsets. ACE/ACE2 ratios were higher in RA compared to AS at all time points. There have been no studies on the effects of biologics on ACE and ACE2 in RA or AS, therefore, we cannot compare our data to other reports.

The baseline time point represents a pre-treatment status when both RA and AS patients had higher inflammatory state and disease activity. After 12 M, as anti-TNF therapy was proven to be clinically effective, most RA and AS patients had remission or at least low disease activity (LDA). That is why it is important to compare correlations between ACE, ACE2 or ACE/ACE2 and other parameters at baseline and after 12 M. In the regression analyses, at baseline ACE concentration only correlated with age, RF and IMT. However, after one-year treatment it also correlated with CRP and FMD. The correlation between 6 and 12 M ACE and CRP or disease activity was observed in the full cohort (CRP), as well as in the RA (CRP) and AS subsets (BASDAI). Thus, in treated arthritis patients with lower degree of inflammation, ACE levels may become a marker of remaining systemic inflammation or disease activity. Moreover, high baseline CRP and RF levels may predict ACE levels after 12 M. Increased plasma ACE levels were found in some cohorts (44), while others reported similar ACE levels in RA and controls (46). Our study was an uncontrolled, longitudinal therapeutic study comparing post- and pre-treatment ACE levels. ACE2 activity after 6 M positively correlated with baseline CRP suggesting that more extensive baseline inflammation may predict higher ACE2 activity after 6 M, when inflammation is already dampened. In another study of Tang et al. (39), decreased ACE2 levels were found in RA vs. healthy controls. Yet, that study included RA patients with mixed characteristics and the study did not assess longitudinal treatment effects (39). ACE/ACE2 ratios at baseline exerted correlations with disease duration, RF and IMT. Again, after 6 and 12 M, ACE/ACE2 ratios also correlated with CRP and FMD, which pattern is similar to that observed with ACE discussed above.

In the RM-ANOVA analysis, changes of ACE levels or ACE/ACE2 ratios over 12 M were positively associated with baseline RF and FMD in the full cohort and with baseline RF in the RA subset. Thus, in RA, high baseline RF may be the most important denominator of ACE concentration changes among the disease-related parameters included in this study.

Our study certainly has strengths and limitations. The strength of this study is that, for the first time, we assessed the effects of biologics on ACE and ACE2 in arthritides in a prospective manner. In addition, ours is the first study to evaluate ACE and ACE2 in association with multiple disease-related laboratory markers and those of vascular pathophysiology. Possible limitations may include the relatively low patient number and the lack of control groups.

In conclusion, anti-TNF treatment may increase ACE and ACE2 in the sera of RA and AS patients, which may reflect the shedding and redistribution of ACE and ACE2 from the tissue to the blood. Baseline ACE and ACE2 may be associated with disease duration, markers of inflammation (CRP), autoimmunity (RF) and vascular pathophysiology (FMD, IMT). The effects of TNF inhibition on ACE and ACE2 release may reflect, in part, the beneficial effects of biologics on vascular pathology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Hungarian Scientific Research Council Ethical Committee (Approval No. 14804-2/2011/EKU). Written informed consent was obtained from each patient and assessments were carried out according to the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BS: study conceptualization, patient recruitment, data collection, and draft writing. MF, ZPa, and AC: ACE and ACE2 measurements, data analysis, and manuscript drafting. ÁHo, EV, AHa, ZPe, NB, SSzam, and SSzán: patient recruitment and examination and data collection. AP and MC: laboratory assessments and data analysis. GK: vascular ultrasound examination and data collection. KH: statistical analysis and interpretation. ÉS: study concept, data interpretation, and draft writing. GS: study concept, draft writing, manuscript finalization, and senior coordinator. ZS: study concept, principal investigator, senior coordinator, and manuscript finalization. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.785744/full#supplementary-material

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PERSPECTIVE
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Challenges in Implementing Cardiovascular Risk Scores for Assessment of Young People With Childhood-Onset Autoimmune Rheumatic Conditions

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Cardio-vascular risk (CVR) stratification tools have been implemented in clinical practice to guide management decision for primary prevention of cardiovascular disease. Less is known about how we can optimally estimate the CVR in children and adolescents or about the reliability of the risk stratification tools validated in adult populations. Chronic inflammation associated with autoimmune rheumatic disease (ARD) drives an increased risk for accelerated atherosclerosis in patients of all ages. Although the research is less advanced than in adult populations, it is recognized that young people with ARDs with childhood-onset have increased CVR compared to age-matched healthy controls, as supported by studies investigating lipid biomarker profile and markers of endothelial dysfunction. Further research is needed to address the unmet need for adequate CVR identification and management strategies in young people in general, and in those with underlying chronic inflammation in particular. This perspective paper explores various challenges in adequately identifying and managing CVR in younger populations and potential directions for future research.

Keywords: cardiovascular risk scores, autoimmune rheumatic diseases with childhood onset, young population, cardiovascular risk biomarkers, atherosclerosis

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INTRODUCTION

Ischemic cardiovascular disease (CVD) is an umbrella term which comprises disorders of the heart and blood vessels caused by atherosclerosis, characterized by build-up of lipid deposits within the large and medium arteries leading to increased blood vessel stiffness and impaired blood supply to vital organs, as well as increased risk of blood clots (thrombosis). Atherosclerosis, although it progresses silently over many years, can eventually lead to significant organ damage, such as coronary heart disease, stroke, peripheral arterial disease and aortic disease. The natural evolution of atherosclerotic plaques has been inferred from various studies involving autopsies of individuals of all ages, which in particular revealed the existence of vascular lesions from younger age (1–3). Fatty streaks, defined as the first sign of atherosclerosis visible within the inner layer of blood vessels, start in early childhood. Although some of these arterial deposits can be reversible, they can also progress from an early age to more advanced atherosclerotic lesions through accumulation

of lipid-engorged macrophages, T cells recruitment, necrotic core formation due to defective cell death and cellular debris removal mechanisms and development of a fibromuscular cap (4, 5). The existence of early atherosclerotic manifestations in children and adolescents suggests that strategies for cardiovascular risk (CVR) assessment for preventing the development of CVD should start earlier (6). Here we discuss the suitability of using validated CVR stratification tools in younger cohorts, with particular focus on children and adolescents with autoimmune rheumatic diseases (ARDs) who have increased CVR, as well as propose future strategies for improvement of CVR assessment in young patients.

MARKERS OF EARLY ATHEROSCLEROSIS IN CHILDREN AND ADOLESCENTS

The presence of atherosclerotic lesions in young people has been detected with high prevalence in various cohorts. Young soldiers who died in the Korean War at a mean age of 22 had evidence of coronary artery atherosclerosis in 70% of cases (7), while more than 50% of children aged 10–14 years killed in road traffic accidents had early atherosclerosis lesions on post-mortem examination (4). Age, in addition to other CVR factors significantly influences the prevalence of atherosclerotic lesions. The large PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study found evidence of aortic atherosclerosis in 20% of healthy subjects aged 14–19 compared to 40% in those age 30–34 (3). In addition, an intravascular ultrasound study detected coronary artery atherosclerosis in 17% of healthy heart donors younger than 20 years, while this proportion increased to 37% in those aged 20–29 and to 60% in adults aged 30–39 years (8). The number and severity of CVR factors, such as increased body mass index (BMI), blood pressure, and levels of serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) all correlated with more severe atherosclerosis lesions in children and young people in the large Bogalusa Heart Study (1). Regarding biological sex, a pro-atherogenic lipid profile has been identified in healthy male adolescents post-puberty, while post-puberal girls had an athero-protective profile when compared to sex-matched prepubertal children (9). This provides evidence that sex-hormones drive changes in lipid metabolism which are relevant for the male-bias in CVD and that these changes start early in life. Lipid abnormalities could be one of the important drivers the driver of the early development of atherosclerotic lesions found in various post-mortem studies, especially as many studies included predominantly young male subjects (10).

AUTOIMMUNE RHEUMATIC DISEASES (ARDS) WITH ONSET IN CHILDHOOD ARE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS AND CVD

Having an inflammatory chronic condition, such as inflammatory arthritis, is associated with increased risk for CVD as well as evidence for accelerated atherosclerosis (11, 12). It is not clearly established how significant the contribution of traditional risk factors, such as age, gender, smoking, or hypertension, are to the development of atherosclerosis in ARD patients (13). Evidence that controlling chronic inflammation associated with ARDs decreases the atherosclerotic risk (14, 15) supports the role of pro-inflammatory cytokines in driving CVR. It is also recognized that autoantibodies frequently present in patients with ARDs could interfere with lipid metabolism (16) and endothelial function (17), therefore contributing to the increased CVR in ARDs. However, there is no current consensus regarding the exact mechanism of accelerated atherosclerosis in ARDs (18).

This is particularly relevant for people with ARDs with childhood-onset because of the longer disease duration and potential long-life exposure to fluctuating chronic inflammation and other detrimental factors. Endothelial dysfunction associated with systemic inflammation represents the first stage in the development of atherosclerosis and can be evaluated through arterial wall dynamic assessments and measurements of intima-media thickness (IMT), which have been shown as being altered in both children and adults with ARDs (19–21).

Juvenile idiopathic arthritis (JIA) is associated with increased prevalence of family history of CVD, hypertension, and smoking, as well as alterations of lipid profile (22, 23). Young adults with JIA have subclinical atherosclerosis even if their arthritis is well-controlled on or off medication (24).

Juvenile systemic lupus erythematosus (JSLE), the prototypical systemic ARD, is associated with a 100- to 300-fold increased mortality from CVD in young patients compared to age-matched controls (25). In addition, JSLE patients are younger when the first CVD event (myocardial infarction) occurs (32.2 years, range 24–43 years) compared with patients with adult-onset SLE (48.1 years, range 19–75 years) (26). Increased CIMT, as marker of subclinical atherosclerosis, has been found to be associated with both traditional and non-traditional CVR factors in a large cohort of JSLE patients included in the APPLE trial of atorvastatin for atherosclerosis prevention (27).

Children with juvenile dermatomyositis (JDM) with a median age of 10, and disease duration of 1.6 years have been shown to already have increased endothelial injury and arterial stiffness, as well as increased markers of inflammation, platelet activation and thrombotic risk compared to age-matched healthy children (28). JDM in children was also associated with premature atherosclerosis reflected in endothelial dysfunction as measured by flow-mediated dilation (FMD) (29). Similarly, young adults with JDM had higher systolic and diastolic blood pressure, increased proinflammatory oxidized high density lipoprotein cholesterol (HDL-cholesterol), IMT and endothelial dysfunction, despite decreased BMI and adiponectin compared to CVD controls (30).

Therefore, there is published evidence that juvenile ARDs are associated with accelerated atherosclerosis and increased CVR factors during both childhood and early adulthood, as

well as increased prevalence of both CVR and CVD events in early adulthood.

WHAT SCORES CAN WE USE TO ASSESS CVR IN YOUNGER ADULTS?

Although significant progress has been made in assessing CVR in the general population for the purpose of primary prevention of CVD, there is less guidance regarding assessment of CVR in younger people with or without associated comorbidities. The Framingham risk score (FRS) was one of the first CVR assessment tools developed in 1998. It uses a gender- tailored algorithm to estimate the 10-year CVR of an individual, and subsequently it is used to guide lifestyle and therapeutic management decisions by identifying the individuals more likely to benefit from such interventions (31). Individuals are arbitrarily grouped in low (<10%), moderate (10–20%), and high (>20%) CVD risk. It has been revised several times, and the most used versions include lipid measurements or BMI (FRS-lipids or FRS-BMI), as BMI has been shown to be an independent predictor of CVR (32). FRS considers traditional CVR factors, such as sex, age, blood pressure, smoking status, and diagnosis of type II diabetes mellitus (which was excluded from the most recent version and replaced with dyslipidemia) (31). As a consequence, although FRS is the oldest and the most widely used CVR stratification tool, it is difficult to appreciate its performance in patients with chronic inflammatory conditions as it does not consider associated CVR burden driven by chronic inflammation. In addition, FRS did not perform well when tested in younger adults (age 18–30), as despite significant CVR burden in some individuals, none of these young people were classified as high risk (33). Despite this, FRS is recommended to be used in individuals older than 20 years of age (34).

More recently, various other CVR assessment instruments have been developed to address the heterogeneity of CVR factors in different populations, by accounting for more CVR determinants, including both modifiable and non-modifiable risk factors, e.g., the atherosclerotic cardiovascular disease (ASCVD) risk score included in the 2019 American College of Cardiology (ACA)/American Heart Association (AHA) guidelines for primary prevention of CVD (35), the QRISK score developed by University of Nottingham and included in the National Institute of Care Excellence guidance for CVD prevention (version 3 the most recent) (36), the Systematic Coronary Risk Evaluation (SCORE) tool developed by the European Heart Association (version 2 the most recent) (37), and the Reynolds Risk Score (RSS) developed in US cohorts in 2007 (38) (**Table 1**).

The ASCVD risk score classified people younger than 40 years of age as low risk in the absence of risk factors (39); however, it is not very clear how well this score performs in younger populations as it has not been tested in children and adolescents. An updated version of the QRISK2 score, aiming at estimating life-long CVR to enable adequate classification of young people, was proposed in 2010—the QRISK®-lifetime cardiovascular risk (40). This score had the significant advantage of being able to identify individuals suitable for CVR management interventions at a younger age, with a higher proportion of men, individuals from non-white ethnic groups or with family history of premature coronary heart disease compared to the 10-year estimation of CVR using the QRISK2 score (40).

A systematic review of CVD risk of studies including children age 5–15 revealed that increased BMI significantly worsened other CVR parameters, such as systolic and diastolic blood pressure, serum lipids, fasting insulin, and insulin resistance, suggesting that an adequate CVR stratification tool for young people should take into account these parameters (41). The PDAY study (3) led to the development of a risk score formula to estimate the probability of advanced atherosclerosis in young people age 15-34, using CVD risk factors (42). The PDAY score has been shown to prevent advanced coronary atherosclerosis in both middle-age and young populations (42, 43).

WHAT CVR SCORES CAN BE USED IN YOUNGER PATIENTS WITH ARDS?

Despite the wide consensus that ARDs are associated with increased CVR (44, 45), and recent initiatives to drive collaborations between Rheumatology and Cardiology to improve the risk stratification of ARD patients (46), there is a paucity of data regarding the performance of various CVR assessment tools in ARD cohorts of all ages. A recent survey of Italian rheumatologists revealed that 67.2% rheumatologists routinely assess the CVR in their patients, while only 18.6% declared that they were managing the patients' CVR themselves, and 50% refer them to other specialties and 23.4% to the general practitioners (47).

Two of the CVR scores described above (**Table 1**) take into consideration additional clinical information contributing to CVR burden relevant for patients with ARDs, such as a previous diagnosis of rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) and concomitant steroid treatment (the QRISK3 and QRISK-lifetime scores) (36) and only one includes the high sensitivity C-reactive protein (hsCRP) levels (RSS) (38).

In a large cohort of 31,366 adult patients with RA, there were 1,648 CVD events over a median period of 4 years and the higher ASCVD risk score was associated with the male sex, older age, presence of comorbidities, worse disability, prior fracture, higher disease activity, and glucocorticoid use (48), suggesting that CVR assessment for primary prevention of CVD using validated tools are more tailored to detect CVR in older age. A large study including 1,050 RA patients also found that FRS, RRS, and SCORE all underestimated CVR associated with RA, while the QRISK2 score tended to overestimate it (49). A inception cohort study of 500 RA patients followed up for 8 years found that the observed CVR was higher than predicted by both FRS and RSS (50). The QRISK®-lifetime cardiovascular risk also classified inaccurately the CVR of middle-aged males with RA associated with chronic kidney disease as low risk (51), in keeping with

TABLE 1 | Comparison between various CVR assessment tools.

CVR scores / parameters	FRS-lipids/FRS-BMI	QRISK3	QRISK®-lifetime CVR	PDAY score	ASCVD	SCORE 2#	RSS
Age	✓	✓	✓	✓	✓	✓	✓
Sex	✓	✓	✓	✓	✓	✓	✓
Ethnicity/Race			✓		✓		
Height (cm):			✓				
Clinical information							
Diabetic?	✓±	✓	✓		✓		
Previous migraines		✓					
Previous CVD events*?		✓	✓				
Angina/heart attack-1st degree relative <60?		✓	✓				✓
Chronic kidney disease (stage 4 or 5)?		✓	✓				
Atrial fibrillation?		✓	✓				
On blood pressure treatment?	✓	✓	✓		✓		
On statin?					✓		
On aspirin?					✓		
Rheumatoid arthritis?		✓	✓				
SLE		✓					
hsCRP							✓
Severe mental illness		✓					
On atypical antipsychotic medication?		✓					
On regular steroid tablets?		✓					
Diagnosis/treatment for erectile dysfunction		✓					
Modifiable risk factors							
Smoking	✓	✓	✓	✓	✓	✓	✓
Hyperglycaemia				✓			
Cholesterol	✓				✓	✓	✓
Cholesterol/HDL ratio:		✓	✓				
HDL—cholesterol	✓			✓	✓	✓	✓
LDH—cholesterol					✓		
Non-HDL-cholesterol				✓			
Triglycerides				✓			
Systolic blood pressure (mmHg)	✓	✓	✓	✓	✓	✓	✓
Diastolic blood pressure (mmHg)				✓	✓		
SD of at least two recent BP readings (mmHg)		✓					
Weight (kg)			✓				
BMI	✓	✓		✓			
Ages for which the score is recommended/has been tested	20+	40+	30+	15–34 35–54	30+	40+	40+
Tested in ARDs	✗, ✗~	✓**			✓***	✗	✗

ARD, autoimmune rheumatic diseases; BMI, bone mass index; CVR, cardiovascular risk; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; SD, standard deviation; SLE, systemic lupus erythematosus.

#SCORE-2 is calibrated according to each European country CVD mortality risk.

*±Excluded from the updated FRS; *heart attack, angina, stroke, or transient ischemic accident.*

***QRISK2 tested in RA patients aged 40–75 and QRISK3 tested in SLE patients aged 35–44.*

****RA patients (40–75 years) classified as moderate/high risk had carotid plaque.*

✗Underestimated CVR in RA patients.

✗~Performed better in SLE if all items multiplied by 2.

the guideline recommendation for its use in younger, female populations (52).

Another study, published only as an abstract, investigated the accuracy of 6 different CVR scores (FRS-lipids, FRS-BMI, RRS, QRISK2, and SCORE) in a cohort of 130 RA patients, age 40–75 screened for the presence of carotid plaque (50% had plaque on ultrasound examination), and found that the presence of plaque was higher in patients classified as moderate/high risk using ASCVD and QRISK2 scores (53).

The inclusion of RA-related indicators, such as disease activity and duration, patient disability, and daily prednisolone use, improved the classification of RA patients based on CVR

assessment in addition to the use of traditional CVR factors in a large study from the Consortium of Rheumatology Researchers of North America registry, which requires further validation (54).

Although patients with SLE are usually younger than patients with other ARDs, the analysis of several modified version of FRS revealed that a modified FRS, in which each item was multiplied by 2, was more accurate in predicting coronary artery disease in a large cohort of 904 SLE patients (55). In another study, five conventional stratification tools underestimated the CVR associated with SLE by 50%, and three "lupus adapted" scores (the QRISK3, modified FRS, and modified SCORE risk scores) misclassified 25% of the SLE patients whose CVD risk was defined by the presence of atherosclerotic plaque detected by ultrasound (56).

No validated CVR scores have been used in JIA, although a few studies investigated the prevalence of increased blood pressure in children and young people with JIA compared to healthy controls. Both systolic and diastolic blood pressure were increased in prepubertal children with oligo- and polyarticular JIA (57) as well as in another cohort of 45 children with JIA (58), while HDL-cholesterol levels were lower in a separate study involving 51 JIA patients (59), when compared to age and sex-matched healthy controls.

Despite limitations of QRISK scores in assessing risk in younger populations, the newest version of QRISK score-QRISK3 performed better than the FRS and QRISK2 score in terms of identifying significantly more SLE patients with an increased 10-year risk for CVD, and this risk stratification correlated with markers for endothelial dysfunction and with patients' systolic blood pressure (60). In addition, QRISK3 score also classified a higher number of SLE patients as at risk for developing CVD than the FRS and ASCVD scores (61). A comparison between the FRS and ACC/AHA ASCVD (2013 version) found that 7 and 11.5% of SLE and RA patients, respectively, had discordant CVR scores, which were influenced by disease duration, hsCRP levels, African-American race, diabetes, current use of anti-hypertensive medication, higher age, and higher systolic blood pressure (62). To our knowledge, there are no studies investigating the performance of CVR stratification tools in JSLE or other ARDs with childhood onset.

SHOULD CVR STRATIFICATION TOOLS FOR YOUNG PATIENTS WITH ARD INCLUDE OTHER BIOMARKERS?

Although there is no consensus regarding the best risk stratification tool for use in young patients with ARDs, some studies investigated correlations between traditional and non-traditional CVR factors and CVD outcomes in younger patients with ARDs.

Patients with JIA had decreased FMD measured at the brachial artery and increased carotid IMT (CIMT compared to matched controls). The systemic JIA phenotype was characterized by the most pronounced abnormalities, with CIMT increase correlating with age, BMI, blood pressure, disease activity, and corticosteroids use (63). A recent study exploring lipid abnormalities in JIA found them present in 83.3% of patients, with low HDL-cholesterol levels being the most common (64). Similarly, systemic JIA was associated more frequently with abnormal LDL-cholesterol and non-HDL-cholesterol, as well as apolipoprotein B levels. Biologic treatment was associated with increased apolipoprotein A1 levels, which correlated negatively with the erythrocyte sedimentation rate (ESR).

A study evaluating 54 adolescents with JSLE found that various risk factors, such as hypertension, elevated triglycerides, apolipoprotein B, hemoglobin A1c and insulin levels, in addition to non-traditional CVR, such as elevated homocysteine and fibrinogen, were altered in adolescents with JSLE compared to matched healthy controls (65). In addition, vascular dynamic testing found increased arterial stiffness measures, central pulse wave velocity and characteristic impedance in JSLE. In multivariate analysis, LDL-cholesterol correlated positively with cumulative prednisone dose and negatively with hydroxychloroquine treatment, providing evidence that both disease and treatment can influence CVD risk.

Recent research has identified lipid biomarker abnormalities in JSLE using an in-depth metabolomic profiling including 230 metabolites, which enabled patient stratification in two groups, one with a pro-atherogenic and one with an athero-protective lipid profile (66). The apolipoprotein-B:A1 ratio distinguished between the two JSLE patient groups with high specificity (96.2%) and sensitivity (96.7%). The lipid signatures identified in the JSLE patients group with an atherogenic lipid profile overlapped significantly with lipid biomarkers associated with sub-clinical atherosclerosis in an independent adult SLE cohort, providing evidence that apolipoprotein-B:A1 ratio could be useful for CVR stratification in JSLE. Interestingly, these lipid signatures were associated with changes in gene expression in T cells, which are now recognized important players in the pathogenesis of atherosclerosis (67).

Lipid abnormalities in female adolescents (10–19 years old) with JSLE have been targeted by a dietary intervention which led to an improved lipid profile in the active treatment group (68), providing evidence that diet could be a suitable strategy for improving JSLE CVR profile.

DISCUSSION

Despite evidence of progress achieved in identifying CVR biomarkers in young patients with ARDs, there are currently no validated CVR stratification tools recommended for use in these patients, and therefore an unmet patient need to identify and manage CVR earlier in life.

In our opinion, testing of available CVR tools that perform adequately in younger populations (such as QRISK-lifetime CVR score or the PDAY score) or considering clinical history relevant for these patients' background of chronic inflammatory conditions and/or stratifying patients based on inflammatory markers and/or use of steroid treatment (such as QRISK3, RSS) could be a good starting point to identify which stratification tools perform best in children and adolescents with ARDs.

The next step will be to include previously tested or new CVR biomarkers to investigate whether the prediction power of the available scores can be improved. More investment in early detection of atherosclerotic lesions in young patients with ARDs using vascular scans/cardiac MRI or other less-invasive validated measures would facilitate adequate testing of the performance of various CVR stratification tools in real-life.

The greatest investment should be dedicated to following young patients with childhood onset ARDs into adulthood to collect real-life data related to prevalence of CVR events through linking pediatric and adult registries. In order to address the unmet patient need, well-designed clinical trials of various CVR interventions should be performed to investigate if young patients with ARDs have been stratified adequately for CVR interventions using the risk scores proposed, as well as to assess the impact of various interventions on CVD outcomes.

AUTHOR CONTRIBUTIONS

CC performed the literature review and wrote the first draft of the manuscript. All authors reviewed the manuscript and approved the final version.

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Cardiovascular Risks and Risk Stratification in Inflammatory Joint Diseases: A Cross-Sectional Study

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Background: It is well established that patients with inflammatory joint diseases (IJD) have an increased cardiovascular (CV) mortality and morbidity. According to the 2016 EULAR recommendations on CV risk management, rheumatologists should ensure appropriate management of CV risk in rheumatoid arthritis (RA) and other IJDs. The aim was to assess the CV risk and CV disease in Middle-European patients with IJD.

Methods: A retrospective chart review was performed for CV risk factors and CV disease in outpatients of a rheumatology outpatient clinic. CV risk was assessed according to the 2016 European Guidelines on CV disease prevention and also using 2 other approaches to compare the results with data from Norwegian and Spanish cohorts.

Results: Out of 432 patients, the prevalence of CV disease reached from 8.7% in spondyloarthritis (SpA) and 12.8% in psoriatic arthritis (PsA) to 18.7% in patients with RA. The number of CV risk factors did not differ between patients with RA, SpA, PsA, and non-inflammatory rheumatic disease (NIRD) (with 1.68 ± 0.13, 1.70 ± 0.13, 2.04 ± 0.16, and 1.78 ± 0.34, respectively). CV risk assessment could be performed in 82 patients after exclusion because of missing data and age. Stratification according to ESC guidelines showed low in 50%, moderate in 12.2%, high in 20.7%, and very high CV risk in 17.1% of patients aged between 40 and 65 years. CV risk in the Middle-European patients with IJD was higher than in the German general population ($p = 0.004$), and similar to the Norwegian patients with IJD, although patients with Middle-European PsA were at higher risk than the Norwegian patients ($p = 0.045$). Compared to the Spanish patients, Middle-European patients with IJD were more likely assigned to the high- to a very high-risk group (34.2 vs. 16.2%, $p < 0.001$), especially in RA disease (49.1 vs. 21%, respectively, $p < 0.001$).

Discussion: High prevalence of established CV disease together with high CV risk in patients with IJD urges for increased vigilance for CV risk factors followed by appropriate interaction by the treating physicians. The prospective use of an international CV risk assessment tool will allow not only estimation of the individual CV risk but also provide data for direct comparisons with the general population and other international cohorts.

Keywords: quality of health care (MeSH), risk assessment, rheumatology, cardiovascular system, SCORE, systematic coronary risk evaluation, musculoskeletal diseases, inflammatory disease

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INTRODUCTION

Cardiovascular (CV) disease has to be considered as the main cause of mortality in the general population. According to the 2017 Global Burden of Disease Study, 31.59% of all deaths in the world are attributable to CV disease (1). Therefore, the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention (ESC) make enormous efforts to develop guidelines, leading to reduction of the CV burden both on the individual and the population levels (2). As systematic screening for CV risks may result only in improvements of risk factors but has an effect on CV disease outcomes on its own, opportunistic screening for CV risk factors is recommended, although a beneficial effect on a clinical outcome is uncertain (2).

Several studies have shown, that patients with rheumatoid arthritis (RA) have the same risk of an adverse CV event as patients with diabetes mellitus (3, 4). The large Nurse's Health study showed a 2-fold increased myocardial infarction risk in patients with RA compared to those without, even after adjusting for traditional CV risk factors (5). Other inflammatory joint diseases (IJD) like spondylarthritis (SpA) and psoriatic arthritis (PsA) may be also linked to increased CV mortality and morbidity, as a large Canadian retrospective study reported a 36–49% increase in vascular deaths in patients with SpA compared to the general population (6). Although the higher prevalence of traditional CV risk factors in patients with RA plays a major role in higher CV disease prevalence, the association between CV risk factors and a CV outcome seems to be weaker in patients with RA compared to the general population (7), indicating the presence of additional risk factors in IJDs, such as systemic inflammation.

As a consequence, the EULAR (European Alliance of Associations for Rheumatology) recommendations on CV disease risk management propose that risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, including terms of disease duration, seropositivity, or some extra-articular manifestations if this is not already included in the model (8). Whether the use of the 1.5 multiplication factor increases the percentage of patients initially classified with intermediate risk as having high CV risk is still under debate (9, 10). For clinical practice, CV disease risk assessment is recommended for all patients with IJD at least one time every 5 years and should be reconsidered following major changes in antirheumatic therapy. Indeed, the inflammatory burden of IJD-diseases as a potential risk factor is not incorporated into currently proposed risk prediction models like SCORE (11), SCORE2 (12), and the Framingham tool (13). As a consequence, several works demonstrate that risk assessment tools only provide moderate estimations of the actual risk in patients with inflammatory, when subclinical atherosclerosis screening is used (14) or when further CV outcomes are seen in the follow-up (15).

Data on the use of CV risk assessment in clinical rheumatological routine, however, are rare. Therefore, this study aims to evaluate the prevalence of CV risk factors and CV disease in patients with IJD identified from an Austrian cohort of consecutive rheumatological outpatients and compare the results with two other cohorts from Norway and Spain.

MATERIALS AND METHODS

Study Design

This is a cross-sectional study with data retrospectively obtained from a prospective cohort study in the setting of a secondary/tertiary referral rheumatology clinic. This study is part of the prospective SolutionX project, which recruits consecutive rheumatological outpatients. All patients included in the project between September 27, 2017, and July 5, 2020, and diagnosed with RA, SpA, PsA, or a non-inflammatory rheumatic disease (NIRD) were selected for chart review.

Chart Review

The chart review was performed from July to August 2020 according to the STROBE recommendations for cross-sectional studies (**Supplementary Table 1**). Diagnoses are routinely based on the 2010 ACR/EULAR classification criteria for RA (16), the 2010 ASAS criteria for SpA (17), and the 2006 CASPAR criteria for PsA (18), respectively. For the chart review, SpA was defined as ankylosing spondylitis or all other axial and peripheral forms of SpA, except PsA. NIRDs include muscular disbalances, cervical, thoracal, and lumbar syndromes as well as osteoarthritis after exclusion of any other inflammatory rheumatic or hemato-oncologic disease.

Charts were manually screened in the hospital information system (KIS by Cerner, locally adapted). Data from the most complete visit record were used. Missing data were supplemented with data obtained within half a year prior or after the main visit as far as available. The absence of searched comorbidities and medications in the record was interpreted as not diagnosed.

Cardiovascular Risk Assessment

Cardiovascular Risk Factors

Study parameters included patient's and disease's characteristics, as well as CV risk parameters, CV diseases, and CV therapies. CV risk factors included smoking status, diabetes mellitus, and arterial hypertension. Systolic and diastolic blood pressures and body mass index were included as reported; laboratory CV parameters included lipid profiles and HbA1c%. CV diseases included coronary heart disease, myocardial infarction, coronary revascularization, cerebrovascular events with ischemic or hemorrhagic stroke, transient ischemic attack, and/or peripheral artery disease. CV therapies included antihypertensive, lipid lowering, and antiplatelet drugs.

Cardiovascular Risk Assessment According to 2016 ESC Recommendation

According to the 2016 ESC guidelines, CV risk assessment was performed using the SCORE calculation for data from patients aged 40 to 65 years, if all parameters were available (gender, age, systolic blood pressure, HDL-c, smoking status) (11). Patients were then stratified into four risk categories in accordance with the abovementioned ESC guidelines on cardiovascular disease prevention. The participants with a background of diabetes or established CV disease as well as those with BP $\geq$ 180/110 mmHg and total cholesterol $>$ 310 mg/dl were excluded from SCORE application and directly classified, as indicated by ESC guidelines.

TABLE 1 | Cardiovascular 10-year-mortality risk groups based on the 2016 ESC guidelines on cardiovascular disease prevention (11).

Low-risk	SCORE < 1%
Moderate-risk	SCORE is ≥ 1% and < 5%.
High-risk	Subjects with: - Markedly elevated single risk factors, in particular cholesterol > 310 mg/dL (e.g., in familial hypercholesterolemia) or BP ≥ 180/110 mmHg. - People with DM without major risk factors. - A calculated SCORE ≥ 5 and < 10%.
Very high-risk	Subjects with any of the following: - Documented CV disease includes previous acute coronary syndrome or myocardial infarction, coronary revascularization and other arterial revascularization procedures, stroke and transitory ischemic attack, aortic aneurysm and peripheral artery disease. - DM with a major risk factor such as smoking or marked hypercholesterolemia or marked hypertension. - A calculated SCORE ≥ 10%.

CV, cardiovascular; DM, diabetes mellitus; SCORE, systematic coronary risk evaluation; BP, blood pressure.

TABLE 2 | Age-dependent risk stratification based on the SCORE 2 protocol (12).

	<50 years	50–65 years
Low- to moderate-risk	<2.5%	<5%
High-risk	2.5 to <7.5%	5 to <10%
Very high-risk	≥7.5%	≥10%

Risk stratification does not include chronic kidney disease and proteinuria, as data were not available. The stratification criteria are presented in **Table 1**.

Risk Assessments Based on SCORE 2 and the EULAR-Endorsed 1.5 Multiplicator

According to the recently published 2021 ESC guidelines using the new SCORE 2 algorithm, the SCORE 2 was calculated for all those patients, for whom the original SCORE was calculated to compare the SCORE with the new SCORE 2 (2, 12). The patients were then stratified into three risk categories as proposed by the SCORE 2 protocol (**Table 2**).

Norwegian Approach of Risk Stratification

This approach using the HeartScore version was applied for patients aged 30 to 80 years without established CV disease, diabetes mellitus, antihypertensive drugs, and lipid lowering therapy (19). The HeartScore version of the SCORE with HDL-c for low-risk countries was calculated using a publicly available online tool (11).

Spanish Approach of Risk Stratification

This approach with the original 2003 version of the SCORE without HDL was applied for data from patients older than 40 years without established CV disease (20).

Comparison of CV Risk With German General Population

Data of the general population from a German cohort were used to estimate the level of CV risk in the patients with IJD (21). According to the German protocol, the patients with established CV disease were excluded.

Statistical Considerations

All data were anonymized before further analysis using the SPSS program for Windows (version 26).

Continuous data were tested for normal distribution using the Kolmogorov–Smirnov test. Means with SD for the normally distributed and medians with interquartile ranges (IQR) for not normally distributed values were calculated.

The Mann-Whitney U and the Kruskal–Wallis tests were used to compare non-parametric variables between two or more groups, respectively. To compare parametric variables between groups, the Student's *t*-test or a one-way ANOVA test was used as indicated. Differences between nominal variables were analyzed using the chi-square test. For comparison of two non-parametric dependent samples, the Wilcoxon signed-rank test was used.

RESULTS

Patient's Demographics and Disease's Characteristics

Out of the 1,353 patients recruited into the SolutionX project, the most prevalent diagnoses are SpA ($n = 244$, 18%), RA ($n = 221$, 16%), and PsA ($n = 123$, 9%). As shown in **Figure 1**, charts of these and 404 patients with a non-inflammatory rheumatic diagnosis (NIRD) were screened, and predefined CV risk parameters including at least the lipid profile were available for 432 patients. Out of these, 134 were diagnosed with RA, 115 with SpA, 78 with PsA, and 105 with NIRD.

Patient's and disease's characteristics are summarized in **Table 3**. Comparative analyses show higher age and more women in the RA group, compared to both other patients with IJDs and NIRD ($p < 0.001$ and < 0.007, respectively). The patients with SpA have the longest disease duration among the patients with IJD.

Prevalence of Cardiovascular Disease and Risk Factors

Prevalence of CV disease did not differ between disease groups, but, with 18.7%, the patients with RA show the highest prevalence compared to 8.7, 12.8, and 9.5% in patients with SpA, PsA, and NIRD, respectively (**Table 4**). Prevalence of established CV disease in different IJDs was higher in this cohort than in the Spanish cohort (with 18.7 vs. 10.5%, respectively; $p = 0.006$).

The mean number of CV risk factors is 1.77 per patient and does not differ between disease groups, with PsA patients, showing the highest number of CV risk factors (1.68 ± 0.13 for RA, 1.7 ± 0.13 for SpA, 2.04 ± 0.16 for PsA, and 1.78 ± 0.34 for NIRD). Hypercholesterolemia, hypertriglyceridemia, and arterial hypertension are the most prevalent CV risk factors (with 32.5–49.5, 25.6–32.1, and 28.7–37.2% of patients, respectively) (**Table 4**).

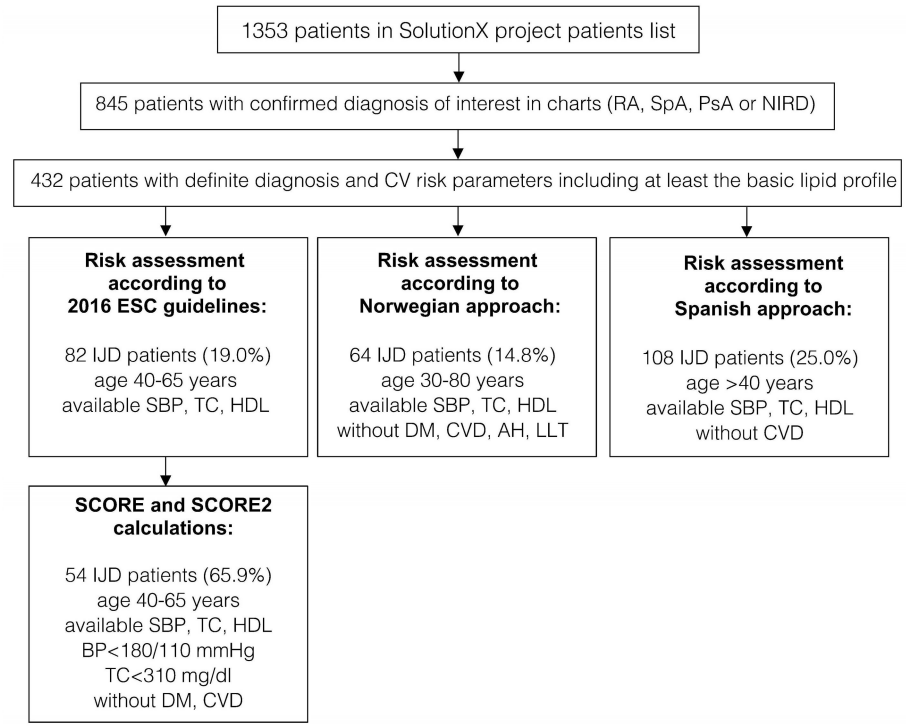

FIGURE 1 | A flow chart of patients' selection and data availability for different analyses (original SCORE and SCORE 2 calculation, risk assessment according to 2016 ESC Guidelines, the Norwegian and the Spanish approaches). RA, rheumatoid arthritis; SpA, spondyloarthritis; PsA, psoriatic arthritis; IJD, inflammatory joint disease (aggregate of RA, SpA, and PsA); NIRD, non-inflammatory rheumatic disease; AH, arterial hypertension; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; ESC, European Society of Cardiology; HDL, high density lipoprotein; LLT, lipid-lowering therapy; TC, total cholesterol; SBP, systolic blood pressure; BP, blood pressure.

Prevalence of hypercholesterolemia and previous smoking status varies between the groups ($p = 0.035$ and 0.014, respectively). About 32.5% of the patients with PsA show hypercholesterolemia compared to 48.5% of patients with RA, 53% of patients with SpA, and 49.5% of patients with NIRD ($p = 0.035$). Despite the similar prevalence of current smokers in the different groups, the percentage of previous smokers varies between 11.9% of patients with RA, 12.4% of patients with NIRD, 21.8% of patients with PsA, and 25.2% of patients with SpA. There is no difference in the prevalence of diabetes mellitus (with levels of HbA1c%), arterial hypertension (with systolic and diastolic blood pressure), and obesity (with body mass index) between groups as well as between the combined IJD group and the NIRD group. There was only a trend toward higher prevalence of obesity in PsA (with 25 vs. 21.4% in SpA and 14.4% in RA; $p = 0.179$) and a higher BMI in PsA (with 27.4 vs. 25.5% in SpA and 24.8 in RA; $p = 0.126$).

Assessment of Cardiovascular Risk

Patient's characteristics of the Norwegian and the Spanish cohort are presented in **Supplementary Table 2**. The Norwegian and the Spanish SpA group included only patients with ankylosing spondylitis. As the Austrian SpA group did not exclusively consist of patients with ankylosing spondylitis, the percentage of women was higher (with 60% compared to 35.1 and 27.1% in the Norwegian and the Spanish groups, respectively) and HLA-B27 positivity was less frequent than in the other cohorts (with 48.6% compared to 85.6 and 76.0% in the Norwegian and the Spanish groups, respectively).

Risk Assessment According to 2016 ESC Guidelines

According to the 2016 ESC guidelines, CV risk is assessed in patients aged 40 to 65 years (11). After SCORE calculation and including those patients with established CV disease or diabetes mellitus, the patients are stratified into four CV risk groups (**Table 1**). Out of the 432 patients, all parameters needed for SCORE calculation were available for 139 patients with IJD. Fifty-seven of them were not within the eligible age of 40 to 65 years and were excluded.

A total of 50% of patients with IJD were classified into the low-risk group, 12.2% into the moderate-, 20.7% into the high-, and 17.1% into the very high-risk groups. As shown in **Figure 2**, there is no difference in CV risk between the different IJD diseases ($p = 0.299$), although CV risk increases with age ($p < 0.001$), and the median age is highest in the RA group. The median age in the low-risk group is 51.8 (7.4) years, 58.0 (5.5) years in the moderate, 60.0 (9.5) years in the high, and 60.1 (6.2) years in the very high-risk group. Groups do not differ concerning C-reactive protein, erythrocyte sedimentation rate, disease duration, and anti-inflammatory treatment (**Supplementary Table 3**).

TABLE 3 | Patient's and disease's characteristics.

	RA $n = 134$ (31%)	SpA $n = 115$ (26.6%)	PsA $n = 78$ (18.1%)	IJD $n = 327$ (75.7%)	NIRD $n = 105$ (24.3%)	*p*-value for all groups	*p*-value IJD vs. NIRD
Median age [years]	64.1 (19.9)	54.2 (16.4)	54.5 (14.1)	57.6 (18.9)	53.9 (21.2)	<0.001*	0.025+
<45 years [%]	6.7	23.5	17.9	15.3	25.7		
45-60 years [%]	33.6	46.1	47.4	41.3	41.0		
>60 years [%]	59.7	30.4	34.7	43.4	33.3		
Female [%]	76.9	60.0	59.0	66.7	72.4	0.007°	0.275°
RF+ [%]	66.2						
ACPA+ [%]	66.7						
ANA ≧ 1:80 [%]	44.7						
HLA-B27+ [%]		48.6	20.9				
CRP [mg/dl]	0.27 (0.56)	0.22 (0.39)	0.19 (0.30)	0.22 (0.60)	0.14 (0.26)	<0.001*	<0.001+
ESR [mm/h]	13 (21)	8 (11)	8 (10)	12 (18)	5 (8)	<0.001*	<0.001+
Disease duration [years]	11.7 (11)	20.6 (26.7)	9.9 (20.4)	13.2 (15.1)		<0.001*	
						***p*-value for IJD groups**	***p*-value IJD vs. NIRD**
NSAID, regular [%]	4.5	19.1	17.9	12.8	9.7		<0.001°
- On request [%]	36.1	55.7	44.9	45.1	11.7		<0.001°
Median CS [mg/day]	0.0 (2.0)	0.0 (1.0)	0.0 (0.9)	0.0 (1.6)	0.0 (0.4)	0.001*	<0.001+
csDMARD [%]	82.0	19.1	47.7	51.5		<0.001°	
tsDMARD [%]	6.0	0.0	12.8	5.5		0.001°	
bDMARD [%]	27.8	27.0	20.5	25.8		0.471°	

IJD includes patients diagnosed with RA, SpA, or PsA. ACPA, anti-citrullinated protein antibodies; ANA, antinuclear antibodies; bDMARD, biological disease modifying anti-rheumatic drug; CRP, C-reactive protein; CS, dosis of methylprednisolone; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; IJD, inflammatory joint disease; NIRD, non-inflammatory rheumatic disease; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PsO, psoriatic disease; RA, rheumatoid arthritis; RF, rheumatoid factor; SpA, spondylarthritis; tsDMARD, targeted synthetic disease modifying anti-rheumatic drug., Kruskal–Wallis Test; +, Mann–Whitney-U Test; °, chi-squared test. All values are medians with interquartile ranges, if not specified otherwise.*

Stratification into the risk groups was based on the calculated SCORE in 65.9% of patients with IJD and based on additional stratification into higher risk categories in 13.4% due to markedly elevated blood pressure (≥180/110 mmHg), in 12.2% due to established CV disease, and in 8.5% of patients with IJD due to diabetes mellitus as comorbidity.

Risk Assessments Based on SCORE 2 and the EULAR-Endorsed 1.5 Multiplicator

In those 54 patients, who had been stratified based on the SCORE values, SCORE 2 was calculated for direct comparison of the 2 scores. There was an increase of patients in the high and the very high-risk groups after applying the new SCORE 2 protocol by 40.7 and 7.4%, respectively ($p < 0.001$ using the Wilcoxon-signed-rank test). This can be explained by the definition of SCORE 2, assessing risks for 10-year fatal and non-fatal cardiovascular disease, while the SCORE assesses only risks for 10-year fatal cardiovascular disease. Results are detailed in **Supplementary Figure S1**.

Application of the 1.5 multiplicators for SCORE values in the RA group as proposed by the EULAR recommendation led to the reclassification of 1 patient (=5%) when using the original SCORE and reclassification of 6 out of the 20 patients (=30%) when using the new SCORE 2.

Risk Assessment According to the Norwegian Approach

To compare the retrospective data with Norwegian data, the HeartScore version of the SCORE was calculated for patients with IJD aged 30 to 80 years without established CV disease, diabetes mellitus, lipid-lowering, and antihypertensive therapy (19). Out of 432 patients, parameters for SCORE calculation were available for 139 patients with IJD. Thirteen patients were excluded because of age. SCORE was not calculated for 31 patients because of established CV disease or diabetes mellitus and for 31 other patients because of lipid-lowering or antihypertensive therapy, as they already had an increased CV risk (=62 patients with IJD = 49.2%), compared to 987 Norwegian patients (=39.0%) ($p < 0.022$).

The other 64 out of the 126 eligible patients with IJD (=50.8%) were stratified into two CV risk categories and compared to the Norwegian data (**Table 5A**). There was no difference in CV risk between these two otherwise CV healthy retrospective disease groups aged 30 to 80 years. Only patients with PsA were at higher risk than Norwegian patients with PsA ($p = 0.045$).

Risk Assessment According to the Spanish Approach

According to the Spanish approach, the original 2003 version of the SCORE without HDL was calculated, including patients older

TABLE 4 | Cardiovascular disease, cardiovascular risk factors (in alphabetical order) with laboratory findings and current management of patients with RA, SpA, and PsA, grouped as IJD- and compared to patients with NIRD (data given as medians with interquartile ranges, if not specified otherwise).

	RA $n = 134$ (31%)	SpA $n = 115$ (26.6%)	PsA $n = 78$ (18.1%)	IJD $n = 327$ (75.7%)	NIRD $n = 105$ (24.3%)	*p*-value between all groups
CV disease [%]	18.7	8.7	12.8	13.8	9.5	0.075^{o}
Acetylsalicylic acid [%]	15.7	10.4	17.9	14.4	11.4	0.371^{o}
Arterial hypertension [%]	35.1	28.7	37.2	33.3	31.4	0.581^{o}
SBP [mmHg]	141 (32)	148 (41)	145 (31)	147 (32)	143 (27)	0.971*
DBP [mmHg]	92 (15)	96 (13)	93 (12)	93 (14)	89 (17)	0.371*
Antihypertensive therapy [%]	35.8	29.6	33.3	33.0	29.5	0.668^{o}
Diabetes mellitus [%]	11.2	7.0	9.0	9.2	7.6	0.653^{o}
HbA1c%	5.7 (0.6)	5.7 (0.5)	5.6 (0.6)	5.7 (0.5)	5.6 (0.5)	0.446*
Hypercholesterolemia [%]	48.5	53.0	32.5	46.3	49.5	0.035^{o}
Cholesterol [mg/dl] ± SD	196.3 ± 41.5	203.4 ± 44.5	190.6 ± 38.2	197.5 ± 42	200.1 ± 40.5	0.165^{A}
Hypertriglyceridemia [%]	25.6	30.4	32.1	28.9	29.5	0.742^{o}
Triglycerides [mg/dl]	102 (50.8)	122 (72.0)	140 (100.0)	114 (76.3)	132 (82.5)	0.386*
LDL-C [mg/dl] ± SD	126.4 ± 38.5	132 ± 41.7	125.2 ± 33.6	128.1 ± 38.6	129.9 ± 36	0.550^{A}
HDL-C [mg/dl]	54.5 (19.3)	61(21)	55 (19)	55 (19.3)	69 (19.8)	0.200*
Lp (a) [nmol/l]	19 (27.9)	29.5 (59.1)	27.8 (59.6)	19 (51)	19 (43.5)	0.862*
Lipid-lowering therapy [%]	18.7	13.0	19.2	16.8	17.1	0.611^{o}
Obesity [%]	14.4	21.4	25.0	19.6	23.9	0.251^{o}
Body-mass index	24.8 (4.5)	25.5 (8)	27.4 (6.9)	25.5 (5.4)	25.0 (2.5)	0.242*
Smoking						
Current	27.6	25.2	26.9	26.6	27.6	0.973^{o}
Previous	11.9	25.2	21.8	19.0	12.4	0.014^{o}

Differences between the groups of patients with IJD and NIRD were not significant; p-values of the differences between all groups of RA, SpA, PsA, and NIRD are indicated in the last column. CV, cardiovascular; DBP, diastolic blood pressure; HbA1c%, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IJD, inflammatory joint disease; Lp (a), lipoprotein (a); NIRD, non-inflammatory rheumatic disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SBP, systolic blood pressure; SD, standard deviation; SpA, spondyloarthritis; *, Kruskal–Wallis Test; ^{o}, chi-squared test; ^{A}, one-way ANOVA.

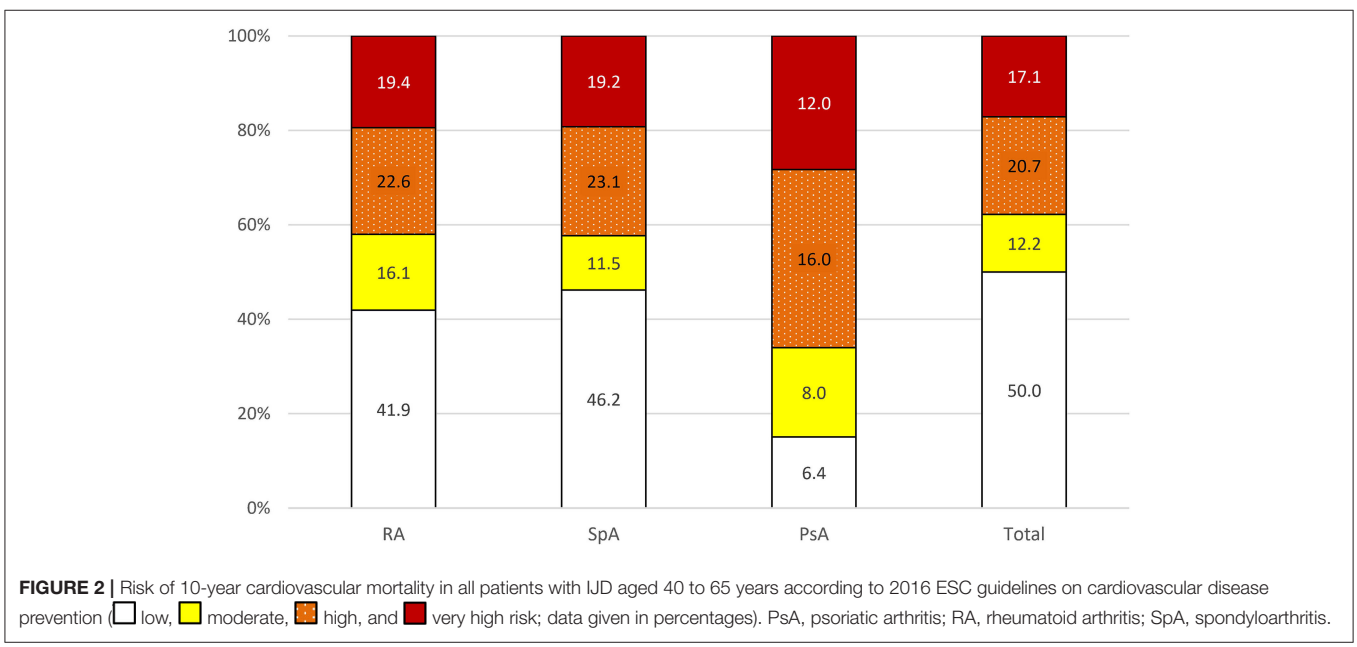

FIGURE 2 | Risk of 10-year cardiovascular mortality in all patients with IJD aged 40 to 65 years according to 2016 ESC guidelines on cardiovascular disease prevention (□ low, ■ moderate, ▩ high, and ■ very high risk; data given in percentages). PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.

TABLE 5 | Cardiovascular risk in patients with IJD (A) without CV disease, diabetes mellitus, lipid-lowering or antihypertensive therapy between the age of 30 and 80 years according to the Norwegian approach (data based only on SCORE values) and in patients with IJD (B) without CV disease older than 40 years according to the Spanish approach (original 2003 SCORE was used).

CV Risk	IJD	RA	SpA	PsA
(A)				
Middle-European cohort	$n = 64$	$n = 29$	$n = 18$	$n = 17$
Low to moderate (<5%)	93.8%	93.1%	100%	88.2%
High to very high (≥5%)	6.3%	6.9%	0	11.8%
Norwegian cohort	$n = 2,410$	$n = 1,293$	$n = 613$	$n = 504$
Low to moderate (<5%), n	96.8%	95.5%	99.2%	97.0%
High to very high (≥5%)	3.2%	4.5%	0.9%	3.0%
p-value	0.184°	0.537°	0.673°	0.045°
(B)				
Middle-European cohort	$n = 108$	$n = 53$	$n = 29$	$n = 26$
Low to moderate (<5%)	65.7%	50.9%	75.9%	84.6%
High to very high (≥5%)	34.2%	49.1%	24.1%	15.3%
Spanish cohort	$n = 1,836$	$n = 693$	$n = 545$	$n = 598$
Low to moderate (<5%)	83.8%	79.0%	88.0%	85.6%
High to very high (≥5%)	16.2%	21.0%	12.0%	14.4%
p-value	<0.001°	<0.001°	0.053°	0.848°

CV, cardiovascular; IJD, inflammatory joint disease (composite of RA, SpA, and PsA); PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; PsA, psoriatic arthritis; °, chi-squared test.

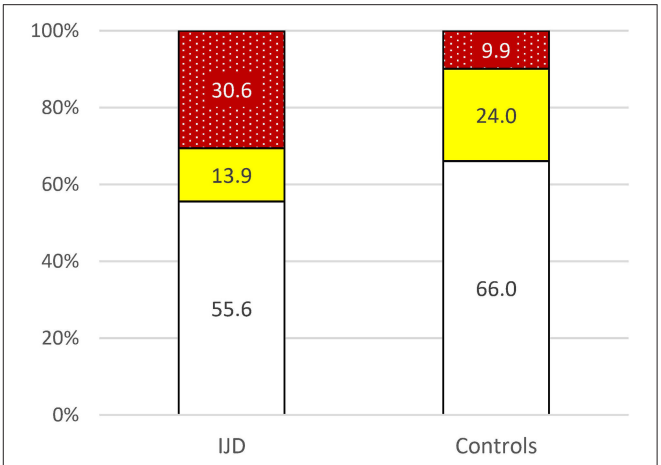

FIGURE 3 | Risk of 10-year cardiovascular mortality in patients with IJD aged 40 to 65 years old and the German control group according to 2016 ESC guidelines on cardiovascular disease prevention but without established CVD for comparison reasons ($p = 0.004$) (□ low, ■ moderate, ■ high to very high risk; data given in percentages).

than 40 years without established CV disease (20). One hundred eight patients with IJD were included in the stratification according to the Spanish approach.

As shown in **Table 5B**, our patients with IJD are more likely to be assigned to the high- to the very high-risk group than Spanish patients (34.2 vs. 16.2%; $p < 0.001$). Especially, patients with RA are more often assigned to the high- to very high-risk group compared to the Spanish cohort (49.1 vs. 21.0%, respectively; $p < 0.001$). For RA, there was a trend toward a higher prevalence of hypercholesterolemia than the Spanish patients with RA (43.4 vs. 30.7%; $p = 0.054$). There was also a trend toward a higher prevalence of high to very high risk in the SpA cohort (24.1 vs. 12.0%; $p = 0.053$) but not in the PsA group (15.3 vs. 14.4%; $p = 0.848$).

Comparison of CV Risk of Patients With IJD With German General Population

Data of the general population are available for Germany, although patients with established CV disease were excluded (21). The CV risk is higher in the IJD cohort than in the German general population as shown in **Figure 3** ($p = 0.004$).

DISCUSSION

In this cohort, the CV risk was moderate in 12.2%, high in 20.7%, and very high in 17.1% of all patients with IJD aged between 40 and 65 years according to the ESC guidelines (11). This CV risk is higher than the CV risk in the general German population (in persons without established CV disease) (21). Such increased CV mortality is well established for patients with different IJDs (5, 6, 22), but, although the 50% moderate to very high CV risk appears high, it may still underestimate the true CV risk, especially in older patients with IJD (15, 23).

The underlying reason for such underestimation is assumed to be the inflammatory burden of IJD diseases, which is not incorporated into the currently proposed risk prediction models as a potential CV risk factor. Detection of subclinical atherosclerosis could provide more detailed information (14). However, according to the recent 2021 ESC guidelines on CV disease prevention, systematic use of intima-media thickness is not recommended to improve risk assessment due to the lack of methodological standardization and the absence of added value of intima-media thickness in predicting future CV disease events even in the intermediate-risk group (2). In clinical practice, remission or at least low disease activity by the use of potent DMARDs certainly reduces but may not completely abandon the inflammatory burden over time. In this cohort, low disease activity is observed in most patients with normal levels of erythrocyte sedimentation rate and C-reactive protein levels, which was comparable to the Norwegian and the Spanish cohorts (as outlined in **Supplementary Table 2**).

The EULAR guidelines for the management of CV disease in patients with IJD, therefore, proposed a 1.5-multiplicator for CV risk assessment in patients with RA (8). As this study compared the CV risk in different IJD diseases and multiplicators for patients with SpA and PsA are not available, we applied the risk assessment both with and without the 1.5-multiplicator for patients with RA. Indeed, using the new SCORE 2 algorithm of the ESC group led to the reclassification of patients to a higher risk group in 30% compared to only 5% when using the original SCORE algorithm. Therefore, longitudinal data will be needed to conclude whether the new SCORE 2 algorithm can substitute the 1.5 multiplicators in RA and other inflammatory diseases.

To compare the results with data from different cohorts, this study further assessed the 10-year CV mortality risk both according to the NOCAR project in Norway and the CARMA project in Spain (19, 20). According to the Norwegian approach, CV risk in our patients with IJD aged 30 to 80 years without established CV disease, diabetes mellitus, and lipid lowering and antihypertensive therapy is similar to the Norwegian findings. Only the patients with PsA showed a higher risk than the Norwegian patients with PsA ($p = 0.045$), which could be attributed to the low number of our patients with PsA ($n = 17$). Compared to the Spanish cohort, all our patients with IJD older than 40 years without established CV disease were more likely in the high- to a very high-risk group (with 34.2% vs. 16.2), especially as more patients with RA were assigned to the high- and very high-risk group (49.1 vs. 21%, respectively).

These data fully support the need for lifestyle recommendations, regular CV disease risk management, cautious prescription of non-steroidal anti-rheumatic drugs in RA and PsA, and minimal dosages of corticosteroids as recommended by EULAR (8). Whether and how they are implemented in daily routine care remains open to local organizational concepts. Especially, the benefits of a healthy diet, regular exercise, and smoking cessation should be recommended to all patients with IJD. For this purpose, healthcare teams including nurses may support the rheumatologist and then work in close collaboration with the patients and their families as appropriate (24). Of note, risk assessment is not a one-time event but should be repeated, e.g., every 5 years, although there are no empirical data to guide the length of the intervals (2). Anyhow, for future studies and quality issues, the prospective use of one internationally recommended SCORE will allow both the estimation of the individual CV risk and provide data for benchmarking.

Of note, not only the CV risk but also the prevalence of established CV disease in different IJDs was higher in this cohort than in the Spanish cohort (with 18.7 vs. 10.5%, respectively; $p = 0.006$) (19, 20). Both age and disease duration may explain this finding, as longer disease duration is associated with the development of CV disease in RA (25, 26). Norwegian data were not available for a direct comparison.

Concerning the traditional CV risk factors, lipid abnormalities are often reported in IJD entities (27), with the comparable prevalence of dyslipidemia in different IJDs (19, 20, 28). Hypercholesterolemia was the most frequent CV risk factor in this cohort, but less frequent in patients with PsA than in patients with RA, SpA, and NIRD (with 32.5, 48.5, 53.0, and 49.5%, respectively; $p = 0.035$). This can be partially attributed to slightly albeit not significantly higher use of lipid-lowering medications in these patients. It is well-known that statins have anti-inflammatory effects and can even lower levels of C-reactive protein (29), but levels of C-reactive protein were comparable between patients with IJD, both with and without lipid-lowering therapy (data not shown). For diabetes mellitus, the prevalence was slightly higher in this cohort than reported in other studies. Contrary to an American study (30), our results did not show a higher prevalence of diabetes mellitus in PsA compared to patients with RA (data not shown). Obesity (defined as BMI $\geq$ 30) is a known risk factor in both CV and rheumatic diseases (31–33), with an increased prevalence of obesity reported for patients with PsA when compared to other patients with IJD (19, 20, 28). In this study, the prevalence of obesity was similar in patients with IJD compared to the general Austrian population (19.6 vs. 20.1%, respectively) (34), and there was only a trend toward a higher prevalence of obesity and a higher BMI in patients with PsA compared to the other patients with IJD.

Concerning arterial hypertension, studies from the literature report varying prevalence between 20 and 40% in patients with IJD, sometimes, even lower than in the control groups (35–37). In line with the literature, the prevalence in this study was similar across the IJD and NIRD disease groups, with the lowest numbers in SpA (with 28.7% in SpA, 35.1% in RA, 37.2% in PsA, and 31.4% in the NIRD group) (19, 20, 28). Smoking is an important risk factor not only for CV but also for the course and, sometimes, even for the treatment responses of disease-modifying antirheumatic drugs in rheumatic diseases (38, 39). In this study, 26.9% of patients are current smokers. These data are comparable to the prevalence of 25.9% in the Austrian general population as published by the WHO (40). Interestingly, the number of ex-smokers was higher in SpA than in the other diseases ($p = 0.014$). Given the varying percentages of CV risk in the different countries, it appears that data cannot be generalized and have to be assessed in each country separately.

Considering the limitations of this study, the retrospective study design with manual data search is certainly inferior to prospective data collection, potentially leading to missing or even biased reporting. Second, the limited number of patients resulted in a lack of statistical power or even unfeasibility of analyses, especially for solid comparisons with patients with NIRD and analyses concerning treatments with CV side effects like non-steroidal anti-inflammatory drugs. Furthermore, a manual not software-supported search of required data in patient's records could produce numerous errors. As real data on the mortality of patients with IJD were missing, a direct comparison between the ESC-derived mortality risk and the use of the 1.5-multiplicator as recommended by EULAR could not be performed. Also, comparisons with the Norwegian and the Spanish cohorts are not adjusted for age as individual data were not available. Complete stratification according to the 2021 ESC guidelines could not be performed in this study, as data for proposed stratification of patients with diabetes mellitus are not routinely available in this center. Contrary to the 2016 guidelines, risk stratification of patients with blood pressure >180/110 mmHg is not detailed in the 2021 version of the ESC guidelines. As controls, the patients with NIRD have selected the best controls we could identify in this setting. For better comparison with the normal population, data were then used from Germany, but we were not able to identify data from the local area or even from Austria as control data.

In view of these data, higher vigilance for CV risk factors followed by appropriate interaction by the treating physicians appears to be justified for all rheumatic patients both with IJD and NIRD to improve the calculated 10-year rate of a major CV event. Routine clinical assessment of

the CV risk factors and the use of an international SCORE tool to calculate the CV risk may further support patient's motivation to actively improve their risk of CV disease, e.g., with life-style changes, including dietary efforts and smoking cessation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Medical University Innsbruck (AN 2017-0041 317/4.18). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VY and MS substantially contributed to the conception of the study, data acquisition, analysis, and interpretation of the data. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, drafted and revised critically the important intellectual content, and finally approved the manuscript version to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.786776/full#supplementary-material

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The Association of Hyperuricemia and Gout With the Risk of Cardiovascular Diseases: A Cohort and Mendelian Randomization Study in UK Biobank

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Background: The association between hyperuricemia/gout with cardiovascular diseases (CVD) have been investigated. However, whether the magnitude of associations differs between hyperuricemia and gout, and the causality of these associations, remains inconclusive.

Methods: Based on UK Biobank, we conducted a cohort analysis including 431,967 participants, who were categorized as gout, hyperuricemia, and normal groups at recruitment, and followed up for CVD until December 2019. The phenotypic association of hyperuricemia/gout with CVD was estimated by Cox regression, adjusting for multiple confounders. Further exploration on the causality of such links was performed using Mendelian Randomization (MR) analysis, where we selected exclusive genetic variants for hyperuricemia and for gout based on summary GWAS data from independent populations.

Results: During mean 10.20 years of follow-up, hyperuricemia patients were associated with increased CVD (HR = 1.33, 95% CI: 1.29–1.36), compared to individuals who were free of hyperuricemia/gout. The risk elevation was even higher for gout patients (HR = 1.54, 95% CI: 1.48–1.62). Furthermore, we found significantly positive association between genetic liability for hyperuricemia and CVD in both one-sample (OR = 1.06, 95% CI: 1.02–1.11) and two-sample (OR = 1.09, 95% CI: 1.03–1.16) MR analysis. However, genetic liability for gout was not associated with CVD (OR = 0.89, 95% CI: 0.79–1.01 in one-sample, and OR = 0.92, 95% CI: 0.82–1.21 in two-sample MR analysis).

Conclusion: Individuals with hyperuricemia/gout were at increased risk of various types of CVD. As the MR analyses suggest a causal effect of hyperuricemia, but not gout, on CVD, these results indicate the possible effects of other gout-associated factors on the development of CVD, in addition to the uric acid pathway.

Keywords: hyperuricemia, gout, cardiovascular diseases, cohort study, Mendelian randomization

INTRODUCTION

The association between hyperuricemia or gout and the risk of cardiovascular diseases (CVDs) have been widely investigated in previous epidemiologic studies (1–4). Specifically, hyperuricemia has been associated with the increased risk of any (2) and specific subtypes of CVD, including stroke (1), coronary heart disease (5), incident hypertension (2), atherosclerosis (6), and atrial fibrillation (7). Likewise, with further enhanced magnitude of association (8), gout was noted as an independent risk factor for coronary heart disease (3, 4, 9), peripheral arterial disease (10), heart failure (11), stroke (12), and CVD mortality (8), suggesting a continuum of increase in CVD risk from hyperuricemia to gout (8). However, with methodological shortcomings of previous studies, such as cross-sectional design (3), selection bias due to various indications for prescription of blood test (3, 4), and insufficient control for important confounders such as lifestyle factors (6, 9, 10), as well as the absence of study examining the differential effects of hyperuricemia and gout on CVD using longitudinal data of the same population, the associations between level of serum urate, gout, and CVD need further assessments, with ideally population-based data and vigorous study design.

Moreover, as the supportive data mainly derived from observational studies, with so far limited knowledge on the underlying mechanisms, the causality between hyperuricemia or gout and CVD remains inconclusive. Using Mendelian randomization (MR) analysis, an approach utilizing genetic instrumental variants associated with the exposure phenotype as a proxy to infer causality (13), previous study showed a potential causality between hyperuricemia with hypertension and myocardial infarction (14), whereas a recent MR study focusing on hyperuricemia and ischemic heart diseases failed to provide consistent evidence (15). In addition, no well-powered causality assessment was found for gout and CVD comorbidities to date, which leads to uncertainties on the question whether serum urate lowering therapy is enough for preventing CVD-related consequence among patients with gout.

Therefore, taking advantage of the multi-dimensional prospective cohort data in UK Biobank, which provides available information on serum urate level and enriched phenotypical variables collected at baseline, complete follow-up data from linked national health registers, and individual-level genotyping data, for more than half million participants (16), we conducted a cohort analysis to elucidate the association between hyperuricemia, gout and subsequent CVD. We further aimed to examine the causal relation between hyperuricemia/gout and CVD. With additional attempts on distinguishing genetic variants specifically associated to asymptotic hyperuricemia from those to gout in MR analysis, our study explored to what extent the progressive order of these two traits (i.e., a part of individuals with hyperuricemia can progress to gout) attributed to the observed phenotypical associations.

METHODS

Data Source

UK Biobank is a cohort study where 502,507 participants, aged 40–69 years, were recruited across the UK between 2006 and 2010 (https://www.ukbiobank.ac.uk/) (16). Baseline information including social-demographic characteristics, lifestyle, and environmental factors was collected for all participants at recruitment. Future health and survival status can be monitored through data linkages with multiple national health registers (e.g., inpatient, primary care, and death registers) (17). Moreover, UK Biobank obtained genotyping data from blood samples of 487,409 participants (18).

Study Design

A Cohort for Assessing the Phenotypic Association Between Hyperuricemia/Gout and Subsequent CVD

We conducted a cohort analysis including all individuals from UK Biobank. After exclusion of individuals who had withdrawn their data ($n = 19$), without serum urate test ($n = 33{,}478$), and with a history of CVD at recruitment ($n = 37{,}043$), our analytic population comprised of 431,967 eligible participants (**Figure 1**).

At baseline, all participants were categorized as gout, hyperuricemia, and normal groups, and followed up from the recruitment date. Specifically, the level of serum urate >400 μmol/L for males or >360 μmol/L for females was considered as hyperuricemia, based on baseline blood assay test. Individuals with a self-reported medical diagnosis of gout at baseline were assigned into the gout group. Furthermore, individuals (i.e., those in hyperuricemia and normal groups) received a primary diagnosis of gout from inpatient or primary care data according to International Classification of Diseases-10th (ICD-10: M10) during follow-up, were further moved to gout group from the date of gout diagnosis.

All participants were followed until a diagnosis of CVD, death, or the end of study (31st December 2019), whichever occurred first. CVD during follow-up were ascertained by a primary diagnosis of CVD (ICD-10: I00-I70, I730, and I74) in inpatient data, or a death with CVD as the underlying cause from mortality data. In sub-analysis, we studied six

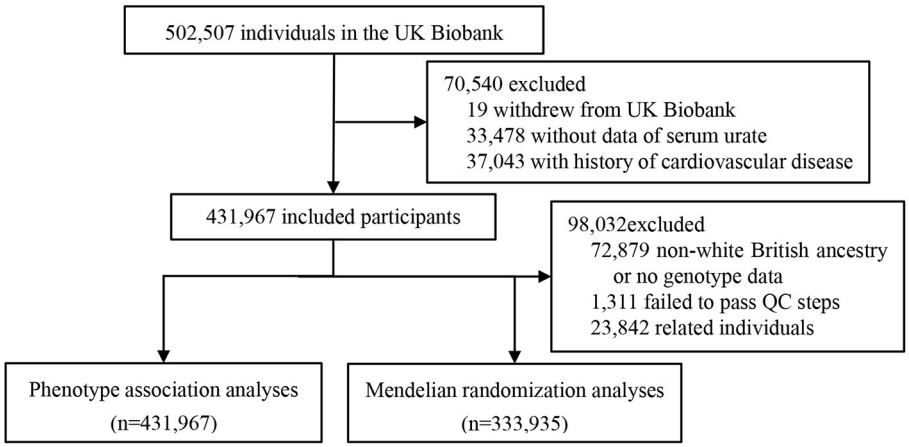

FIGURE 1 | Flow chart for study population selection.

major subtypes of CVD (including ischemic heart disease, cerebrovascular disease, emboli/thrombosis, hypertensive disease, heart failure, and arrhythmia/conduction disorder, **Supplementary Table 1**).

Individual-Level Genotyping Data for MR Analysis and Single Nucleotide Polymorphisms Selection

To estimate the causal effect of hyperuricemia or gout on CVD, we conducted MR analysis using imputed genotyping data of 359,088 White British UK Biobank participants. Based on standard genome-wide association study (GWAS) quality control, we first excluded 1,311 individuals who were outliers based on a variant call <98% and 23,842 shared relatedness indicated by a kinship coefficient >0.0884. Ultimately, the analytic dataset contained a total of 7,134,341 variants for 333,935 participants (**Figure 1**).

We identified 114 independent SNPs associated with hyperuricemia ($p < 5 \times 10^{-8}$) based on a GWAS study of 288,649 participants of European ancestry (19), among which 96 SNPs were available in our analytic dataset. Particularly, to distinguish the genetic influence of hyperuricemia from that of gout, we further excluded 15 SNPs associated with gout in previous report (19), leaving 81 independent SNPs as instrumental variables for hyperuricemia (explained 1.14% of the variance in hyperuricemia, with corresponding F statistic of 41, list see **Supplementary Table 2**). Likewise, 92 independent SNPs significantly associated with gout ($p < 5 \times 10^{-8}$) were retrieved from summary GWAS data (19). After removing 86 SNPs that also associated with hyperuricemia [$p < 5.34 \times 10^{-4}$ (0.05/92)], six SNPs remained as instrumental variables for gout (explained 0.08% of the variance in gout, with corresponding F statistic of 36, list see **Supplementary Table 3**).

Participants of UK Biobank have signed an informed consent before data collection. The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274), and this study was approved by the biomedical research ethics committee of West China Hospital (2019.1171).

Statistical Analysis

Cohort Analysis on the Phenotypic Association Between Hyperuricemia/Gout and Subsequent CVD

We used Cox regression to assess the associations of hyperuricemia and gout with risk of CVD, presenting as hazard ratios (HRs) with their 95% confidence intervals (CIs). We first estimated the overall associations of hyperuricemia and gout with any CVD, by comparing the CVD risk in the exposed groups to that in unexposed group. Then, such assessments were done for different subtypes of CVD. In all Cox models, we adjusted for sex (female/male), age at follow-up (as continuous variable), ethnicity (White, non-White, or unknown), smoking, alcohol drinking (never, previous, current, or unknown), tea/coffee intake (for each, <2/2–3/4–5/≥6 cups/day, or unknown), physical activity (low, moderate, or high), intake of fish oil and vitamin C/D/E supplementation (for each, yes/no, or unknown), intake of fresh fruit/vegetable (for each, <2/2–2.9/3–3.9/≥4 serving/day, or unknown), intake of processed meat/cheese (for each, never/<1/1–/≥2 times/week, or unknown), Charlson Comorbidity Index (as continuous variable), and self-reported family history of CVD (yes/no).

MR Analysis for Inferring Causal Relationships

In one-sample MR analysis, we used the inverse-variance weighted (IVW) method to pool the individual effect of each eligible SNP in UK Biobank genetic dataset. Specifically, the effect of each genetic instrument on hyperuricemia (51,200 cases and 282,735 controls), gout (9,855 cases and 324,080 controls), and CVD (32,222 cases and 301,713 controls) was assessed by logistic regression model, adjusting for sex, age, genotyping array, and 5 PCs, respectively. Then the causal estimates from multiple SNPs were combined using the inverse square of the standard error for CVD as weight. Besides, as the IVW approach assumed no horizontal pleiotropy (20), we evaluated the presence of horizontal pleiotropy by MR-PRESSO global test (21), and excluded potential outlier SNPs ($p < 0.05$) to correct estimations by MR-PRESSO Outlier-corrected methods.

In two-sample MR analysis, the effect of each genetic instrument on serum urate or gout was obtained from public available summary GWAS data (19), whereas on the CVD was generated from data of White British UK Biobank participants (32,222 cases and 301,713 controls) by logistic regression, adjusting covariates mentioned above.

Sensitivity Analysis

To demonstrate the validity of the observed phenotypic associations among individuals involved in the MR analysis, we repeated the cohort analysis among eligible White British UK Biobank participants (n = 333,935). To further confirm the differential effects of hyperuricemia and gout on CVD development (i.e., requiring a certain time interval from the studied exposure condition to outcome), as well as to reduce the potential reverse causality, we did a sensitivity analysis by excluding the first 2 years of observation and outcomes detected during this period in each group. Additionally, in order to test the robustness of our analyses to the choice of genetic instruments, we performed 10 times one-sample MR analysis by excluding a randomly selected 10% SNPs from the genetic instrument set at a time, to leave out a subset of the selected variants (21). To further release the concern about possible horizontal pleiotropy of selected genetic instruments, in addition to use MR-PRESSO global test in the main analyses, in a sensitivity analysis, we repeated the MR analyses by additionally excluding SNPs that reported to be also associated with other traits in GWAS Catalog database (i.e., focusing on SNPs with exclusive association with urate or gout, see **Supplementary Tables 2, 3**).

Statistical analysis was conducted using R, version 4.0.2 (R Project for Statistical Computing). A 2-sided $p < 0.05$ was considered statistically significant.

RESULTS

The Phenotypic Association Between Hyperuricemia/Gout and Subsequent CVDs

During a mean follow-up of 10.20 years, 62,752 individuals were into hyperuricemia group, and 12,508 individuals were diagnosed as gout and into group. A higher proportion of both individuals with hyperuricemia and gout was male (66.40 and 84.79%, respectively, compared to 39.32% in normal group, **Table 1**). No difference was noticed for life style and diet habit among individuals with hyperuricemia and gout, compared with normal group (**Table 1**).

Compared to individuals without hyperuricemia and gout throughout the study period, patients with hyperuricemia at baseline had higher incidence of any CVDs during follow-up [incidence rate (IR) = 13.54 vs. 8.15), which corresponded to a HR of 1.33 (95% CI: 1.29–1.36, **Table 2**). Notably, patients exposed to a diagnosis of gout experienced even higher elevation in CVD risk (IR = 19.53; HR = 1.54, 95% CI: 1.48–1.62, **Table 2**).

The sub-analysis for specific CVD revealed the increased risk associated with hyperuricemia/gout generally existed for all studied subtypes of CVD, with the top estimates always observed for hypertensive diseases (**Figure 2**). Furthermore, while the level of risk increase was comparable between hyperuricemia and gout for most studied CVDs, we observed that patients with gout

TABLE 1 | Baseline characteristics of study participants in a cohort study of 431,967 individuals from UK Biobank.

Characteristics	Normal group[a] (*N* = 361,199)	Hyperuricemia[b] (*N* = 62,752)	Gout[c] (*N* = 12,508)
Age at follow-up, years, mean (SD)[d]	56.4 (8.11)	57.7 (7.93)	61.0 (7.62)
Sex, *N* (%)[e]			
Female	219,164 (60.68)	21,082 (33.60)	1,902 (15.21)
Male	142,035 (39.32)	41,670 (66.40)	10,606 (84.79)
Race/ethnicity, *N* (%)			
White	341,332 (94.50)	59,010 (94.04)	11,900 (95.14)
Non-white	18,711 (5.18)	3,486 (5.56)	567 (4.53)
Unknown	1,156 (0.32)	256 (0.41)	41 (0.33)
Smoking status, *N* (%)			
Never	205,977 (57.03)	30,903 (49.25)	5,609 (44.84)
Previous	116,129 (32.15)	25,557 (40.73)	5,682 (45.43)
Current	37,875 (10.49)	6,034 (9.62)	1,170 (9.35)
Unknown	1,218 (0.34)	258 (0.41)	47 (0.38)
Alcohol status, *N* (%)			
Never	15,990 (4.43)	2,210 (3.52)	273 (2.18)
Previous	12,327 (3.41)	1,900 (3.03)	376 (3.01)
Current	332,503 (92.06)	58,566 (93.33)	11,842 (94.68)
Unknown	379 (0.10)	76 (0.12)	17 (0.14)
Tea intake[f], *N* (%)			
<2	94,598 (26.19)	16,794 (26.76)	3,359 (26.85)
2–3	106,018 (29.35)	18,564 (29.58)	3,936 (31.47)
4–5	91,837 (25.43)	15,838 (25.24)	3,103 (24.81)
≥6	68,003 (18.83)	11,418 (18.20)	2,084 (16.66)
Unknown	743 (0.21)	138 (0.22)	26 (0.21)
Coffee intake[f], *N* (%)			
<2	176,310 (48.81)	31,718 (50.55)	6,642 (53.10)
2–3	113,234 (31.35)	18,891 (30.10)	3,739 (29.89)
4–5	48,564 (13.45)	8,434 (13.44)	1,467 (11.73)
≥6	22,303 (6.17)	3,548 (5.65)	638 (5.10)
Unknown	788 (0.22)	161 (0.26)	22 (0.18)
Vitamins C, *N* (%)			
Yes	32,651 (9.04)	4,858 (7.74)	961 (7.68)
No	327,150 (90.57)	57,577 (91.75)	11,475 (91.74)
Unknown	1,398 (0.39)	317 (0.51)	72 (0.58)
Vitamins D, *N* (%)			
Yes	15,291 (4.23)	1,928 (3.07)	378 (3.02)
No	344,510 (95.38)	60,507 (96.42)	12,058 (96.40)
Unknown	1,398 (0.39)	317 (0.51)	72 (0.58)
Vitamins E, *N* (%)			
Yes	11,427 (3.16)	1,548 (2.47)	322 (2.57)
No	348,374 (96.45)	60,887 (97.03)	12,114 (96.85)
Unknown	1,398 (0.39)	317 (0.51)	72 (0.58)
Fish oil supplementation, *N* (%)			
Yes	114,246 (31.63)	18,605 (29.65)	3,912 (31.28)
No	246,225 (68.17)	43,999 (70.12)	8,576 (68.56)
Unknown	728 (0.20)	148 (0.24)	20 (0.16)
Fruit intake[g], *N* (%),			
<2	114,671 (31.75)	24,102 (38.41)	4,779 (38.21)
2-	92,293 (25.55)	15,539 (24.76)	3,103 (24.81)

(Continued)

TABLE 1 | Continued

Characteristics	Normal group[a] (*N* = 361,199)	Hyperuricemia[b] (*N* = 62,752)	Gout[c] (*N* = 12,508)
3-	71,417 (19.77)	11,097 (17.68)	2,157 (17.24)
≥4	82,116 (22.73)	11,852 (18.89)	2,439 (19.50)
Unknown	702 (0.19)	162 (0.26)	30 (0.24)
Vegetable intake[g], *N* (%)			
<2	124,600 (34.50)	22,550 (35.94)	4,533 (36.24)
2-	121,702 (33.69)	20,498 (32.67)	4,011 (32.07)
3-	63,744 (17.65)	10,849 (17.29)	2,148 (17.17)
≥4	48,963 (13.56)	8,327 (13.27)	1,715 (13.71)
Unknown	2,190 (0.61)	528 (0.84)	101 (0.81)
Process meat[h], *N* (%)			
Never	37,132 (10.28)	3,357 (5.35)	509 (4.07)
<1	114,863 (31.80)	15,740 (25.08)	2,789 (22.30)
1-	104,249 (28.86)	18,870 (30.07)	3,675 (29.38)
≥2	104,207 (28.85)	24,625 (39.24)	5,511 (44.06)
Unknown	748 (0.21)	160 (0.25)	24 (0.19)
Cheese[h], N (%)			
Never	9,048 (2.50)	1,798 (2.87)	380 (3.04)
<1	59,784 (16.55)	10,449 (16.65)	2,043 (16.33)
1-	74,227 (20.55)	13,551 (21.59)	2,786 (22.27)
≥2	209,267 (57.94)	35,168 (56.04)	6,899 (55.16)
Unknown	8,873 (2.46)	1,786 (2.85)	400 (3.20)
Physical activity, *N* (%)			
Low	71,521 (19.80)	14,416 (22.97)	2,868 (22.93)
Moderate	156,282 (43.27)	27,165 (43.29)	5,347 (42.75)
High	133,396 (36.93)	21,171 (33.74)	4,293 (34.32)
Family history of CVD, *N* (%)			
Yes	198,953 (55.08)	35,406 (56.42)	7,155 (57.20)
No	162,246 (44.92)	27,346 (43.58)	5,353 (42.80)
CCI score, mean (SD)	0.184 (0.783)	0.247 (0.915)	0.445 (1.22)

[a]*Normal group: Individuals were not defined as hyperuricemia and gout at baseline and during follow-up.*
[b]*Hyperuricemia: The level of serum urate at baseline, >400 μmol/L (6.8 mg/dL, for males) or >360 μmol/L (6 mg/dL, for females).*
[c]*Gout: Either diagnosis in UK Biobank inpatient or primary care data (ICD-10: M10), or self-reported a medical diagnosis of gout, at baseline or during the follow-up.*
[d]*Mean (SD): Mean (Standard Deviation).*
[e]*N (%): Number (%).*
[f]*Measured as cups per day.*
[g]*Servings/day: Two heaped tablespoons of vegetables were counted as a serving; two pieces of fresh fruit or four pieces of dried fruit were counted as a serving.*
[h]*Measured as times per week.*

tended to have higher risk for heart failure and hypertensive diseases, compared to individuals with hyperuricemia (**Figure 2**).

In the sensitivity analysis restricting to eligible White British UK Biobank participants, largely identical estimates were obtained, compared to the results of the main analysis (**Supplementary Table 4**; **Supplementary Figure 1**). Similarly, these observed associations stayed robust after excluding the first 2 years of follow-up (**Supplementary Table 5**).

Causal Relationships Between Hyperuricemia/Gout and CVDs

The application of MR-PRESSO global test identified only one outlier SNP (rs10857147) for hyperuricemia, while indicated no violation of horizontal pleiotropy assumption for selected genetically instrumental variants for gout ($p > 0.05$). Utilizing the IVM methods, we found significantly positive association between genetic liability for serum urate level and CVDs in both one-sample (OR = 1.06, 95% CI: 1.02–1.11, $p < 0.05$) and two-sample (OR = 1.09, 95% CI: 1.03–1.16, $p < 0.05$, **Table 3**) MR analysis. Further outlier-correction did not materially change the OR estimates (OR = 1.07, 95% CI: 1.02–1.11, $p < 0.05$, and OR = 1.10, 95% CI: 1.04–1.16, $p < 0.05$ for one- and two-sample MR, respectively). However, using SNPs specifically associated with gout but not serum urate, we found on association between genetic liability for gout and CVD in either one-sample (OR = 0.89, 95% CI: 0.79–1.01, $p = 0.078$) or two-sample (OR = 0.92, 95% CI: 0.82–1.21, $p = 0.192$, **Table 3**) MR analysis.

In the sensitivity analysis, exclusion of 10% selected SNPs led to similar estimates as the main analysis, where we also observed significantly positive effect of genetic liability for serum urate level on CVD in one-sample MR analysis (**Supplementary Figure 2**). Again, nine of 10 times one-sample MR sensitivity analysis showed no causal association for gout (**Supplementary Figure 2**). Also, by additionally removing SNPs associated with other traits (e.g., weight, chronic kidney disease, etc., leaving 44 SNPs for hyperuricemia and five SNPs for gout), the estimates obtained from the MR analyses were not modified largely (**Supplementary Table 6**).

TABLE 2 | Incidence rate and hazard ratios of any cardiovascular disease (CVD)[a] among patients with studied hyperuricemia or gout when compared with patients without hyperuricemia and gout.

Any CVD	Hyperuricemia[b]		Gout[c]	
	Incidence rate[d]	HR (95% CI)[e]	Incidence rate	HR (95% CI)
Unexposed group	25,852/3,117.77 (8.29)	Ref	2,5852/3,117.77 (8.29)	Ref
Exposed group	6,965/509 (13.68)	1.32 (1.28–1.35)	1,731/89.08 (19.43)	1.51 (1.44–1.59)

[a]*A primary diagnosis of CVD in UK Biobank inpatient data, or a death with CVD as the underlying cause, according to UK Biobank mortality data (ICD-10: I00-I70, I730, and I74).*
[b]*Hyperuricemia: The level of serum urate at baseline, >400 μmol/L (6.8 mg/dL, for males) or >360 μmol/L (6 mg/dL, for females).*
[c]*Gout: Either diagnosis in UK Biobank inpatient or primary care data (ICD-10: M10), or self-reported a medical diagnosis of gout, at baseline or during the follow-up.*
[d]*Incidence rate was measured as No. of Cases/No. of Accumulated Person-Years × 1,000 (Incidence Rate/1,000 Person-Years).*
[e]*HR, hazard ratio; CI, confidence interval; models adjusted for sex, age at follow-up, ethnicity, smoking, alcohol drinking, tea intake, coffee intake, physical activity, intake of fish oil supplementation, intake of vitamin C/D/E supplementation, intake of fresh fruit/vegetable, intake of processed meat/cheese, Charlson Comorbidity Index, and self-reported family history of CVD; individuals without hyperuricemia and gout were used.*

DISCUSSION

Based on this cohort study of over 460,000 participants, our results concluded that both individuals with hyperuricemia detected through screening and those got a clinical diagnosis of gout experienced increased risk of developing multiple types of CVD and CVD death. Particularly, together with the special efforts on distinguishing the effect of asymptomatic

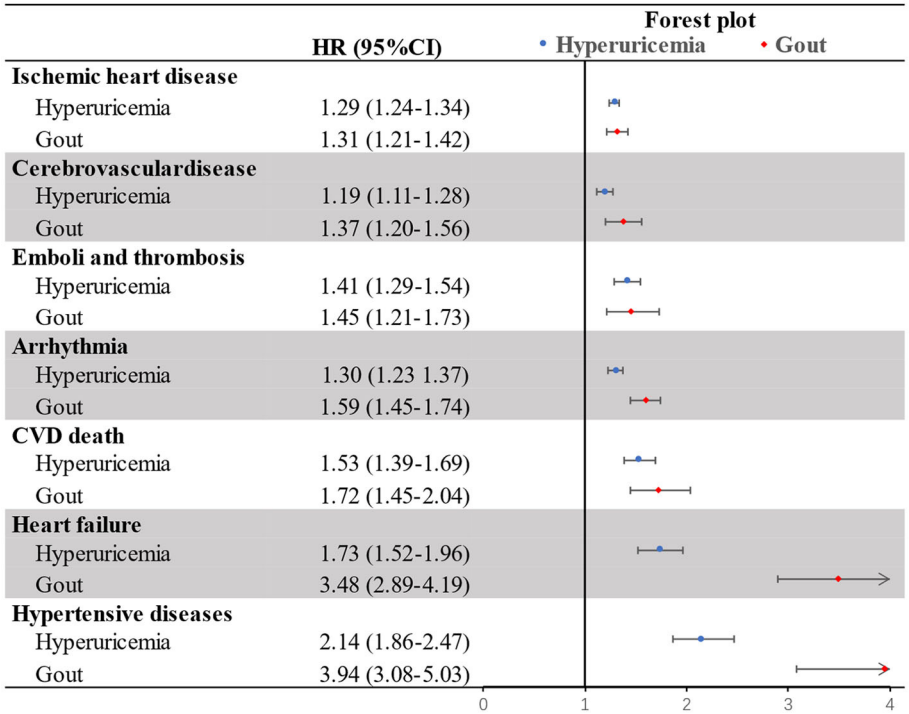

FIGURE 2 | Hazard ratios of specific cardiovascular diseases (CVDs) among patients with studied hyperuricemia or gout when compared with patients without hyperuricemia and gout.

TABLE 3 | Association of hyperuricemia and gout with risk of cardiovascular disease (CVD)[a] using Mendelian Randomization (MR) analyses.

	One-sample MR analysis		Two-sample MR analysis	
Exposure	**OR (95% CI)[d]**	***P***	**OR (95% CI)[d]**	***P***
Hyperuricemia[b]	1.06 (1.02–1.11)	0.009	1.09 (1.03–1.16)	0.005
Gout[c]	0.89 (0.79–1.01)	0.078	0.92 (0.82–1.21)	0.192

[a]A primary diagnosis of CVD in UK Biobank inpatient data, or a death with CVD as the underlying cause, according to UK Biobank mortality data (ICD-10: I00-I70, I730, and I74).
[b]Hyperuricemia: 81 independent and not related to gout SNPs derived from published GWAS data were used as instrumental variables to infer causality.
[c]Gout: 6 SNPs were used instrumental variables, which was not related to hyperuricemia.
[d]OR, Odds ratio; CI, confidence interval; models adjusted for sex, age, genotyping array, and 5 PCs.

hyperuricemia from that of gout on CVD outcomes in the cohort analysis, our selection of instrumental genetic variables in MR analysis also aimed separate SNPs genetically association with hyperuricemia from those with a clinical diagnosis of gout. Consequently, based on results of both one-sample and two-sample MR analyses, we found only supportive evidence on the causal relationship between hyperuricemia and CVD, while the association between genetically determined gout on CVD outcomes seems to be not causal.

Our findings of increased CVD risk among individuals with hyperuricemia and gout is consistent with previous studies. A study with 16.4 years follow-up, included 5,926 subjects who had serum urate level measurements at baseline, found that increased serum urate levels had a positive relationship to CVD mortality in men and women, among black and white persons (22). Furthermore, using data on a clinic-based cohort of 706 patients with gout, the presence of subcutaneous tophi and high baseline serum urate level were found as independent risk factor for increased CVD mortality (23). Importantly, such risk increase was in parallel with serum urate levels (23), and with increasing severity of gout (24). While most of these analyses were conducted when serum urate level and gout status was measured at the same time, our results add existing literature by demonstrating the independency of screening-identified serum urate and gout diagnosis on CVD risk, using longitudinal data.

The causality between hyperuricemia with CVD remains inclusive. Li et al. reported a potentially causal linkage between genetic determined higher serum urate level and increased risk of hypertensive disease, including essential hypertension and myocardial infarction, which however might be attributed to the pleiotropic effect of multiple instruments and unbalanced pleiotropy (14). A more recent meta-analysis of 58 studies suggested a causal role of urate in the development of coronary heart disease by MR analysis, while the possibility of unbalanced pleiotropy which have inflated the estimates was also noted (25). In contrast, null results were also described in other studies where no evidence was found for a causal relationship between urate

and CHD and heart failure (26). Our attempts of examining the causal effect of serum urate level or gout specifically on CVDs are novel. Importantly, as the results support an association between genetic liability for serum urate level, but not gout, and CVDs, our findings imply that the presence of hyperuricemia can increase the risk of CVDs, while the further enhanced risk elevation for individuals with gout (i.e., the increasing effect from hyperuricemia-gout on CVD) may due to either higher level and prolonged effect of serum urate, or joint impacts of between serum urate and environmental risk factors (e.g., obesity, reduced physical activity, reduced fish intake, etc.) on CVDs among such a population.

Although the detailed mechanisms remain inconclusive, several potential pathways have been proposed for the explanation of the association between hyperuricemia and increased CVDs. First, both experimental and human studies demonstrate that the increase of serum urate may induce endothelial dysfunction through increased oxidative stress and inflammation (27). Also, uric acid can stimulate vascular smooth muscle cell proliferation and oxidative stress possibly through the vascular renin-angiotensin system (28), which further play a central role in the development of various CVDs. Furthermore, hyperuricemia has been noted as a cause of arteriolar disease in kidney by impairing autoregulatory response (29); and the impaired autoregulatory response of the cerebral arterioles was closely associated with increased risk for stroke (30). Instead, biological evidence linking gout with CVD is limited, which mainly focus on the inflammation status (e.g., the overproduction of proinflammatory cytokines) in joints (27, 31). However, as the precipitation and deposition of uric acid crystals in synovial fluid and tissues is a well-identified consequence of hyperuricemia. It keeps unknown whether gout can increase the risk of CVD outside of the uric acid pathway. Here, our MR analysis indicates the stronger effect of gout on CVDs, relative to hyperuricemia on CVD in phenotypic analysis, might attribute to some important lifestyle factors that generally observed among the gout patients, such as the incapability of physical activity and reduced fish intake. Also, some comorbidities of gout, such as hyperlipidemia, obesity, and diabetes, are also identified as risk factors for CVD (32). Collectively, although need further verification, this finding highlights the necessities and importance of exploring feasible interventions on comorbid conditions and lifestyles among individuals with gout, in the terms of CVD prevention.

Our present study has several strengths. First, the application of UK Biobank, where the combination use of enriched phenotypic data, complete medical follow-up data, and individual-level genotyping data is possible, enabled a comprehensive assessment on the temporal relationship, as well as its underlying mechanisms, of hyperuricemia, gout, and CVD. Second, because we separated the genetic variants for hyperuricemia from those for gout specifically as instrumental variables in MR analysis, our results add to the existing literature by elucidating the effects of other factors that associated with gout on CVDs, in addition to the uric acid pathway.

Notable limitations include the small number of genetic instruments for both serum urate and gout in MR analysis. Therefore, future studies on causal assessment are needed for verification of our results, with ideally improved knowledge on genetic determinants on these traits. In addition, although the MR-PRESSO global test indicated no violation of horizontal pleiotropy and the sensitivity MR analyses where SNPs with reported association with other traits were additionally removed showed similar estimates, the concern that these genetic variants may the outcome through other pathways than the studied exposures cannot be completely addressed. However, the robustness of our results on the choose of genetic instruments has been partly demonstrated by the similar estimates observed in sensitivity analyses where we repeated 10 times of the analysis by randomly removing 10% of analyzed SNPs at each time. Moreover, our measurement on serum urate level was merely based on the blood tests at recruitment. Further studies, with ideally dynamic surveillance on serum urate, are warranted to provide more accurate assessment on the association between asymptotic hyperuricemia and CVD. Nevertheless, as a causal link was suggested between serum urate level and CVD in our analysis, the timely intervention on hyperuricemia may need, regardless of the presence of clinical symptoms nor the diagnosis of gout. Last, as the primary care data covered only 45% of UK Biobank patients, a part of patients with mild to moderate gout may be missed in our analysis. Also, as the absence of information on the use of uric acid lowering therapy among our participants, there are possibilities of misclassification, which renders unclear impacts on our estimates.

In conclusion, based on a longitudinal cohort study in UK Biobank, our results demonstrated a reliable association between hyperuricemia/gout on various types of CVD. Furthermore, as the MR analyses where we applied exclusive genetic variants for hyperuricemia and for gout suggest a causal effect of serum urate level, but not gout, on CVDs, our results indicate the possible effects of other gout-associated factors on the development of CVDs, in addition to the uric acid pathway, underscoring the exploration of feasible interventions on comorbid conditions and lifestyles among individuals with gout, for CVD prevention.

DATA AVAILABILITY STATEMENT

Data from the UK Biobank (http://www.ukbiobank.ac.uk/) are available to all researchers upon making an application.

ETHICS STATEMENT

Participants of UK Biobank have signed an informed consent before data collection. The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274), and this study was approved by the biomedical research ethics committee of West China Hospital (2019.1171).

AUTHOR CONTRIBUTIONS

JZ and HS were responsible for the study's concept and design. HY, WC, YH, YS, ZY, and YQ did the data and project management. YZ and HZ did the data cleaning and analysis. JZ, YZ, HZ, HY, WC, and HS interpreted the data. JZ, YZ, HZ,

and HS drafted the manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.817150/full#supplementary-material

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SYSTEMATIC REVIEW
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Arterial Stiffness and Adult Onset Vasculitis: A Systematic Review

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Chronic inflammation represents the cornerstone of the raised cardiovascular (CV) risk in patients with inflammatory rheumatic diseases (IRD), including vasculitis. Standardized mortality ratios in these patients are higher as compared to the general population, and the excess of premature mortality is due to early atherosclerotic events. Thus, IRD patients need appropriate CV risk assessment and management according to this CV disease (CVD) burden. Adequate control of CV risk is still lacking in usual care, but early diagnosis of silent and subclinical CVD is crucial to improve the long-term prognosis of these patients. Increased arterial stiffness may provide a pathophysiological link between inflammation and increased cardiovascular risk. Several noninvasive methods are now available to estimate artery stiffness in the clinical setting, including pulse wave velocity assessment. The independent predictive value of arterial stiffness for cardiovascular events has been demonstrated in general as well as in selected populations, and reference values adjusted for age and blood pressure have been suggested. Thus, arterial stiffness is an interesting biomarker for cardiovascular risk stratification. This systematic review summarizes the additional value that PWV measurement can provide in the setting of vasculitis, with a focus in the different clinical stages and CV risk prevention. This systematic review is registered with registration number: Prospero CRD42021259603.

Keywords: vasculitis, inflammation, atherosclerosis, arterial stiffness, Behcet disease, Takayasu arteritis, ANCA vasculitis

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INTRODUCTION

Patients with chronic inflammatory rheumatic diseases (IRD) including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), connective tissue disease, and also vasculitis have increased risk of developing premature CVD (1–3). The pathogenesis of CVD in these conditions is multi-factorial, and is thought to result from an interaction among inflammation, metabolic factors, therapies and disease-related factors (4). Emerging evidence suggest that the two classical pathways of arterial damage, namely, atheromatosis (i.e., atheromatic plaque formation), and arteriosclerosis (i.e., arterial stiffening), are accelerated, thus participating in the development of microvascular and macrovascular complications in rheumatic disease (5).

Remarkably, atherosclerosis in patients with IRD is often characterized by higher plaque vulnerability; Karpouzas and coll. showed that patients with RA present with a greater coronary atherosclerotic burden, and higher prevalence of more vulnerable non-calcified and mixed plaque compared with controls (6). Moreover, vulnerability and the risk of plaques rupture are characteristics ascribed to disease activity, as well as the risk of thrombosis in IRD (7).

The primary systemic vasculitis are rare autoimmune diseases potentially resulting in life-threatening organ ischemia and infarction; they are characterized by idiopathic inflammation of blood vessel walls and are classified by size of blood vessel affected (8). Although death typically occurs prematurely as a consequence of either uncontrolled vasculitis or infection due to immunosuppression, atherosclerotic cardiovascular disease (ASCVD) is now the leading cause of mortality in these patients (9, 10).

Atherosclerosis and Vasculitis

Potential mechanisms underlying the accelerated atherosclerosis in systemic vasculitis also include the infiltration of activated inflammatory cells within the affected artery wall (11). In addition, different mediators including metalloproteinase, VEGF and PDGF are increased in vasculitis, thus contributing to intimal hyperplasia and luminal narrowing (11). Increased plasma levels of CRP as well as other pro-inflammatory cytokines lead to pro-atherogenic profile, through the increased expression of adhesion molecules, cell recruitment, and smooth muscle cell stimulation and macrophage apoptosis, enhance atherogenesis (12). Inflammatory cytokines also affects coagulation via thrombomodulin-C (11). In addition, autoantibodies such as anti-endothelial cell, anti-cardiolipin, and MPO-ANCA, may contribute in damaging endothelial cell, leading to a pro-thrombotic state. These antibodies may directly activate TNF-primed neutrophils, leading to generation of reactive oxygen species and subsequent endothelial damage; immune complexes further contribute to pathogenesis by fixing complement and by binding to neutrophil Fcg receptors and activating neutrophils (13). The formation of neutrophil extracellular traps (or NETosis), which play a key role in increasing inflammation and autoantibody production in ANCA-associated vasculitis, also seems to have a crucial role in initiating macrophage activation in atherosclerosis (14). Furthermore, the vasculitic injury of arterial wall may accelerate atherosclerosis and may alter arterial anatomy perturbing arterial blood flow and leading to a pro-inflammatory status on vascular endothelium. Even therapies could affect the endothelium homeostasis. Despite certain targeted immunosuppressive drugs seems to reduce the risk of CVD, glucocorticoids could have detrimental metabolic effects, promoting weight gain, hypertension, dyslipidemia and hyperglycemia (15), further exacerbating vascular dysfunction and promoting atherosclerotic process. Lastly, traditional CV risk factors are more prevalent in vasculitis, with increased rate of target organ involvement. Microbiome is currently investigated in order to assess its role in both atherosclerosis (16) and the systemic vasculitis (17); potential mechanism involved are the stimulation of the immune system, and the increased availability of certain pro-atherogenic metabolites including trimethylamine-N-oxide. RA in remission shows lower values of laboratory inflammatory markers, lower blood pressure, and better arterial compliance; moreover, MTX has been associated with lowered rates of CVD in different studies, and TNF inhibitors may protect against CV events in patients with RA (18). Furthermore, the recent successes of targeted anti-inflammatory medications including canakinumab and colchicine in reducing the incidence of cardiovascular events in patients with atherosclerosis provide strong support for the critical role of inflammation in atherosclerosis pathogenesis (19, 20).

Arterial Stiffness

Patients at high risk of CV events could be stratified with the use of noninvasive surrogate markers of CVD (21), such as carotid US, particularly those included in the category of moderate CV risk according to risk chart algorithms. In addition to maintaining a tight control of the rheumatic disease, looking for clinical remission and management of traditional CVRFs such as dyslipidemia and hypertension should be routinely assessed in patients with IRD.

Increased arterial stiffness (AS) is one of the earliest stages of the atherosclerotic process (22, 23), and PWV is widely accepted as an accurate and non-invasive method to assess AS in humans (24). While PWV is a direct measure of arterial distensibility, the AIx is a more complex parameter depending on vascular elasticity and peripheral resistance (25). Arterial wall rigidity is considered an independent predictor of all-cause and cardiovascular mortality in several clinical settings, including hypertensives, end-stage renal disease, dyslipidemic, in elderly people, and also in IRD patients (26–28).

Mechanic properties could be altered long before the appearance of clinical lesions, reflecting alterations in the arteries structure and affecting their functional features. The pulse wave velocity (PWV) is measures the travel speed of the pulse pressure along a segment of the arterial tree; the augmentation index

Abbreviations: AAV, Anca associated vasculitis; AIx, augmentation index; ANCA, anti-neutrophil cytoplasmic antibodies; AS, Arterial Stiffness; AUC, area under the curve; baPWV, brachial-ankle pulse wave velocity; BD, Behcet's disease; BMI, body mass index; BNP, B-type natriuretic peptide; BSAS, Behcet's Syndrome Activity Scale; C-reactive protein, CRP; CAD, coronary artery disease; CDAI, clinical disease activity index; CSS, Churg-Strauss syndrome; CV, cardiovascular; CVD, cardiovascular disease; CVE, cardiovascular events; DAS28, disease activity score 28-joints; DBP, diastolic blood pressure; DMARD, disease-modifying anti-rheumatic drugs; ECM, extracellular matrix; EF, ejection fraction; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GPA, Granulomatosis with Polyangiitis; HDL=high-density lipoprotein; HF, heart failure; HR, heart rate; Hcy homocysteine; IHD, ischemic heart disease; IL, interleukin; IRD, inflammatory rheumatic diseases; LDD, Long Disease Duration; LDL=low-density lipoprotein; MACE, mayor adverse cardiovascular events; MAP = mean arterial blood pressure; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; MRI, magnetic resonance imaging; PDGF, platelet-derived growth factor; PP, pulse pressure; PR3, proteinase 3; PVAS, Pediatric Vasculitis Activity Score; PWV, pulse-wave velocity; PWV-CF, pulse-wave velocity carotid femoral; PWC-CR. pulse-wave velocity carotid radial; SBP, systolic blood pressure; SDD, short disease duration; SLE, systemic lupus erythematosus; TAK; Takayasu's arteritis; TNF, tumor necrosis factor; US, ultra-sonography; VEGF, vascular endothelial growth factor.

(AIx) is defined as the increment in pressure after the first systolic shoulder to the peak of the aortic pressure expressed as a percentage of aortic pulse pressure (29).

To assess AS indices some features are generally required. The distance between the recording sites and the suprasternal notch are measured using a tape measure. Electrocardiography is used to determine the start of the pulse wave. The PWV is determined as the differential time between the 2 different recording sites divided by the travel distance of the pulse waveform. Several methods and technologies have been proposed to evaluate AS parameters, including PWV and AIx. The classical "two-points" evaluation was long considered the—noninvasive—gold standard to assess PWV (30); later, semi-automated tools were developed to assess more easily PWV and/or AIx. Of these, the SphygmoCor^{TM} CVMS (AtCor Medical, Sydney, Australia) uses a tonometer and 2 different pressure waves obtained at the common carotid artery (proximal recording site) and at the femoral artery (distal recording site); the Arteriograph^{TM} (TensioMed, Budapest, Hungary) -applied to the upper arm- explores the time difference between the first and second waves originates from the aortic bifurcation and the sum of travel time of the pulse in the descending aorta forward and backward; the Complior^{TM} (Artech Medical, Pantin, France) system uses two sensors simultaneously exploring carotid and femoral waveforms, thus estimating cfPWV by dividing the distance separating the two sensors by the time corresponding to the period separating the start of the rising phase of the carotid pulse wave and that of the femoral pulse wave. Also, AS tracking systems could implemented in the ultrasound machine(s) (30–33).

PWV typically increases from the proximal aorta (3–4 m/s), through the descending aorta (5–6 m/s), the ilial-femoral segment (7–8 m/s), to the foot (9–10 m/s) or hand. The wall-to-lumen ratio and the amount of collagen relative to elastin are major contributors to this heterogeneity of PWV in the human circulation. Increasing the wall-to-lumen and/or the collagen to elastin ratios *favor* increased stiffness (34–37). Also, AS independently predicts death (from all causes and from cardiovascular causes in particular) and CV outcomes in healthy elderly people, diabetic patients, hypertensive patients, general adult populations such as those sampled by the Framingham Study, and patients with end-stage renal disease (35, 38).

Several factors, including cardiac performance, structural elements in the vessel wall and rheological characteristic of the blood, are recognized as determinants of the arterial stiffness. Arterial stiffening reflects the degenerative changes of ECM in the media layer, and is characterized by elastin fatigue fracture and collagen deposition and cross-linking. Arterial stiffening differ from atherosclerosis, a process that typically involves the intima layer and is characterized by lipid accumulation, inflammatory cells and vascular smooth muscle cell migration, and foam cell development. On the other hand, both processes often coexist in the same vascular *territories*, share some mutual risk factors, and are part of the vascular aging process. Furthermore, experimental studies have shown that changes in ECM proteins and in mechanical properties of the vessel wall may activate some pathophysiologic mechanisms involved in the atherosclerotic process, and clinical studies have demonstrated an independent association between AS and atherosclerotic load, as well as between AS and risk of incident cardiovascular events (39). AS is determined principally by age and blood pressure (30, 40) that may account up to 70% of its variance (36). Chronic inflammation is another pathological condition involved in both arterial stiffening and atherosclerosis (34). Altogether, these evidences suggest AS as a promising biomarker for cardiovascular risk stratification.

With this systematic review we aimed to describe the potential usefulness to estimate AS indices in vasculitis in relation to disease activity, also to better identify patients at high cardiovascular risk.

METHODS

This research was performed following methods that are reported in the PRISMA Statement, and the systematic review is registered with registration number: Prospero CRD42021259603. Two authors (ALG, GM) independently searched published studies that were indexed in MEDLINE and EMBASE from January 1990 to May 2021. If needed, a manual search was performed according to the citation lists of the relevant literature. The following key words were used: (Takayasu arteritis[Title/Abstract] OR Takayasu's arteritis [Title/Abstract] OR pulseless disease[Title/Abstract] OR aortitis syndrome[Title/Abstract] OR Behçet syndrome[Title/Abstract] OR Behçet disease[Title/Abstract] OR Behçet's disease[Title/Abstract] OR antineutrophil cytoplasmic antibody-associated systemic vasculitis[Title/Abstract] OR ANCA associated vasculitis[Title/Abstract] OR granulomatosis with polyangiitis[Title/Abstract] OR eosinophilic granulomatosis with polyangiitis[Title/Abstract] OR microscopic polyangiitis[Title/Abstract] OR Churg-Strauss syndrome[Title/Abstract] OR Wegener's granulomatosis[Title/Abstract]) which were combined with (arterial stiffness[Title/Abstract] OR artery stiffness[Title/Abstract] OR vascular stiffness[Title/Abstract] OR pulse wave velocity[Title/Abstract] OR pulse wave analysis[Title/Abstract] OR pulse wave[Title/Abstract] OR carotid stiffness[Title/Abstract] OR aortic stiffness[Title/Abstract] OR pulse pressure[Title/Abstract]).

The studies were restricted to those written in the English language. The list of titles and abstracts was initially screened for relevance by the two review authors (ALG and GM). We then selected original articles that were full-length publications in peer-reviewed journals. In addition, the reference lists of selected articles were also manually reviewed. Any disagreements were resolved by discussion, or by involving a third review author (CM). Articles were excluded if any of the following criteria were present: (a) lacking of a healthy control group; (b) article based on animal studies; (c) article based on *in vitro* or experimental model-based studies; or (d) review (e) case report (f) poster abstract.

The preliminary search by using the research strategy retrieved 58 articles. Out of these, 27 articles were excluded after

judgment of their eligibility according to screening of titles and abstracts; in details, 7 articles were excluded as they were case-reports, 6 articles due to lacking of investigation on AS, 4 due to no full text available ("poster abstract", "focus imaging", "letter", "comment on"), 8 as they were review articles, 1 study was a study protocol for a randomized controlled trial, 1 study included pediatric patients. A total of 31 studies were eligible for the present systematic review.

RESULTS

Takayasu Arteritis

Takayasu's arteritis (TAK) is a chronic vasculitis of unknown etiology with a predilection for the major elastic arteries such as the aorta, its main branches and the pulmonary arteries (41, 42). The media and the adventitia of the arterial walls are predominantly involved, with intimal thickening and arterial occlusions as important late phenomena (42, 43). During the early active stage of the disease, arterial biopsy shows granulomatous inflammation and patchy destruction of the medial musculoelastic lamellae (41, 44). Later the microscopic changes become nonspecific and consist of sclerosing arteritis, fibrous intimal hyperplasia, medial scarring and adventitial fibrosis (43, 45). TAK patients had a higher prevalence of cardiovascular risk factors, and dramatically experienced more CVE, when compared to the general population (46, 47). Inflammatory response and platelet hyperactivity both contribute to increasing the risk of acute CVE (48, 49). Coronary artery disease has been reported to be present in 10–20% of TAK patients, and cerebrovascular disease could occur in 10% of TAK patients (50, 51).

For the first time, Raninen reported in 2002 that 16 patients with TAK presented with an increased AS with respect to 16 age and sex matched controls. They used Peterson's elastic modulus (that estimates vascular stiffness without taking into account the influence of wall thickness), the Young's modulus (that may reflect the true elastic characteristics of the arterial wall better because wall thickness is included in the calculation) and thee stiffness index beta as markers of AS, in order to obtain a pressure-independent estimation of arterial distensibility. All indices of carotid artery stiffness were increased in the TAK group as compared to healthy subjects. The indices of femoral artery stiffness were also higher in patients with TA, even though the difference in the stiffness constant b was not statistically significant (52).

Ng enrolled 10 patients with TAK and 11 woman as healthy controls. Mean PWV-CF was higher among TAK patients. In contrast, there was no difference between the two groups in PWV-CR. The mean estimated carotid AI and aortic AI derived from the radial artery was higher in TAK patients compared with controls. Both PWV values did not correlate with CRP or ESR, nor with clinical disease activity. No difference between active and inactive disease regarding PWV was reported; indeed, this could be due also to the diagnosis of TAK, often late, when an irreversible structural damage to the vasculature is already established. Furthermore, the available clinical criteria of disease activity, including CRP and ESR, may be not so accurate. The multiple regression model estimating the dependence of PWV-CF from SBP, DBP, BMI, and also the diagnosis of TAK, suggested DBP, BMI and TAK as potential contributors, but not SBP. Accordingly, TAK seems to contribute significantly to the increase in PWV-CF (53).

Salles Rosa Neto analyzed CF-PWV in 27 female patients compared to 27 controls, reporting increased AS in TAK disease. PWV values were not correlated with ESR, CRP, cumulative dose of steroid, ejection fraction, or lipid levels; indeed, vascular procedure only was significantly associated with CF-PWV, whereas no association was observed as regards disease activity, history of HTN, or disease duration. The multivariate linear regression model showed that age, mean BP, and TAK explained the 93.8% variability of the PWV (54).

Liu et al. recruited seventy-two patients with TAK. Twenty-four patients were classified into the high-ba-PWV group. BMI, SBP, DBP, mean blood pressure, plasma NT-proBNP levels and total cholesterol levels were significantly higher in the high-baPWV group than in the low-ba-PWV group. Ba-PWV values were significantly higher in the patients with active disease than in those in remission. However, there were no significant correlations between the ba-PWV values and inflammatory markers. A stepwise multiple linear regression analysis showed that the mean blood pressure, age, and BNP levels were independently associated with the ba-PWV values in TAK after adjusting these parameters for the body mass index, total cholesterol level and use of calcium channel blockers and statins (55).

Wang et al. evaluated 48 TAK coronary artery disease patients, and they found increased ba-PWV in TA-related CAD as compared with CAD patients. CAD patients had atherogenic lipid profiles, including higher levels of low-density lipoprotein cholesterol. In the multiple regression analysis ba-PWV was independently associated with the severity of TAK in patients with coronary artery involvement, even after adjusting the confounding factors (such as age, BMI, total cholesterol, and systolic blood pressure). Multiple linear regression analysis suggested ba-PWV as independent predictor of the extent of CAD, assessed by SYNTAX score in TAK patients. In the multivariate logistic regression analysis, the significant independent determinant of in-stent restenosis was a ba-PWV of 17.00 m/s or higher; the multivariate Cox proportional hazards model confirmed a ba-PWV of 17.00 m/s or higher an independent predictor of MACE. Authors concluded that increased AS assessed by ba-PWV would be of great clinical value to identify TAK patients with drug-eluting stent who have a high risk for in-stent restenosis and MACE (56).

Yang et enrolled 15 tan patients and 15 matched controls; the patients with TAK had a higher PWV-CF value measured by echocardiography, compared with healthy controls. The echocardiographic measured PWV-CF was significantly dependent on the TAK, age and pulse pressure. PWV-CF did not correlate with the echocardiographic measured cardiac systolic and diastolic parameters and the laboratory variables in TAK patients (57).

Yurdakul included 33 patients with TAK, 18 patients with SLE; and 20 age- and sex-matched control subjects. Aortic

strain and distensibility were decreased, whereas aortic stiffness was markedly increased in patients with TAK. There was no difference in aortic strain and stiffness measurements between the SLE group and the control group, while aortic distensibility was impaired in both groups (58).

He et al. analyzed 240 patients with TAK of which 74 had cardiovascular disease. They found that increased ba-PWV was independently associated with CVE and the strongest determinants for ba-PWV in TAK were age, angiographic type V, mean blood pressure, renal dysfunction, hyperlipidemia. The ROC curve analysis estimated 16.26 m/s as optimal cut-off value of ba-PWV for CVE (area under the curve: 0.672, 95% CI: 0.594–0.750, $p < 0.001$; sensitivity and specificity were 45.9 and 83.7%, respectively). Increased ba-PWV was independently associated with CVEs in patients with TAK, therefore according to this study higher ba-PWV may be a potential marker to predict CVE in TAK (59).

In another study 67 patients with TAK and 67 age and sex matched healthy controls were recruited. Patients with TAK were grouped according to disease activity. ba-PWV was significantly higher in the patients with TAK than in the healthy subjects, and it was also significantly higher in the patients with inactive TAK than in the healthy subjects; moreover, ba-PWV was significantly higher in the patients with active TAK than the patients with inactive TAK. In the multiple linear regression analysis estimated with ba-PWV as dependent variable, TAK, and MAP were significantly associated with ba-PWV also after adjusting for confounder (age, SBP, DBP, PP, BMI, HR, total cholesterol, HDL, and LDL). No significant associations between ba-PWV and ESR or CRP were found in overall patients with TAK, and in patients with active or inactive TAK. However, in patients with TAK without immunosuppressive therapy, ba-PWV was significantly correlated with CRP, but not with ESR. The AS as measured by ba-PWV is significantly increased in patients with TAK, likely correlated with systematic inflammation, and it is significantly associated with TAK disease activity probably serving as an independent predictor of active TAK (60).

In conclusion, all the above studies reported an increased arterial stiffness in TAK and in some studies one of the principle factors influencing the arterial stiffness measurement was the disease itself proving a role of inflammation in accelerated atherosclerotic process in this conditions.

ANCA Vasculitis

ANCA-associated vasculitides (AAV) are a heterogeneous group of systemic diseases characterized by inflammation of small- and medium-sized vessels, variably associated with ANCA directed against PR3 or MPO (61, 62). Among AAV, GPA (formerly Wegener granulomatosis) and MPA are the two most common subtypes and, together with EGPA, (formerly Churg-Strauss syndrome) account for an estimated combined prevalence of 42.1 per 100,000 adult population in the United States (63). A well-established long-term complication of many inflammatory diseases is premature atherosclerosis and CVE (64). A high incidence of cardiovascular events has also been reported in AAV (65, 66); therefore, the most recent EULAR guidelines for AAV recommend periodic assessment of cardiovascular risk in AAV patients (67).

Booth (68) enrolled 31 patients (15 with active AAV) and the 32 matched controls; disease subgroups included Wegener's granulomatosis (n 23), microscopic polyangiitis (n 4), and Churg-Strauss disease (n 4). AIx and PWV were higher as compared to controls, and both these AS parameters were correlated to CRP. PWV was positively associated with increasing age and blood pressure, whereas AIx was positively associated with female sex and MAP, but negatively associated with heart rate. No correlation was found between AS parameters and ANCA levels, disease duration, organ involvement and severity (serum creatinine), or prednisolone dose.

Yildiz (69) enrolled 5 patients with GPA and reported that PWV-CF were increased in patients with GPA as compared with control group. Although they found a positive correlation between PWV and heart rate, they did not find any significant correlation between PWV and anthropometric or other hemodynamic parameters. In addition, they described a positive correlation between PWV and ESR in patients with GPA.

In another study from Netherland, 40 ANCA vasculitis patients were enrolled and compared to 38 controls. Femoral PWV was comparable between AAV patients and controls, as was radial PWV. However, when PWV values were corrected for MAP, femoral PWV was higher in AAV patients. In addition, radial MAP-corrected PWV was higher in patients with AAV. Furthermore, PWV measurements did not differ between patients with a high or low percentage of CD4+CD28^{null} T cells (70).

CD4+ T cells not co-expressing the co-stimulatory molecule CD28 (CD4+CD28^{null}) are acknowledged as potential players in accelerating the atherosclerotic processes, also in patients with AAV; this subset of T cells in fact was found preferentially in unstable rather than stable atherosclerotic plaques, and also they have been shown to exhibit endothelial cytotoxicity in the context of acute coronary syndrome and AAV in *in vitro* assays. These evidences may suggest a direct involvement in plaque disruption (71).

Chanouzas et al. (72) enrolled 56 patients diagnosed with ANCA vasculitis, of which 34 were PR3 positive, and 18 MPO positive. Also for this study, CD4^{+}CD28^{null} T cells were evaluated. The univariable analysis showed that age, percentage of CD4^{+}CD28^{null} T cells, plasma concentration of TNF, and blood pressure parameters were associated with increased PWV. Furthermore, the multivariable linear regression model demonstrated that the percentage of CD4^{+}CD28^{null} T cells were associated with increased AS independently of age, proteinuria, peripheral MAP, and plasma concentration of TNF. A PWV increase of 0.66 m/s for each 10% increase in CD4^{+}CD28^{null} T cells was reported. This relationship did not change when systolic blood pressure or pulse pressure was replaced by MAP, and the size of the CD4^{+}CD28^{null} T-cell expansion remained independently associated with increased PWV.

Forty four patients (21 men and 23 women) diagnosed with GPA and 53 controls matched for age, sex, BMI and typical risk factors for cardiovascular diseases (22 men and 31 women) were enrolled in the study by Pacholczak et al. (73). Aortic stiffness

was similar between GPA patients and controls, and it was negatively associated with blood leukocyte count and CRP levels. Comorbidities and medication had no impact on aortic stiffness.

In conclusion, a definite role of AS measurements in ANCA vasculitis is not clear, in fact only in two studies AS values were higher compared to controls, in particular after adjusting for confounders while in others studies AS was similar to controls. None of the above-mentioned trials analyzed the impact of the disease activity nor the early and late phase of the disease in assessing AS or the limited and diffuse GPA, therefore further studies are needed to assess AS in ANCA vasculitis.

Behcet Disease

Behcet's syndrome (BS) is a chronic, multisystem disorder characterized by genital and oral aphthae, skin lesions, and uveitis (74). BS is characterized by the contemporaneous involvement of both arteries and veins of all sizes, and presents a unique tendency for aneurysm formation (75). Within BS, patients suffering from recurrent inflammatory thromboses involving the venous and, more rarely, the arterial vasculature constitute a specific cluster, called the "vascular cluster" or "Angio-Behcet" (76). Arterial involvement is considered an uncommon vascular feature of BS, although BS could induce aneurysms affecting peripheral, visceral and pulmonary arteries. The simultaneous occurrence of arterial pulmonary aneurysms and peripheral venous thrombosis is the hallmark of Hughes–Stovin syndrome, which is to date considered by some authors as a clinical variant of Angio-Behcet (75, 77). The vascular involvement in BS has a major impact on morbidity and long-term mortality, and has been identified as the leading cause of death in these patients (78).

Kurum et al. (79) analyzed 14 patients with Behcet matched with 28 controls; oral aphthae (in 14 patients, 100%), genital ulcers (11, 84.6%), erythema nodosum (7, 50%), uveitis (7, 50%), arthritis (5, 35%), deep venous thrombosis (4, 33.3%), and neurologic involvement (3, 23.3%) were detected over the entire disease duration. Similar values of PWV were found in patients and controls; in addition, no correlation between duration of disease and PWV was found. Differences of mean PWV of the patients who did and did not have genital ulcers or erythema nodosum or eye involvement or deep vein thrombosis or neurologic involvement were not found to be statistically significant.

Protogerou et al. (80) selected 47 patients made up the study population, 11 of whom had active BD, defined as having at least two symptoms according to the ISG criteria. No sign of clinically active vascular disease was present in any patient at the time of the vascular tests. Subjects with active BD ($n = 11$) had lower AIx and central systolic blood pressure (CSBP), but similar peripheral blood pressure, stroke volume, and slightly higher local aortic stiffness in comparison to patients with inactive BD ($n = 36$). Lower AIx was found in patients with active BD compared to those with inactive disease; we also found that AIx in patients with inactive BD had a trend to be higher compared to the control group. The differences in central SBP and AIx were not affected after adjustment for age, sex height and heart rate.

Tunc et al. (81) included 26 patients with BD compared to 20 controls, finding beta aortic stiffness values higher than controls.

Rhee et al. (82) enrolled 41 patients with Behcet matched with 53 controls. All patients with Behcet had an increased beta stiffness compared to controls; furthermore, patients with peripheral arthritis exhibited a higher Beta stiffness than those without peripheral arthritis. In addition, a positive relationship between age of onset and beta stiffness was also noted in linear regression analysis.

Protogerou et al. (83) reported that aortic stiffness evaluated by AI in patients with Behcet was similar to the control group; however, BD patients taking corticosteroids showed values lower than those without corticosteroids and similar to controls, while BD patients not taking corticosteroids showed aortic AI values higher than controls. The negative association between corticosteroids administration and aortic AI was maintained also after adjustment for heart rate, age, gender, blood pressure, reflected wave time transit, height, and cholesterol. Authors suggested a role of inflammation or immuno-modulatory mechanisms in the regulation of pressure wave reflections.

Kobacay et al. (84) found that PWV was higher in rheumatoid arthritis, systemic lupus erythematosus, and Behcet's disease groups as compared to the control group. However, when all variables were included in the regression analysis only age was found to affect PWV independently.

Caldas et al. (85) found that 23 BD patients had significantly higher PWV values as compared with 23 controls. Moreover, the 15 BD patients presenting with systemic disease had PWV values significantly higher than those with exclusive muco-cutaneous manifestations. BD patients with vascular involvement had higher total and LDL cholesterol levels, but similar PWV compared to those without vascular involvement. The bivariate analysis within the BD group demonstrated significant correlations between PWV and systolic and diastolic blood pressure, BMI, total cholesterol, and triglycerides, but triglycerides only were independently associated to PWV in the multivariate linear regression analysis.

Balta et al. (86) evaluated PWV in 36 patients with Behcet compared to 35 controls. AS was higher in patients with BD compared with control group and AS correlated positively with age, the duration of disease, BMI, total cholesterol and Mean Platelet Volume levels in patients with BD.

Yilmaz et al. (87) recruited 96 patients with BD. Each subject was evaluated in active and inactive disease periods. For the control group, 54 healthy age- and sex-matched subjects were enrolled. 24-h PWV was positively correlated with age, duration of BD, weight, BMI, fasting blood glucose, total cholesterol, and LDL-C values. Linear regression analysis assessed that 24-h PWV was positively correlated with age and duration of BD. There were statistically significant differences between the control group and patients with inactive and active BD in terms of 24-h PWV, day PWV, night PWV, day central DBP in this study ($p < 0.05$). No significant difference between the control group and patients with inactive and active BD in terms of 24-h MBP, central SBP, central DBP, and AIx in this study ($p > 0.05$). Patients with active BD had higher PWV values than patients with inactive BD and the controls. According to the vascular function parameters of patients with active and inactive BD, 24-h PWV (6.16 ± 1.26 vs. 5.58 ± 0.73, $p < 0.012$), day PWV (6.22 ± 1.27 vs. 5.63

± 0.74, $p < 0.011$), and night PWV (6.06 ± 1.30 vs. 5.49 ± 0.74, $p < 0.015$) were higher in patients with active BD than in patients with inactive BD. Other vascular function parameters did not differ between the two groups. This may be explained by more prominent inflammatory changes in the vascular wall in the active disease period.

Celik et al. (88) enrolled 96 BD patients and 60 controls. They evaluated the 24 h profile of blood pressure, AIx and PWV, finding that worse PWV an AIx indices were correlated with the non-dipping status. Authors concluded that non-dipping status and AS may concur to exacerbate the harmful effects on cardiovascular system also in BD, and that these aspects should not be overlooked during the follow-up evaluations of patients with Behcet's disease in addition to conventional risk factors.

Yildirim et al. (89) enrolled 30 patients with BD compared to 30 controls. PWV was 6.35 ± 1.05 m/s in BD group and 5.75 ± 0.83 m/s in control group, and the difference between the two groups was statistically significant. In addition, they found no difference regarding PWV in patients with systemic disease compared to patients with muco-cutaneous involvement. Even in the absence of major atherosclerotic risk factors, BD patients might be at a higher risk for development of atherosclerosis and endothelial dysfunction compared with healthy subjects.

Yolbas (90) compared 49 BD patients to 64 rheumatoid arthritis and 40 controls. The author did not find any difference regarding beta stiffness, also considering active and non-active BD patients or BD patients actively smoking, and there was no correlation with disease activity. In addition, patients with a pathergy reaction have lower arterial distensibility, Young and Peterson elastic modulus.

Ozdemir (91) enrolled 68 patients compared to 40 controls. The authors further divided BD patients according to homocysteine levels in group 1: with homocysteine >15 μmol/L and group 2: homocysteine <15 μmol/L. Both BD patient subgroups beta stiffness indices higher than controls (group 1: 3.73 ± 0.45 and group 2: 3.33 ± 0.24 vs. healthy control group: 3.07 ± 0.17, $p < 0.001$, respectively). Homocysteine level was positively correlated with carotid beta stiffness index ($r = 0.769$, $p < 0.001$), c-IMT ($r = 0.565$, $p < 0.001$) and disease duration.

Ozisler and Kaplanoglu (92) included a total of 33 BD patients (19 women and 14 men); the control group consisted of 33 sex-matched healthy individuals aged 23–58 years. The AS indices (left, right, and mean α- and β-stiffness indices, and the right, left and mean PWV values) they reported were significantly higher in the patient group; moreover, they found higher values in patients with major organ involvement with respect to those with muco-cutaneous involvement, although this difference was not statistically significant. They reported no significant correlation between ESR or CRP and AS parameters, both in the patient and control groups, and also when patients were subdivided according to systemic or muco-cutaneous involvement. Patients with muco-cutaneous involvement were assuming colchicine only, while patients with major organ involvement were receiving immunosuppressive therapy. Therefore, inflammatory status could be different according to treatment needs.

Ayar et al. (93) included 54 patients with BD (27 with Short Disease Duration—SDD and 27 with Long Disease Duration—LDD), and 34 healthy age and sex matched subjects. BSAS scores were not statistically different in patients with BD with SDD or LDD. AIx was significantly higher in all patients with SDD or LDD BD, as compared with controls. However, PWV values were reported not different between BD and controls. When patients with BD with SDD and LDD were compared with each other, PWV was significantly higher in patients with BD with LDD. There was a moderate correlation between PWV and disease duration. AIx was higher in patients with BD than controls regardless of disease duration.

Zencirkiran Agus et al. (94) enrolled 50 BD patients and 49 controls. Carotid-femoral (aortic) PWV was increased significantly in patients with BD as compared with control group, there were no connection between PWV and clinical manifestations. PWV was correlated with age, diastolic BP, mean BP, waist, waist/hip ratio and heart rate in patients with BD, but not with disease duration.

PWV, an ideal indicator of arterial stiffness, is increased in patients with Behcet's disease compared with the controls; furthermore, seem that some features of the disease for example active arthritis could influence AS status. In these studies authors found difference values of AS in patients with active or nor active disease or with long disease duration. Moreover, patients treated with steroids have a lower AI compared to non-treated patients. This data confirm the role on inflammation in driving atherosclerosis in BD. Prospective trials in a large population should be carried out to evaluate the prognostic implications of increased arterial stiffness in BD.

STRENGHTS AND LIMITATIONS

The strength of this review is the evaluation of several studies regarding arterial stiffness in vasculitis covering a long period of time. Moreover, we have pointed out that the measurement of arterial stiffness is a valid method to determine the atherosclerotic burden in patients with vasculitis and it could have a potential role as a screening test also in patients with rheumatic conditions. In fact, PWV might be a easier-to-assess and reproducible marker of early atherosclerosis.

The limitations is that PWV and AIx measurement may be influenced by many confounding factors, significantly limiting reproducibility of arterial stiffness assessment and, in turn, the relevance of our results; in fact the heart rate may affect results, and, with the only exception of AIx@75, all the other outcomes have not been standardized to a specific heart rate. In general population PWV is a surrogate of clinical CV events but in patients with vasculitis, there are no data to suggest whether PWV is a good surrogate of future CVD events. Moreover, the differences among assessment techniques and devices could limit the validity of arterial stiffness parameters as markers of early atherosclerosis and therefore caution is necessary in overall results interpretation.

CONCLUSION

Vasculitides are a group of several diseases affecting the cardiovascular system. These disorders lead to premature atherosclerosis, increasing morbidity and mortality and worsening the prognosis; furthermore, they may involve the heart too, due to the extension of the inflammatory process they cause also in the coronary vessel wall and eventually in the heart, including pericardium, myocardium and conduction system. Cardiovascular events are increased in all the major subtypes of systemic vasculitis. Vascular properties impairment, as measured by PWV, is observed in most subtypes of vasculitis, and in particular during active disease, but evidence of accelerated atherosclerosis is reported in Takayasu's arteritis only, and in ANCA-associated vasculitides. The increased CV event rate observed in patients with vasculitis is likely due to the contribution of active vasculitis, persistent endothelial dysfunction—also causing a prothrombotic state, and accelerated atherosclerosis. Early treatment and adequate control of vasculitis is crucial to minimize inflammation and to prevent vascular damage. The findings summarized in this review underline the importance of an effective treatment of conventional CV risk factors, and call for additional investigation of ways to mitigate the risk excess. How much the anti-inflammatory therapies used to treat rheumatic diseases may improve CV outcomes is unknown so far, and it requires further study. Additional, rigorous, clinical trials are required to develop and validate novel biomarkers to stratify CV risk and to support the intensity of therapy required to improve the prognosis of patients with rheumatologic diseases, also through an evidence-based approach. These strategies should help to avoid complications associated with unnecessary invasive evaluation, prevent over-testing, and minimize imaging radiation exposure, as well as save healthcare resources.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AL and GM: conceptualization. LR and PM: methodology. AL, CG, and GM: validation. CM and LR: investigation. CG and PM: data curation. AL, CM, and GM: writing—original draft preparation. CS and GS: writing—review and editing. GM: final supervision. AL and GM: revision and final acceptance. All authors have read and agreed the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.824630/full#supplementary-material

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Increased Cardiovascular Risk in Psoriatic Arthritis: Results From a Case-Control Monocentric Study

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Background: Psoriatic arthritis (PsA) is associated with increased cardiovascular morbidity and mortality. The aims of our real-life study were to compare the prevalence of cardiovascular risk factors (CVRFs) and cardiovascular events (CVEs) among patients with PsA with a control population, to evaluate the impact of correcting factors in equations that assess cardiovascular risk (CVR) in PsA, and to determine the percentage of patients who reach the LDLc target as indicated by the European guidelines.

Methods: In this observational cross-sectional monocentric case-control study, we used a standardized procedure to systematically assess patients with PsA aged 25–85 years who met the Classification for Psoriatic Arthritis (CASPAR) criteria. Controls were extracted from the MOnitoring NAtionaL du rISque Artériel (MONALISA) study. We compared the prevalence of CVRFs, CVEs, the CVR, and the percentage of patients reaching recommended LDLc target in both populations. The CVR was first assessed using SCORE and QRISK2 equations. Then, the SCORE equation was corrected by applying a 1.5 multiplication factor, as recommended by EULAR for rheumatoid arthritis (SCORE-PsA), and the QRISK2 was corrected using the "rheumatoid arthritis" item (QRISK2-PsA).

Results: A total of 207 PsA and 414 controls were included. CVRFs and CVEs were more frequent in the PsA group. After controlling for age and gender, atherothrombotic disease was increased in the PsA population (SCORE $p = 0.002$, QRISK2 $p = 0.001$). Using the SCORE-PsA increased the percentage of patients with a high or very high CVR from 39.3 to 45.3% in the PsA group. Similarly, using the QRISK2-PsA increased the percentage of patients with a CVR $\geq$ 10% from 44.9 to 53.2%. The percentages of patients with PsA with high LDLc in the high and very high CVR groups were not significantly different from controls, despite a trend in favor of patients with PsA. Of the

83 PsA with a QRISK2 ≥ 10%, only 22.9% were treated with statin vs. 35.8% of the 134 controls. The QRISK2-PsA score did not alter these results.

Conclusion: In real-life, patients with PsA have a higher prevalence of CVRFs, as well as a higher prevalence of CVEs compared to the general population. The CVR is higher in the PsA population than in the controls either using the SCORE and QRISK2 equations or using the corrected SCORE- PsA and QRISK2-PsA equations.

Keywords: psoriatic arthritis, cardiovascular risk, cardiovascular events, dyslipidaemia, statins

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease that affects 0.19% of the European population (1). Since 2016, the European Cardiology Association guidelines have included auto-immune inflammatory diseases as an inherent cardiovascular risk factor (CVRF) (2). As is the case with rheumatoid arthritis (RA) (3, 4), many studies have shown an increase in cardiovascular mortality and morbidity (4–6) and more traditional CVRFs in patients with PsA (5–10). Therefore, control of CVRFs is essential. This is exemplified by the decrease in cardiovascular events (CVEs) in RA and patients with PsA treated with statins (11, 12).

The aims of this study were (i) to compare the prevalence of CVRFs and cardiovascular events (CVEs) in patients with PsA and in matched controls from the general population; (ii) to compare the cardiovascular risk (CVR) in both populations with SCORE and QRISK2 equations with or without taking into account the additional risk attributable to PsA; (iii) to compare the proportion of individuals in both populations who reach the recommended low density lipoprotein cholesterol (LDLc) level according to the SCORE equation, and the proportion of individuals treated with statins according to the National Institute for Health and Care Excellence (NICE) recommendations.

MATERIALS AND METHODS

Patients and Controls

Adults with PsA from our Rheumatology Centre (Toulouse University Hospital) who meet the CASPAR criteria were consecutively recruited in this observational cross-sectional case–control study from March 2016 to January 2017 (13).

The control population was from the French MONALISA (14) study, the main objective of which was to estimate the prevalence of CVRFs among adults who were 35–74 years old from 3 French regions. The pairing process included subjects living in the region of our Rheumatology center (Occitanie, France). Controls were paired with cases at a 2:1 ratio, considering gender and age (±2 years).

Ethics

Participants in this study gave their written informed consent. The study was approved by the local Toulouse University Hospital ethics committee (n°07-0316).

Data Collection

Patients were assessed according to a standardized procedure including a questionnaire, a physical examination by the patient's usual rheumatologist, and biological tests. All collected data were computerized and anonymized for analysis.

The questionnaire collected data on (i) PsA characteristics: CASPAR criteria, ACPA (anti-citrullinated peptides antibodies) positivity, medication, and (ii) CVRFs: familial first-degree myocardial infarction or sudden death before the age of 55 in men and 65 in women, diabetes with its treatment and duration, smoking with cessation date and consumption, hypertension (HT) and its treatment, history of CVE with its treatment, and dyslipidaemia and its treatment.

Physical examination included blood pressure measurement after 5 min of rest, twice, with a 5-min interval, sitting or lying down, with an automatic device. We recorded the highest value. We also recorded size, weight, body mass index (BMI), and waist size.

A biological assessment was performed by the patient's usual laboratory and included fasting blood sugar, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine, and glomerular filtration rate, total cholesterol, HDL cholesterol, and triglycerides. LDLc was calculated with the Friedewald formula.

In the control population from the French MONALISA (14) study, each event reported by the subject during the interview was checked using the population register of ischemic heart disease, which has been active in the region since 1984.

Definitions

Hypertension was defined as a history of HT, or use of antihypertensive treatment, or blood pressure ≥ 140/90 mmHg during our standardized examination. Diabetes was defined as a history of type 1 or type 2 diabetes mellitus, or the use of antidiabetic treatment. Dyslipidaemia was defined as a history of dyslipidaemia, or use of lipid-lowering treatment, or abnormal lipid levels. Metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (15). CVEs included myocardial infarction, stroke, and obliterating arteriopathy of the lower limbs (OALL).

Evaluation of the Cardiovascular Risk

The CVR was first assessed using SCORE and QRISK2 equations (16). Given the absence of any published equation to assess CVR with the QRISK2, we used the online calculator available at

https://www.qrisk.org/2016/. Calculation was performed twice for each case and control.

Then, the SCORE equation was corrected by applying a 1.5 multiplication factor as recommended by the European League Against Rheumatism (EULAR) for rheumatoid arthritis patients (SCORE-PsA) and the QRISK2 equation was corrected using the "rheumatoid arthritis" item (QRISK2-PsA) (17). In addition, we performed a specific evaluation of the cardiovascular risk according to the SCORE-PsA equation, in the subset of patients aged 40–65 years, the SCORE equation being validated in this age stratum.

Statistical Analysis

Univariate analysis described data with mean, extreme values standard deviation (SD) for quantitative parameters, and frequency for categorial data. Homoscedasticity and normality were tested and showed that logarithmic transformation was necessary for the following covariates to reach normality and to stabilize variances: triglycerides concentration, systolic blood pressure, blood glucose level, and CRP. The bivariate analysis considered the 2:1 pairing, each matched pair was considered as an extreme stratified sample, each stratum corresponded to the two subjects of the same pair.

A conditional logistic regression was used to test differences in categorial covariates between cases and controls. Considering each pair as independent, we used mixed linear models to compare quantitative covariates between cases and controls, each pair being considered as random. The calculated scores were represented according to decile distribution and cumulated frequencies. The significance threshold was $p < 0.05$. The analysis was performed with the software SAS version 9.4 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Subject Characteristics and Prevalence of Cardiovascular Risk Factors

The main characteristics of the 207 cases and 414 controls are shown in **Table 1**. The mean age and the gender ratio in both populations were not statistically different.

Compared to controls, patients with PsA had a higher CVRFs (BMI, prevalence of HT, triglycerides, CRP, prevalence of smoking, and prevalence of metabolic syndrome). We observed a non-significant trend for a higher prevalence of diabetes (12.1 vs. 7.7%, $p = 0.09$).

In addition, compared to controls, patients with PsA had lower LDLc (g/L; 1.26 ± 0.38 vs. 1.43 ± 0.35, $p < 0.001$), HDLc (g/l; 0.54 ± 0.14 vs. 0.59 ± 0.14, $p < 0.001$), total cholesterol (g/l; 2.04 ± 0.43 vs. 2.23 ± 0.38, $p < 0.001$), serum creatinine (μmol/L; 73.4 ± 17.7 vs. 86.5 ± 14.9, p < 0.001), and prevalence of dyslipidaemia (25.1 vs. 42%, $p = 0.001$).

TABLE 1 | Characteristics of patients with psoriatic arthritis (PsA) and controls.

	PsA ($n = 207$)	Controls ($n = 414$)	*P*-value
Age, years, mean (SD)	54.7 (11.4)	54.8 (10.7)	NS
Women, n (%)	100 (48.3)	200 (48.3)	NS
Disease duration, years, mean (SD)	11.9 (8.5)	NA	
BMI, kg/m^2, mean (SD)	26.6 (4.9)	25.2 (4)	0.001
Systolic blood pressure, mmHg, mean (SD)	134 (15)	129 (22)	0.001
Diastolic blood pressure, mmHg, mean (SD)	79 (11)	80 (12)	0.27
Triglycerides, g/L, mean (SD)	1.24 (0.72)	1.06 (0.63)	0.001
LDLc, g/L, mean (SD)	1.26 (0.38)	1.43 (0.35)	0.001
HDLc, g/L, mean (SD)	0.54 (0.14)	0.59 (0.14)	0.001
Total cholesterol, g//, mean (SD)	2.04 (0.43)	2.23 (0.38)	0.001
Blood sugar, g/L, mean (SD)	1.00 (0.28)	0.99 (0.17)	0.65
CRP, mg/L, mean (SD)	7.0 (14.4)	1.8 (1.9)	0.001
Serum creatinine, μmol/l, mean (SD)	73.4 (17.7)	86.5 (14.9)	0.001
Creatinine clearance MDRD, ml/min/m^2, mean (SD)	91.9 (18.9)	88.3 (17.7)	0.03
HT, n (%)	71 (34.4)	109 (26.3)	0.03
HT treatment, n (%)	64 (30.9)	73 (17.6)	0.001
Diabetes, n (%)	25 (12.1)	32 (7.7)	0.09
Diabetes treatment, n (%)	24 (11.6)	24 (5.8)	0.02
Dyslipidaemia, n (%)	52 (25.1)	174 (42.0)	0.001
Dyslipidaemia treatment, n (%)	30 (14,4)	93 (22.5)	0.14
Smoking			0.04
Never, n (%)	87 (42.0)	199 (48.1)	
Current, n (%)	50 (24.2)	66 (15.9)	
Past, n (%)	70 (33.8)	149 (36.0)	
Metabolic syndrome, n (%)	59 (28.4)	48 (11.6)	0.001
Family history of CVE, n (%)	29 (14.0)	65 (15.7)	0.57
NSAID, n (%)	87 (42.2)	26 (6.3)	0.001
Steroids, n (%)	20 (9.7)	7 (1.7)	0.001
csDMARD, n (%)	112 (54.1)	0 (0)	
bDMARD, n (%)	137 (66.2)	0 (0)	
No DMARD, n (%)	9 (4.3)	382 (92.3)	
Antiplatelet agent, n (%)	17 (8.2)	24 (5.8)	0.23
Anticoagulant, n (%)	7 (3.4)	2 (0.5)	0.02
β-blocker, n (%)	27 (13.0)	35 (8.5)	0.07
ACEi/ARB, n (%)	39 (18.8)	45 (10.9)	0.005

PsA patients and controls were paired according to age and gender. PsA, psoriatic arthritis; NA, not applicable; NS, non-significant BMI, body mass index; LDLc, low density lipoprotein cholesterol; HDLc, high density lipoprotein cholesterol; CRP, C reactive protein; MDRD, modification of diet in renal disease; HT, hypertension; NSAIDs, non-steroidal antiinflammatory drugs; csDMARD, conventional synthetic Disease Modifying Antirheumatic Drug; bDMARD, biological DMARD; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptors blocker; SD, standard deviation.

Prevalence of Cardiovascular Events

The prevalence of myocardial infarction, stroke, and OALL was numerically higher, without statistically significant difference, in patients with PsA (**Table 2**), with, respectively 5.8% vs. 2.9% ($p = 0.08$); 2.4% vs. 1% ($p = 0.18$), and 1.5% vs. 0.5% ($p = 0.23$). Overall, CVE was significantly more frequent in the PsA group (8.7% vs. 4.1%, $p = 0.03$).

TABLE 2 | Prevalence of cardiovascular events in patients with PsA and controls.

	PsA ($n = 207$)	Controls ($n = 414$)	*P*-value
MI, n (%)	12 (5.8)	12 (2.9)	0.08
Stroke, n (%)	5 (2.4)	4 (1.0)	0.18
OALL, n (%)	3 (1.5)	2 (0.5)	0.23
CVE, n (%)	18 (8.7)	17 (4.1)	0.03

MI, myocardial infarction; OALL, obliterating arteriopathy of the lower limbs; CVE, cardiovascular events.

Cardiovascular Risk Assessment With the SCORE and SCORE-PsA Equations

The CVR was estimated for the entire PsA ($n = 201$) and control population ($n = 402$) using the SCORE and the corrected SCORE-PsA equation applying the 1.5 factor recommended by EULAR for RA patients (**Table 3** and **Supplementary Figure 1**) (17). We used a similar approach for the 145 patients with PsA and 286 controls aged 40–65 years (**Table 3** and **Supplementary Figure 2**). The analysis revealed an additional 10-year risk of global cardiovascular mortality in patients with PsA compared to controls, both in the entire population and in patients 40–65 years old, with both the SCORE-PsA and SCORE equations.

Assessment of the Cardiovascular Risk With the QRISK2 and QRISK2-PsA Equations

The CVR was estimated for the entire PsA ($n = 186$) and control population ($n = 397$) using the QRISK2 and the corrected QRISK2-PsA equation applying the "Rheumatoid arthritis" item (**Table 4** and **Supplementary Figures 3, 4**) (17).

The QRISK2 equation highlighted an additional risk of death and CVE in patients with PsA compared to controls ($p < 0.001$). PsA, being considered a CVRF similar to RA, the proportion of patients with PsA with a CVR $\geq$ 10% (QRISK2-PsA) increases from 44.9 to 53.2% (**Table 4**). We observed a global shift in the distribution toward $\geq$ 10% categories. Overall, using QRISK2-PsA equation predicted a significantly higher risk, with a median score of 8.7 with QRISK2 and 11.3 with QRISK2-PsA ($p = 0.0248$).

TABLE 4 | Cardiovascular risk according to QRISK2 and QRISK2-PsA equations.

Risk	PsA ($n = 186$),%	Controls ($n = 372$),%	*P*-value
QRISK2			0.001
<5%	35.1	42.8	
5–9%	20	23.4	
10–19%	26	22.9	
≥20%	18.9	10.8	
QRISK2-PsA			0.001
<5%	29	42.8	
5–9%	17.7	23.4	
10–19%	24.7	22.9	
≥20%	28.5	10.8	

Patients Who Reach the Therapeutic Target According to the SCORE

We then estimated the achievement of the LDLc therapeutic target across the population of cases ($n = 201$) and controls ($n = 410$) or restricted to the population of cases ($n = 145$) and controls ($n = 286$) aged 40–65 years, based on the level of cardiovascular risk derived from the SCORE and SCORE-PsA equations (**Table 5**). Whether in patients with PsA or matched controls, only a small proportion of individuals achieved the LDLc therapeutic target, particularly for high and very high cardiovascular risk levels according to SCORE and SCORE-PsA equations.

Patients Who Reach the Therapeutic Target According to QRISK2

The proportion of cases and controls treated with statin according to the NICE recommendations was estimated for the total population of cases ($n = 186$) and controls ($n = 397$) based on the level of cardiovascular risk derived from the QRISK2 and QRISK2-PsA equations (**Table 6**). In both patients with PsA and controls, we observed a small proportion of individuals with $\geq$ 10% QRISK2 treated with statins (NICE recommendations): 19/83 (22.9%) in the PsA population vs. 48/134 (35.8%) in controls. The QRISK2-PsA score did not change these findings.

TABLE 3 | Cardiovascular risk according to the SCORE and SCORE-PsA equations.

Risk	PsA ($n = 201$),%	Controls ($n = 402$),%	*P*-value	PsA 40–65 ($n = 145$),%	Controls 40–65 ($n = 286$),%	*P*-value
SCORE			0.002			0.002
Low (<1%)	24.4	30.7		21.4	31.5	
Intermediate (1–4%)	36.3	39.0		43.4	46.5	
High (5–9%)	13.9	16.6		14.5	12.6	
Very high (≥10%)	25.4	13.7		20.7	9.4	
SCORE-PsA			0.001			0.001
Low (<1%)	24.4	30.7		21.4	31.5	
Intermediate (1–4%)	30.4	39		37.5	46.5	
High (5–9%)	17.9	16.6		20	12.6	
Very high (≥10%)	27.4	13.7		20.7	9.4	

TABLE 5 | Percentage of patients with PsA at LDLc target according to EU recommendations with SCORE equations.

Estimated risk	PsA ($n = 201$)	Controls ($n = 410$),%	*P*-value	PsA 40–65 ($n = 145$),%	Controls 40–65 ($n = 286$),%	*P*-value
SCORE						
<5%	122	286		94	223	
LDLc < 1.15 g/L (%)	50 (41.0)	63 (22)	0.002	39 (41.5)	36 (16.1)	0.001
5–9%	28	68		21	36	
LDLc < 1 g/L (%)	1 (3.6)	3 (4.4)	NS	0 (0)	2 (5.6)	NS
≥10%	51	56		30	27	
LDLc < 0.7 g/L (%)	7 (13.7)	2 (3.6)	NS	5 (16.7)	1 (3.7)	NS
SCORE-PsA						
<5%	110	286		86	223	
LDLc < 1.15 g/L (%)	46 (41.8)	63 (22)	0.002	36 (41.9)	36 (16.1)	0.001
5–9%	36	68		29	36	
LDLc < 1 g/L (%)	3 (8.3)	3 (4.4)	NS	2 (6.9)	2 (5.6)	NS
≥10%	55	56		30	27	
LDLc < 0.7 g/L (%)	7 (12.7)	2 (3.6)	NS	5 (16.7)	1 (1.7)	NS

DISCUSSION

This monocentric observational case–control study shows an increase in the prevalence of the main cardiovascular risk factors and an increase in the prevalence of cardiovascular events in patients with PsA compared to controls. The use of the SCORE and QRISK2 risk formulas, with or without RA additional cardiovascular risk adjustment factor (SCORE-PsA and QRISK2-PsA), show an increase in the cardiovascular risk level of patients with PsA as compared to controls. In both patients with PsA and controls, this study found very low proportions of individuals who meet the LDLc objective or who were treated with statins in accordance with the recommendations.

Our study found high triglycerides and significantly lower LDLc, HDLc, and total cholesterol compared to controls. A recent review of 6 studies comparing PsA lipid levels to controls showed the same dyslipidaemia profile as in our study (18). It is recognized that under inflammatory conditions, the production of proinflammatory cytokines alters lipid profile by decreasing HDLc and LDLc (19, 20). The precise mechanism is not understood. With the use of anti-TNF or anti-IL6 agents, the lipid profile of treated patients changes with an increase in total cholesterol, HDLc, and LDLc fractions, and possibly triglycerides (21). Despite this change in lipid profile with bDMARDs, there does not appear to be an additional cardiovascular risk (20, 22, 23).

TABLE 6 | Proportion of statin-treated cases and controls by cardiovascular risk level from the QRISK2 equation as per NICE recommendations.

	PsA ($n = 186$)	Controls ($n = 397$),%	*P*-value
QRISK2			
<10%	103	263	
With Statin (%)	5 (4.9)	33 (12.6)	0.05
≥10%	83	134	
With Statin (%)	19 (22.9)	48 (35.8)	NS
QRISK2-PsA			
<10%	87	263	
With Statin (%)	2 (2.3)	33 (12.6)	0.008
≥10%	99	134	
With Statin (%)	22 (22.2)	48 (35.8)	NS

This work also highlights an increased prevalence of hypertension in patients with PsA compared to controls. HT in PsA and RA is widely described in the literature with a prevalence ratio ranging from 1.3 to 1.9 depending on the study (5, 6, 24, 25). The increase in the prevalence of HT in PsA can be partly explained by a significantly higher BMI in rheumatism, as well as the existence of chronic systemic inflammation (7). In addition, DMARDs can also be a source of hypertension, e.g., NSAIDs and leflunomide (26).

Our data confirm the high prevalence of metabolic syndrome in PsA (27, 28). Since metabolic syndrome is a combination of cardiovascular risk factors, it is a marker of cardiovascular risk. Therefore, acting on this syndrome is important since it could influence the effectiveness of treatment. In fact, metabolic syndrome could be associated with a lower probability of obtaining low PsA activity with antiTNF agents (29).

A total of 5.8% of our PsA population had a history of coronary disease, 2.4% of ischemic stroke, and 1.5% of an arterial disease of the lower limbs, with a numerically higher, although not statistically significant, proportion in PsA compared with controls. On the other hand, the combination of these events reveals a significant additional risk of cardiovascular events in patients with PsA of 8.7% vs. 4.1% in controls ($p = 0.03$). Two other studies found a higher proportion of coronary events, ischemic strokes, and MACE in PsA compared to controls (4, 6), with significantly different results for only one of them (4).

Using the SCORE, our study found an additional risk of cardiovascular mortality in 10 years in patients with PsA as compared to controls. The corrected SCORE results (SCORE-PsA) highlight the additional cardiovascular risk in the PsA population. Two articles did not find this additional risk of cardiovascular mortality in PsA with the SCORE (6, 30). In the

study by Gulati et al., the lack of additional risk is explained by the similarity in risk factors between cases and controls. In the study by Rosales et al., the number of RA and controls was low (80 individuals in each group). Another study compared the cardiovascular SCORE levels in Ankylosing spondylitis (SA) and patients with PsA vs. patients with RA. It showed that cardiovascular mortality was significantly higher in RA than in SA, but found no difference between RA and PsA after age and gender adjustments (31). On the other hand, when the SCORE equation of RA was corrected by a factor of 1.5 according to the EULAR recommendations (17), SA and PsA had a significantly lower cardiovascular mortality risk than RA.

Although easy to use and reliable, the SCORE has limitations. First of all, it estimates a fatal cardiovascular risk and not an overall risk. Moreover, the age interval for the table is limited to 40–65 years, although in practice, it can be used outside these limits (2). In addition, the SCORE was created by combining patient cohorts from 12 European countries (16). The cohort was composed of patients recruited between 1967 and 1991 and is therefore outdated. Finally, it does not consider chronic inflammatory diseases as an independent cardiovascular risk factor.

With the QRISK2, our study revealed an additional risk of mortality and cardiovascular events in 10 years in our PsA population. We also applied the "rheumatoid arthritis" item in the QRISK2 calculator for our PsA population (QRISK2-PsA). This increased the proportion of patients with a cardiovascular risk $\geq$ 10%, eligible for statin treatment according to the NICE recommendations, from 44.9 to 53.2%. This proportion was higher than the real-life prescription in our center (22.9%). Algorithms to estimate CVR usually underestimate CVR in PsA. Published data on the adaptation of CVR equations are limited and need to be optimized for use in PsA (32–34). Since PsA has a previously established CV morbidity–mortality, it should be included in the QRISK2 algorithm as an independent risk factor, in the same manner as RA.

A small proportion of high-risk and very high-risk cases and controls were the goal for LDLc. However, the interpretation of these results should be conservative given the small number of individuals per group. To our knowledge, no study has attempted to assess the LDLc objectives in "real life" in inflammatory rheumatism. In common practice, in the general population, approximately 40% of patients meet the LDLc target (35, 36). Rollefstad et al. organized a therapeutic intervention program according to the CV SCORE level of patients followed for inflammatory rheumatism (RA, SA, and PsA) (37). This study showed that, with an adapted intervention program, 92.1% of RA patients, 90% of SA, and 82.9% of patients with PsA reached the target LDLc after 3 consultations.

The limitations of our study are the cross-sectional design, the small number of patients included related to the short duration of the patient inclusion period, as well as the monocentric design. Moreover, data collection using a questionnaire, although led by an experienced rheumatologist, could be a source of information bias. Finally, we did not stratify the results according to PsA or rheumatologic treatment activity levels which may have a direct impact on cardiovascular risk. The strengths of our study include (i) the matching of 1 case for 2 controls from the Occitanie region, (ii) the use of 2 equations to assess cardiovascular risk levels, and (iii) the application of corrective factors to the SCORE and QRISK2 equations to consider PsA as an inherent cardiovascular risk factor (similar to RA).

CONCLUSION

Our study shows an increase in the prevalence of traditional CVRFs, as well as a higher prevalence of CVEs in PsA. The CVR is higher in the PsA population than in the controls using either the SCORE and QRISK2 equations or the corrected SCORE- PsA and QRISK2-PsA equations. Finally, very few cases and controls at high or very high CVR reach the LDLc target and are treated with statins, which highlights the need for treatment optimization.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Toulouse University Hospital Ethics Committee (n°07-0316). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RK, JR, JF, and AC designed the study. RK collected the data. YD, RK, LZ, BJ, GC, JR, AR-W, JF, and AC analyzed and interpreted the data. All authors wrote and revised the manuscript and contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.785719/full#supplementary-material

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MINI REVIEW
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Cardiovascular Abnormalities in Juvenile Dermatomyositis: A Scoping Review for the Clinical Rheumatologists

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Juvenile dermatomyositis (JDM) is a common form of inflammatory myositis in children. Vasculopathy and endothelial dysfunction play significant roles in the pathogenesis of JDM. Cardiac involvement in JDM is often underestimated, and it may be a potential indicator of poor prognosis. Cardiac dysfunction in JDM can occur both in the acute and chronic stages of the disease. Amongst the acute complications, acute congestive heart failure (CHF), myocarditis, arrhythmia, and complete heart block are common. However, these remain unrecognized due to a lack of overt clinical manifestations. Increased rates of cardiovascular abnormalities have been noted with anti-SRP and anti-Jo 1 auto-antibody positivity. Long-term follow-up studies in JDM have shown an increased prevalence of hypertension, atherosclerosis, coronary artery disease, and metabolic syndrome in adolescence and adulthood. Monitoring of body-mass index, blood pressure, and laboratory evaluation of fasting glucose and lipid profile may help in identifying metabolic syndrome in children with JDM. Steroid-sparing agents, daily exercise, and a healthy diet may reduce such long-term cardiac morbidities. Current use of multimodality imaging such as stress-echocardiography, contrast-enhanced echocardiography, cardiac magnetic resonance imaging, and positron emission tomography has increased the diagnostic yield of subclinical heart disease during acute and chronic stages of JDM. This review elaborates on different aspects of cardiac dysfunction in JDM. It also emphasizes the importance of cardiac screening in long-term follow-up of children with JDM.

Keywords: dermatomyositis, vasculopathy, cardiac dysfunction, acute, long-term, screening, imaging

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INTRODUCTION

Juvenile dermatomyositis (JDM) is a common form of inflammatory myositis in children (1). Characteristic clinical features include proximal muscle weakness associated with typical skin lesions, such as heliotrope rash over eyelids and Gottron papules (2). However, any central organ system can be involved in JDM due to systemic vasculopathy (3). Cardiac involvement is often overlooked considering its subclinical course, although it can often cause significant morbidity and mortality. Oppenheim first reported the involvement of the cardiovascular system in patients

with dermatomyositis in Oppenheim (4). With the rapid advancement of imaging techniques and cardiac monitoring tools in recent decades, cardiac complications in JDM are increasingly being recognized.

The exact etiopathogenesis of JDM, especially cardiovascular involvement, has remained an enigma despite decades of research. Histopathology studies have highlighted that systemic vasculopathy plays an integral part in the pathogenesis of JDM (5). Elevated interferon (IFN) signature in JDM and systemic vasculopathy could result in endothelial dysfunction (6). Endothelial damage leads to the progression of vasculopathy. Chronic endothelial dysfunction and systemic inflammation can also predispose patients with JDM to accelerated atherosclerosis (7, 8). In recent years, the significance of type I IFNs in the context of the pathogenesis of JDM has been extensively studied. Several studies have revealed the presence of a distinguishing gene signature suggestive of a type I IFN pathway activation (IFNα/β) in peripheral blood and muscle tissues of children with JDM (9). It has also been observed that these gene signatures strongly correlate with disease activity, suggesting their role as potential biomarkers in JDM. Moneta et al. even reported that expression levels of IFNγ, IFNγ-inducible genes (type II IFN score), and tumor-necrosis factor (TNFα) were significantly high in untreated patients with JDM, suggesting the role of type II IFN as well (9).

Cardiac dysfunction in JDM may either present acutely or manifest late during the disease course. Among the acute complications, congestive heart failure (CHF), myocarditis, arrhythmia, and complete heart block have been commonly noted (**Figure 1**). However, these remain unrecognized in most instances due to a lack of overt clinical manifestations. Late cardiovascular complications are also relatively common in JDM. Left ventricular diastolic and systolic dysfunction, hypertension, atherosclerosis, coronary artery disease, and metabolic syndrome are frequently encountered in adolescence and adulthood. Dyslipidemia, hypertension, abdominal obesity, and impaired glucose tolerance, either due to chronic disease processes or as a complication of long-term use of corticosteroid therapy, may also affect cardiovascular health in children with JDM. Chronic immobility and autonomic dysfunction also contribute to cardiovascular changes in JDM (10, 11). Different ethnic backgrounds, sedentary lifestyles, and dietary habits also impact the prevalence of metabolic syndrome in JDM (12).

There are no consensus guidelines for screening and earlier detection of silent heart disease in children with JDM. Newer imaging modalities such as tissue Doppler imaging, cardiac scintigraphy, and stress echocardiography have also identified subclinical cardiovascular abnormalities in children with JDM. Regular monitoring of carotid media intima thickness and brachial artery reactivity index in children with JDM has been reported to predict the future development of atherosclerosis (13). Clinical assessment such as the extent of lipoatrophy, blood pressure monitoring, and waist circumference measurement can also aid in the early identification of metabolic syndrome in JDM.

Thus, the etiology of cardiac morbidities in JDM is multifactorial and judicious screening, and monitoring of risk factors may reduce overall cardiac morbidity and mortality in children with JDM.

SEARCH CRITERIA FOR ARTICLES

A comprehensive search was made using the Web of Science, Scopus, and PubMed databases to gather English articles published from 1980 to 2021 on cardiovascular abnormalities in JDM. We incorporated the following words in the search strategy: "Juvenile dermatomyositis," "vasculopathy of JDM," "cardiac dysfunction in JDM," "acute and long-term complications in JDM," "screening methods in JDM," " newer imaging modalities in JDM," and "management of cardiac dysfunction in JDM (**Table 1**)."

PREVALENCE OF CARDIOVASCULAR ABNORMALITIES

The exact prevalence of cardiac abnormalities in JDM is unknown, and various authors have reported it to vary from 9 to 72% (14). Cantez et al., in a retrospective study on 105 patients with JDM from Canada, noted abnormalities in electrocardiogram (ECG) and echocardiography in 6 and 25% of children (15). A multicentric study from Latin America and Europe reported cardiac involvement in 2.9% of the 490 patients with JDM (16). In a Korean cohort, the authors found that 6 out of 14 children had changes in ECG (17). Pachman et al. reported abnormalities in ECG in 65% (13/20) of children with JDM in their cohort (18). As can be interpreted above, there is a wide variation in the prevalence of cardiac morbidity in children with JDM and likely causes may include lack of screening due to subtle clinical features as well as the absence of advanced imaging modalities at most centers and hitherto unknown genetic differences across different population groups. Nevertheless, cardiac disease was a significant cause of mortality in JDM in certain studies. A study noted three deaths out of 17 deaths ($n = 329$) with cardiac dysfunction; however, these patients also had other comorbidities (19).

ACUTE CARDIAC COMPLICATIONS IN CHILDREN WITH JUVENILE DERMATOMYOSITIS

Studies have reported a high prevalence of electrocardiographic findings (6% had ECG changes; 25% had echocardiographic changes) (15) and subclinical ventricular diastolic dysfunction in children with JDM (20). The abnormal ECG findings commonly noted include atrial/ventricular arrhythmia, bundle branch block, AV block, abnormal Q waves, and prolongation of PR interval (20). Singh et al. reported a case of ventricular arrhythmia from their cohort of 33 children with JDM (21). Bradycardia has also been reported in a child with JDM (22).

An autopsy study of 16 patients with dermatomyositis showed evidence of myocarditis (25%), focal myocardial fibrosis (25%),

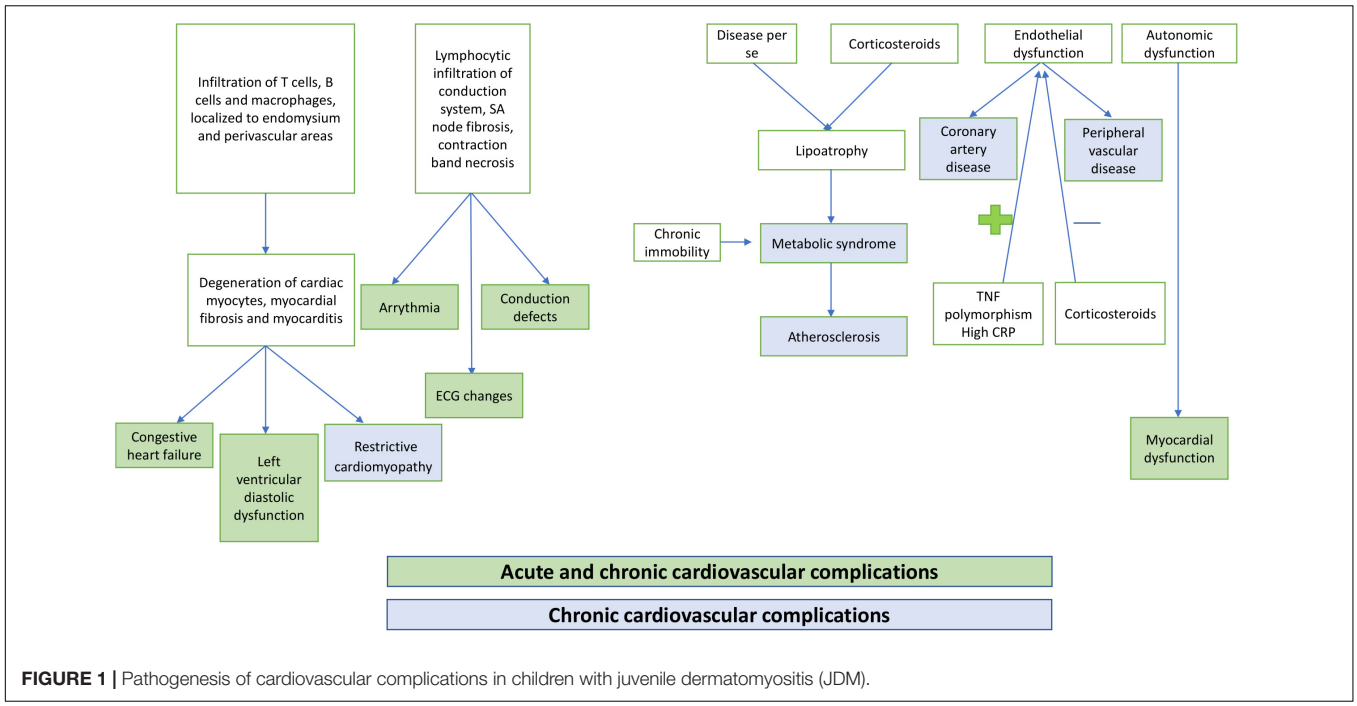

FIGURE 1 | Pathogenesis of cardiovascular complications in children with juvenile dermatomyositis (JDM).

and coronary artery changes in 5 patients (31%) (medial sclerosis with calcification and intimal proliferation in 1 each; active vasculitis in 3) (23). Banker et al. performed an autopsy on eight patients with JDM and reported the presence of inflammatory cells in the sub-endocardium and myocardium; however, none of them had symptomatic heart disease (24).

Pericardial involvement is relatively rare in children with JDM compared to myocardial involvement. However, as a part of systemic vasculopathy and inflammation, pericarditis may be observed in a subset of children with JDM. One study has reported pericarditis in 12–25% of patients with JDM (20). A multicentric study from Europe on 18 children with juvenile idiopathic inflammatory myositis (JIIM) reported that 50% of their children with positive anti-PL7 antibodies had pericarditis during their disease course (25). Pericardial tamponade has also been reported in a patient with JDM (26).

Autonomic dysfunction has been reported to occur in certain patients with dermatomyositis (27). One study showed reduced heart rate variability in patients with JDM due to autonomic instability, and such patients also had myocardial dysfunction (28). Barth et al. demonstrated a correlation between reduced heart rate variability and cardiac dysfunction. Furthermore, the authors noted a positive correlation with high serum levels of inflammatory cytokines, such as TNF alpha, IL-6, monocyte chemoattractant protein-1 (MCP-1) and eotaxin, and cardiac dysfunction (11).

Myositis-Specific Antibodies and Cardiac Dysfunction

A high prevalence of ECG abnormalities in children with JIIM with positive anti-SRP antibodies has been noted (29). Similarly, in a study on the correlation between clinical and myositis specific/myositis-associated antibodies in a subset of patients with adult-onset myositis, overt cardiac manifestations (arrhythmia, cardiomyopathy, and fibrosis) were observed in all four patients with positive anti-SRP antibody (30). A European cohort of patients with inflammatory myositis reported a 4.15-fold increased risk of cardiac involvement in the presence of anti-SRP antibody positivity (31). Albayda et al. showed cardiac involvement (myocarditis, arrhythmia, and cardiomyopathy) in patients with IIM (n = 6/7) with anti-mitochondrial antibody positivity (32). A 13-year male child with JDM had severe cardiomyopathy in the presence of a positive anti-MDA5 antibody (33). However, a Dutch study showed no cardiac morbidity in their cohort of 5 patients with positive anti-SRP antibodies (34). Studies from large and multicentric cohorts are needed to understand the spectrum of cardiovascular abnormalities amongst different auto-antibody subgroups in JDM.

DELAYED ONSET CARDIAC DISEASES IN CHILDREN WITH JUVENILE DERMATOMYOSITIS

Cardiac morbidities are not uncommon during long-term follow-up of children with JDM. However, there is a lack of data on this aspect. With corticosteroid therapy, mortality in children with JDM has reduced significantly in past decades. The improved survival rate has led to increased recognition of chronic morbidities, including cardiovascular complications in children with JDM. The pathogenesis for long-term cardiac complications is different from that of acute cardiovascular complications in JDM. While many patients with JDM have subclinical heart disease, a subset of them can present with overt

TABLE 1 | Previous studies on cardiovascular complications in children with JDM.

Author, country, year	Age (years)	Sex (male:female)	Number of JDM patients	Follow-up (months)	Cardiac abnormalities described	Remarks
Pachman et al., United States, (18)	1.75–13.75	3:4	21	NA	*Acute*: ECG abnormalities, left ventricular dysfunction *Chronic:* NA	ECGs were abnormal in 13 patients, with left ventricular hypertrophy noted in 5
Rider et al., United States, Canada and Europe, (97)	4–9.25	31:63	94	18	*Acute:* Hypertension, ventricular dysfunction *Chronic:* NA	Myositis damage index was described to validate to outcome in JDM with cardiovascular system being included in one of four domains
Na et al., South Korea, (17)	4–12	3:5	16	3–110	ECG abnormalities: ST-T changes, right bundle branch block	ECG abnormalities were found in 6 out of 16 patients with JDM (37.5%)
Schwartz et al., Norway, (20)	1.4–17.3	23:36	59	NA	ECG abnormalities: poor R-wave progression, left ventricular hypertrophy signs, right bundle branch block, pathological Q-wave, P pulmonale and prolonged QTc Echocardiographic changes: Left ventricular dysfunction, valvular regurgitation Hypertension	JDM patients had subclinical left ventricular diastolic dysfunction Patients with elevated E/E' (early diastolic transmitral flow/early diastolic tissue velocity) also had high prevalence of pathological ECG and hypertension High disease activity 1-year post diagnosis predicted high E/E' at follow-up
Lu et al., China, (76)	16–50*	15:31*	46*	NA	*Acute*: Left ventricular diastolic dysfunction	Tissue Doppler imaging was useful in detecting early cardiac complications like left ventricular diastolic dysfunction in patients with dermatomyositis
Huber et al., United States, (19)	5.1–11.6	NA	329	51.6	Congestive cardiac failure	Factors associated with mortality in their cohort of juvenile idiopathic inflammatory myopathies Of 8 deaths in JDM patients, 1 was due to congestive cardiac failure
Barth et al., Norway, (11)	NA	21:34	55	162	Arrhythmia (Heart rate variability) Systolic/diastolic dysfunction	Heart rate variability is decreased in patients with JDM compared with controls. Lower heart rate variability is associated with systolic and diastolic cardiac dysfunction and high-sensitivity CRP and active disease.
Cantez et al., Canada, (15)	2–17.6	11:24	105	122.4	ECG changes (n = 69): Prolonged QTc, prolonged PR and wide QRS Echocardiographic changes (n = 52): pericardial effusions, tricuspid regurgitation, pulmonary insufficiency, aortic insufficiency, mitral valve prolapse, mitral regurgitation, increased right ventricular end diastolic dimension and decreased pulmonary vein D-wave velocity (left ventricular ejection fraction was normal in all)	Cardiac abnormalities at disease onset are frequently seen, but are rarely significant findings. JDM patients should be considered for screening for cardiac disease as late cardiac complications are well recognized.
Diniz et al., Brazil, (35)	11.9–13.3	11:24	35	NA	LV systolic dysfunction Myocardial dysfunction	LV two-dimensional speckle-tracking echocardiography can detect early systolic myocardial compromise in asymptomatic patients with preserved EF. Longitudinal strain impairment was associated with disease activity and cumulative damage, whereas circumferential strain impairment was associated exclusively with cumulative damage.

**Lu et al. included both polymyositis and dermatomyositis in their cohort. NA, not available; ECG, electrocardiogram; JDM, juvenile dermatomyositis; CRP, C-reactive protein; LV, left ventricle; EF, ejection fraction.*

cardiac manifestations secondary to metabolic syndrome during adolescence and adulthood.

Schwartz et al. demonstrated diastolic dysfunction in 22% of children with JDM at a median duration of 16.8 years after initial diagnosis. The authors noted a correlation between myositis damage index (MDI) score, skin disease activity at 1 year, disease duration, and cardiovascular dysfunction. The authors also postulated that myocardial remodeling in JDM was an ongoing chronic process (20). Diastolic dysfunction appears earlier when compared to systolic dysfunction, and systolic dysfunction seems to be less frequent than diastolic dysfunction (28). Diniz et al. detected systolic myocardial compromise (reduction in left ventricular longitudinal and circumferential strain) in 35 asymptomatic children with JDM with preserved ejection fraction by 2-dimensional speckle tracking echocardiography (35). A comparative study on the 6-min walking test (6MWT) among 23 adults with inflammatory myositis and 18 healthy age-matched controls showed reduced distance covered by patients

with myositis due to reduced stroke volume and interstitial lung disease. However, there were no patients with JDM in their cohort, and disease duration was not specified (36).

In JDM, metabolic syndrome is a chronic complication that leads to future cardiovascular compromise in children during adolescence or adulthood. Metabolic syndrome constellates dyslipidemia, hypertension, truncal obesity, and impaired glucose tolerance (37). Lipoatrophy in patients with JDM and prolonged use of corticosteroids for disease control play a role in the development of metabolic syndrome in children with JDM (38). Interestingly, cardiac dysfunction has been noted with metabolic syndrome even in the absence of overt heart disease. Heart rate turbulence, a measure of vagal activity, can predict the risk of cardiovascular disease in metabolic syndrome (39). Verma et al. demonstrated lipoatrophy in 65% of patients with JDM from their cohort (n = 20), and 66% had hypertriglyceridemia at a mean follow-up period of 2.2 years. However, none of them had glucose intolerance (40). Silverberg et al. showed a higher incidence of hypertension (OR 22.25), obesity (OR 5.87), diabetes mellitus (OR 7.95), dyslipidemia (OR 5.84), lipodystrophy (OR 151.08), and organ and peripheral atherosclerosis (10.09) in children with JDM when compared with age-matched healthy controls (41). A study from the National Institute of Health (NIH) has also shown a high rate of cardiovascular risk factors in children with JDM (n = 17, mean duration of active disease course 38 months; 70% had either polycyclic or chronic active disease), such as abnormal lipid profile (47%), hypertension (23%), and obesity (47%) (42).

Coyle et al. showed that beta-cell function was not affected in patients with JDM. However, they reported impaired glucose tolerance test (35.2%), elevated fasting insulin (41.2%), high glucose-insulin ratio (47.1%), and elevated insulin resistance (47.1%) in 17 patients with myositis (16 children with JDM with a mean of 38 months of active disease). Furthermore, they described a positive correlation between muscle inflammation and elevated glucose-insulin ratio, high blood sugar level, and a negative correlation between cytokine profile (increased IL2 and IL12; decreased IL1RA and IL10) and serum glucose/glucose-insulin ratio (42).

In a study with adult patients with a history of JDM, authors reported high carotid intimal thickness and brachial artery reactivity index despite them being young and having lower body mass index (43) (**Supplementary Material**). Weng et al. showed a twofold higher risk for the development of coronary heart disease in children with JDM compared to healthy controls (44). Angina pectoris/Prinz metal angina has been reported in adults with dermatomyositis due to coronary vasospasm (45). A study has shown that Raynaud's phenomenon increased the chance of coronary vasospasm (46). One child with JDM was reported to have coronary artery dilatation which was an unusual finding (47).

Hypertension has been reported in 20% of patients with JDM (20). Hypertension in JDM may be due to metabolic syndrome, premature atherosclerosis, and chronic use of glucocorticoids. Silverberg et al. reported a higher risk of hypertension (OR 40.85) in patients with JDM between 1 and 9 years than in healthy controls (41). Authors also reported a higher risk of arrhythmia (OR 3.77) and obesity (OR 20.20) in this cohort compared with age-matched normal children. In addition, they showed a higher risk of obesity in Whites when compared with Hispanics and Blacks. However, hypertension was more common amongst Asians, and diabetes mellitus was more common amongst Blacks. Besides, the Black population had a high risk of developing bradycardia and cerebrovascular disease (41). A study by Mendez et al. corroborates that hypertension was noted more amongst the Asian population, although the incidence of JDM was high amongst Caucasians (48). This suggests that different genetic predispositions, lifestyle patterns, and differences in access to healthcare facilities may also impact patients with JDM who develop metabolic syndrome. Few studies have reported physical inactivity as a crucial risk factor for the development of cardiovascular disease in several rheumatological conditions, including JDM (49).

Cardiovascular disease in JDM also has a significant impact on mortality. A study from Hungary showed that cardiovascular involvement was the main reason for mortality in 55% of cases in JIIM (50). A Norwegian study reported 14% deaths due to cardiac disease in their cohort of juvenile idiopathic myositis (51). Silverberg et al. showed an increased risk of cerebrovascular morbidity in children with JDM, such as cerebral infarct (OR 10.82), cerebrovascular disease (OR 15.49), and transient ischemic attack (OR 10.82) (41).

CARDIOVASCULAR INVOLVEMENT DUE TO DRUGS USED IN JUVENILE DERMATOMYOSITIS

Certain drugs, such as glucocorticoids and hydroxychloroquine (HCQ), that are commonly used in the management of JDM, have also been associated with cardiac dysfunction (52, 53). There is an increased risk of cardiovascular disease with the use of glucocorticoids, depending on the dose and duration of treatment. Thus, patients on JDM with long-term steroid treatment should have a cardiovascular risk prevention plan considering the time and amount of steroid exposure (52) (**Supplementary Material**).

Although cardiac complications with HCQ are rare, they can occasionally result in irreversible damage and death. The two main clinical manifestations reported are conduction abnormalities (bundle or atrioventricular block) and myocardial hypertrophy (53).

Recently, Janus kinase (JAK) inhibitors have also been tried in refractory cases of JDM. However, most published case reports have used JAK inhibitors in the context of refractory cutaneous disease and arthritis, especially in adults (54–56). A case series by Kurasawa et al. has reported the successful use of tofacitinib in interstitial lung disease in anti-MDA5 antibody-positive dermatomyositis in adults (57). The use of ruxolitinib in the pediatric-age group was first reported by Aeschlimann et al. in a 13-year-old girl with refractory JDM (58). Another case report by Papadopoulou et al. reported the successful use of baricitinib in an 11.5-year-old boy with refractory JDM (59). Although the

literature suggests that JAK inhibitors can increase the risk of dyslipidemia and thromboembolism in adults (60), long-term studies are needed to assess the cardiovascular side effects of these drugs in JDM.

Other immunosuppressants, such as methotrexate and mycophenolate mofetil, may have a protective effect on the heart due to a reduction in overall inflammatory burden (**Supplementary Table 3**) (52, 53, 60–67).

RISK FACTOR ASSESSMENT, DISEASE MONITORING, AND DETECTION OF SILENT HEART DISEASE

There are no consensus guidelines about screening intervals and monitoring for prediction and earlier detection of cardiovascular disease in JDM. However, thorough clinical examination and essential laboratory evaluations may yield clues to recognize cardiovascular complications in JDM (**Supplementary Material**).

Nail-fold capillaroscopy (NFC) is usually used for disease activity monitoring by reading end row capillary loops on nail folds. A previous study has shown a positive correlation between NFC changes and skin disease in JDM (68). A study showed a correlation between NFC changes with lung disease and not with cardiac involvement in patients with JDM (69).

An echocardiogram may detect subclinical heart disease both at diagnosis and on follow-up. ECG detects several underlying silent conduction defects. Screening echocardiography is also essential for earlier recognition of myocardial dysfunction, pericarditis, and valvular heart disease. An image-guided myocardial biopsy can detect subtle myocardial inflammation; however, it is difficult to perform routinely.

There are no available biomarkers to detect underlying heart disease in patients with JDM. However, one study showed a positive correlation between high serum levels of TNF alpha, IL-6, and eotaxin with cardiac dysfunction (11). Type 1 IFNs regulate various cytokines and proteins associated with disease activity in JDM. It has been found that elevated neopterin, CXCL10, CXCL11, and galectin-9 levels correlate with disease activity in JDM. It has been suggested that these parameters may act as potential biomarkers to assess disease activity in JDM (9). Pro-brain natriuretic peptide (BNP) is raised in CHF; however, it has not been studied in JDM. Creatinine kinase (CK): MB isotype (CKMB) is usually elevated in any myocardial damage (70). However, it is not specific to myocardial dysfunction in children with JDM as these children also have inflammatory changes in skeletal muscles (70). Troponin is another biomarker for myocardial damage. Several isotypes are commercially available, such as cardiac troponin I (cTnI) and troponin T (cTnT). cTnT was noted to be elevated in patients with inflammatory myositis without cardiac disease (71). One study with 39 adult patients with IIM showed elevated cTnT in 19 patients (41%), while only one had elevated cTnI (70). cTnT shows cross-reactivity with skeletal muscle TnT due to structural homology. However, different amino acid sequences (31 different amino acids) of cTnI do not show any cross-reactivity with skeletal TnT. So, cTnI may be useful for the earlier detection of silent heart diseases in patients with inflammatory myositis (71, 72).

Abdominal obesity can be assessed by measuring waist circumference (73). However, it cannot differentiate between subcutaneous fat tissue and visceral abdominal fat. A study from Iran has shown that high amounts of visceral fat correlate with increased carotid intimal media thickness (CMT), a surrogate marker for atherosclerosis (74). Dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) can accurately detect fat distribution in internal organs (75). Measurement of subcutaneous fat tissue by slide calipers is another helpful tool for assessing lipodystrophy in children with JDM (40). Regular check-up of blood pressure is also vital for earlier identification of hypertension. Baseline investigations such as lipid profile, random blood sugar, and glycosylated hemoglobin are useful ancillary investigations for diagnosing metabolic syndrome.

In the last few decades, rapid advances in radiodiagnosis have increased the detection rate of silent cardiac dysfunction in children with JDM. Conventional echocardiography may occasionally miss systolic dysfunction with preserved ejection fraction; however, it has been observed that with the use of 2-dimensional speckle tracking echocardiography, mild systolic dysfunction can also be picked up (35). Tissue Doppler imaging is another helpful modality for detecting cardiac morbidity in patients with JDM especially left ventricular dysfunction (76). MRI and myocardial scintigraphy can detect myocardial perfusion (77, 78). Flow-mediated dilatation and CMT are helpful for the earlier detection of atherosclerosis (13).

Intravascular ultrasound and optical coherence tomography are essential tools for detecting coronary changes and changes in large peripheral vessels (79). Coronary calcium score in computed tomography (CT) angiography can predict the internal status of coronaries (80). Perivascular lipid volume, which regulates vascular stiffness, can be identified by multidetector CT and MRI (81). However, the utility of these imaging modalities has not been studied in patients with JDM or DM. Furthermore, such sophisticated tools and techniques are not available at most centers.

Role of Cardiac Magnetic Resonance Imaging in Juvenile Dermatomyositis

Cardiac MRI is a valuable non-invasive tool to assess myocardial inflammation and scarring. A study on cardiac MRI on 16 adults with inflammatory myositis (9 DM and 7 PM) showed epicardial and intramyocardial late gadolinium enhancement (LGE) in 56.3% of the patients suggesting active inflammation. LGE was more commonly noted amongst patients with PM when compared to DM ($p = 0.060$) (82). Another study by Rosenbohm et al. on 53 patients with inflammatory myositis (64.2% PM, 24.5% DM, and 7.5% non-specific myositis) showed that patients with reduced left ventricular ejection fraction had an increased incidence of LGE. Notably, 54% of the patients with DM had LGE, and on most occasions, the lateral segment was involved compared to the anterior segment or septum (77).

Role of Cardiac Positron Emission Tomography Imaging in Juvenile Dermatomyositis

Since Gould et al. first described the utility of cardiac Positron emission tomography (PET) in clinical practice, its use in various inflammatory and autoimmune diseases has seen rapid strides. The premise for using [18F] Fluorodeoxyglucose PET (FDG-PET) is that FDG accumulates in inflammatory lesions where glucose-consuming inflammatory cells are present. Studies in adults with polymyositis and dermatomyositis have shown that inflammatory lesions, especially cardiac lesions, can be identified by calculating the maximum standardized uptake value (SUVmax). However, there are no such studies in children with JDM so far. Somatostatin receptor-targeted PET imaging with 68Ga-DOTANOC (68Ga-DOTA-NaI-octreotide) or 68Ga-DOTATOC (68Ga-DOTA-D-Phe-Tyr-octreotide) (Gallium-based tracers) can have better results in the detection of active cardiac lesions by eliminating the effects of glucose uptake by normal cardiomyocytes. Cardiac PET imaging may have a prominent role in the future, especially in identifying cardiovascular abnormalities in JDM (83, 84).

MANAGEMENT OF CARDIOVASCULAR DISEASE IN CHILDREN WITH JUVENILE DERMATOMYOSITIS

Due to multifactorial etiopathogenesis, therapy with immunosuppressants alone may not be sufficient to prevent cardiovascular morbidity in JDM. There is a lack of literature on cardiac complications in children with JDM. Studies in adult patients with dermatomyositis have shown that cardiac dysfunction can develop even while on steroid therapy (85). Also, adult literature has shown no correlation between cardiac disease and active skeletal muscle inflammation. Some of these patients with dermatomyositis had developed cardiac dysfunction even without active skeletal muscle inflammation (86).

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) and Single hub and access point for pediatric rheumatology in Europe (SHARE) have recommended the use of intravenous immunoglobulin (IVIg) in the context of moderate to severe disease activity, especially severe cutaneous disease in JDM (87, 88). However, it is pertinent to note that since IVIg has an anti-inflammatory and immunomodulatory effect, it may enhance the clearance of inflammatory cytokines that contribute to damage of cardiac myocytes and may have a role in managing active myocarditis. IVIg has been used in many centers for managing active myocarditis in children irrespective of the underlying etiology (89, 90). However, further studies would be required to assess whether IVIg can supplant other immunosuppressive drugs in the management of myocarditis in JDM.

The long-term management is mainly centered around earlier identification of metabolic syndrome and prevention of the development of complications such as coronary artery disease. Supportive care for CHF, arrhythmia, and hypertension is required. It is imperative to screen for metabolic abnormalities during follow-up of children with JDM.

Diet modification in metabolic syndrome is another factor that can lead to a favorable outcome. A calorie-restricted diet may be recommended to prevent complications due to metabolic syndrome (91). Physical exercise in JDM improves muscle strength in JDM and improves aerobic capacity, thereby improving cardiac health. de Oliveira et al. showed that exercise training improves B cell function and metabolic parameters and attenuates cardiovascular risks in patients with autoimmune myopathies (92).

Initiation of hypolipidemic drugs, such as statins and fibrates and lifestyle modifications, may be warranted in some patients to control dyslipidemia and prevent premature atherosclerosis (93). However, the use of statins in the setting of inflammatory myositis is not without controversy. Statins have been linked to the development of autoimmune necrotising myopathy (94, 95). The International myositis assessment and clinical study (IMACS) group evaluated the use of statins in 1,641 patients with myositis. A total of 36 out of 300 patients with inflammatory myositis who received lipid-lowering therapies had worsening myopathy, and the majority of them had exposure to statins. Further research is required to address whether statins can be safely recommended for the management of hyperlipidemia in patients with inflammatory myositis (96).

CONCLUSION

Cardiac complications in children with JDM are not uncommon. Cardiac disease constitutes a significant cause of mortality in children with JDM. However, these are under-recognized on most occasions due to a lack of overt manifestations. A sizeable proportion of children with JDM develop cardiac dysfunction over time. Regular screening and monitoring of risk factors should be carried out for earlier diagnosis and better outcomes. Initiation of lifestyle modification and a balanced diet may significantly reduce cardiac morbidities due to metabolic complications. Besides ECG and conventional echocardiography, several sophisticated imaging tools have evolved over the last few decades, and they may be instrumental in detecting silent heart disease. In addition, timely transition to adult healthcare providers is also essential for earlier detection and management of cardiovascular complications and eventual better outcomes.

AUTHOR CONTRIBUTIONS

SM and PB: preparation of the first draft of the manuscript and literature review. PV: inception of the idea, critical review of the manuscript, and final approval. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.827539/full#supplementary-material

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