Autoimmunity Reviews 22 (2023) 103393

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Posttranslational modifications in psoriatic arthritis: A systematic literature review

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ARTICLE INFO

Keywords:
Psoriatic arthritis
Posttranslational modifications
Citrullination
Phosphorylation
Carbamylation
Glycosylation

ABSTRACT

Background and aims: Psoriatic arthritis (PsA) is an inflammatory complex condition. Posttranslational modifications influence almost all aspects of normal cell biology and pathogenesis. The aim of this systematic review was to collect all published evidence regarding posttranslational modifications in PsA, and the main outcome was to evaluate an association between disease outcomes and specific posttranslational modifications in PsA.
Methods: A systematic electronic search was performed in Medline, PubMed, Cochrane, Virtual Health Library, and Embase databases. A total of 587 articles were identified; 59 were evaluated after removing duplicates and scanning, of which 47 were included. A descriptive analysis was conducted, with results grouped according to the type of posttranslational modification evaluated. The protocol was registered at the PROSPERO database.
Results: Seven posttranslational modifications were identified: citrullination, carbamylation, phosphorylation, glycosylation, acetylation, methylation, and oxidative stress. Anti-citrullinated peptide and anti-carbamylated protein have been evaluated in rheumatoid arthritis. There is now information suggesting that these antibodies may be helpful in improving the diagnosis of PsA and that they may demonstrate a correlation with worse disease progression (erosions, polyarticular involvement, and poor treatment response). Glycosylation was associated with increased inflammation and phosphorylation products related to the expression of SIRT2 and pSTAT3 or the presence of Th17 and cytokine interleukin-22, suggesting a possible therapeutic target.
Conclusions: Posttranslational modifications often play a key role in modulating protein function in PsA and correlate with disease outcomes. Citrullination, carbamylation, phosphorylation, glycosylation, acetylation, methylation, and oxidative stress were identified as associated with diagnosis and prognosis.

1. Introduction

Psoriasis (PsO) is an inflammatory skin condition that affects people between the ages of 30 and 40 years, with similar frequency between men and women. The estimated prevalence is 1%–2% of the population. Of patients with PsO, 40% of cases may have joint involvement, which is

Abbreviations: anti-CCP, Anti-citrullinated peptide; ACPA, Anti-citrullinated protein antibodies; AIP, Atherogenic index of plasma; anti-Carp, Autoantibodies carbamylated peptides; CRP, C-reactive protein; ca-LDL, Carbamylated low-density lipoprotein; CIMT, Carotid intima-media thickness; CIA, Chemiluminescence immunoassay; CFFCP, Chimeric fibrin and citrullinated filaggrin peptide; DLQI, Dermatology Life Quality Index; DeCS, Descriptores en Ciencias de la Salud; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28, Disease activity score 28; DAS44, Disease activity score 44; DMARDs, Disease modifying antirheumatic drugs; ESR, Erythrocyte sedimentation rate; ELISA, Enzyme-linked immunosorbent assay; GS, Gray-scale; HLA, Human leukocyte antigen; HC, Healthy controls; AHCPA, Homocitrullinated/carbamylated peptide; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; MDA, Malondialdehyde; mTOR, Mammalian target of rapamycin; NIH, National Institutes of Health; MeSH, Medical Subject Headings; MAPK, Mitogen-activated protein kinases; NAPSI, Nail Psoriasis Severity Index; OR, Odds ratio; OA, Osteoarthrosis; PBMCs, Peripheral blood mononuclear cells; PI3K, Phosphoinositide 3 kinase; PD, Power Doppler; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; PsO, Psoriasis; PsO-QoL, Psoriatic Arthritis Quality of Life; PASI, Psoriasis Area Severity Index; PsA, Psoriatic arthritis; PTMs, Posttranslational modifications; RA, Rheumatoid arthritis; RF, Rheumatoid factor; anti-CCP2, Second-generation anti-CCP; SF-36, Short Form Health Survey; STAT, Signal Transducer and Activator of Transcription; SIRT2, Sirtuin-2; SpA, Spondyloarthritis; SF, Synovial fluid; TNF, Tumor necrosis factor; US, Ultrasound; anti-MCV, Vimentin antibodies; 4-ONE, 4-oxononenal.

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https://doi.org/10.1016/j.autrev.2023.103393
Received 22 June 2023; Accepted 14 July 2023
Available online 22 July 2023

recognized as psoriatic arthritis (PsA). PsO may precede the onset of arthritis by 10 years [1–3]. Both PsO and PsA represent spectra of the same disease, for which specific diagnostic biomarkers are unavailable. On the other hand, posttranslational modifications (PTMs) refer to amino acid side chain modifications in some proteins after their biosynthesis. There are >400 different types of PTMs, which affect many aspects of protein functions. Such modifications occur as crucial molecular regulatory mechanisms to modulate diverse cellular processes. These processes have a significant impact on the structure and function of proteins. Disruption in PTMs can lead to the dysfunction of vital biological processes and hence to various diseases [4]. Scarce information is available on PsA.

This systematic literature review aims to thoroughly gather all published evidence that meets the search and eligibility criteria regarding PTMs in PsA.

2. Materials and methods

2.1. Protocol and registry

We conducted a systematic review of the literature according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines of 2015 [5]. The protocol was registered in PROSPERO in 2022 (CRD42022360029). The main objective of the study was written in population-intervention-comparator-outcome format. The main outcome was defined as an association in the indices for both diseases such as the Psoriasis Area Severity Index (PASI), Disease Activity in Psoriatic Arthritis (DAPSA), Nail Psoriasis Severity Index (NAPSI), Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsO-QoL), and Short Form Health Survey (SF-36) and PTMs in PsA; secondary outcomes and diagnosis or prognosis were also considered.

2.2. Eligibility criteria

We included studies conducted in humans older than 18 years who were diagnosed with PsA. The search was conducted without a time limit. Original studies (clinical study, clinical trial protocol, comparative study, controlled clinical trial, observational study, cohort studies, case-control study, cross-sectional study, and pragmatic clinical trial) conducted in Spanish and English up to March 27, 2022, were included. Letters to the editor, case reports, book chapters, preliminary publications in congresses, studies in animals/cells, systematic review, meta-analysis or duplicates, as well as studies of poor methodological quality were excluded [6].

2.3. Information, resources, and search

We performed a systematic electronic search including the databases of Medline, PubMed, Cochrane, Virtual Health Library, and Embase. Data from additional sources were reviewed through references handsearched in literature reviews and systematic reviews. Medical Subject Headings (MeSH),Descriptores en Ciencias de la Salud (DeCS) terms, and keywords (Supplementary material 1) were used.

2.4. Data collection and methodological evaluation

Four independent authors carried out the methodological evaluation process of the articles using the Cochrane evaluation strategy (https://handbook.cochrane.org) [7]. Cases of disputes were resolved by a fifth author. Data were extracted from the reference, country of study, study population, type of study, sample size, age, disease duration, type of PTM, measurement method, association with the disease, outcomes, and conclusions. The methodological evaluation of the included studies was performed according to the National Institutes of Health (NIH) quality assessment tool for cross-sectional and observational cohort studies [8]. References relevant to this review were hand searched. Finally, a descriptive analysis was conducted, with studies grouped according to the type of PTM evaluated and results of each study reported. Considering the findings of the articles included, which consisted of multiple measurements, no tests of heterogeneity were performed; thus, the results were not amenable to meta-analysis.

2.5. Ethical considerations

This project does not include experimentation with animals or humans; however, it was conceived in accordance with the considerations contained in the Declaration of Helsinki. This review is based on the collection of previously published scientific information.

3. Results

We identified a total of 587 articles. After removing duplicates and scanning by title and abstract, 437 articles remained. After applying eligibility criteria and evaluating the full text of 58 articles, we ultimately included 47 articles in the analysis (Fig. 1).

3.1. PTMs

3.1.1. Citrullination

With regard to citrullination, we grouped the results of the 31 articles obtained into the following categories: (1) association between anti-citrullinated peptide (anti-CCP) antibodies or anti-citrullinated protein antibodies (ACPA) and clinical characteristics, including differences in response to drug treatments, and (3) specific forms of anti-CCP and diagnostic methods for this type of antibodies (see Table 1).

Hagiwara et al. analyzed the presence of anti-CCP and reported 17.1% anti-CCP positivity in PsA; they identified older age, higher frequency in lung involvement, and rheumatoid factor (RF)–positive titres; however, positivity in patients did not improve with the use of anti–tumor necrosis factor (TNF) therapy [9]. Dai et al. found similar results in Beijing; patients with PsA who were positive for anti-CCP (9,09%) were older and had polyarthritis. However, there were no differences in radiographic erosions, nail changes, or enthesitis [10]. In contrast to some of the previously mentioned results, Perez-Alamino et al. found that most patients with PsA and positive anti-CCP antibodies were females and mainly exhibited significantly more symmetric polyarthritis, higher frequency of erosive disease, and less nail involvement [11].

Otherwise, in response to therapy, in 2021 Rotondo et al. evaluated whether the presence of anti-CCP could determine different clinical subsets and influence methotrexate monotherapy survival and the retention rate of biological disease modifying antirheumatic drugs (DMARDs) [12]. Only 12 of 113 patients were positive for anti-CCP, with lower survival in methotrexate monotherapy. A significantly shorter survival of first-line biological DMARDs was observed in the anti-CCP–positive group, and a significantly higher rate of multifailure. In a study conducted in 2013 of 41 patients from Bucharest, only 5 patients (12,2%) were positive for anti-CCP. Compared with anti-CCP–negative patients with PsA, those who were anti-CCP positive had a more frequent polyarticular disease pattern and were more frequently treated with biological DMARD and less frequently with classic disease-modifying drugs [13].

Candia et al. evaluated anti-CCP in serum between patients with PsO and PsA. They found a significantly higher frequency (albeit only 9.7%) of these antibodies in patients with PsA [14]. Similarly, Alenius et al. found that 7% of patients with PsA had anti-CCP antibodies, which was higher than in patients with PsO; PsA patients more often had polyarticular disease, but there was no association with radiologic changes and/or deformity and functional impairment [15]. Likewise, Gruber et al. evaluated the presence of anti-CCP in serum from patients with PsO as compared with PsA and found no statistically significant differences in frequency [16]. However, there was a difference in

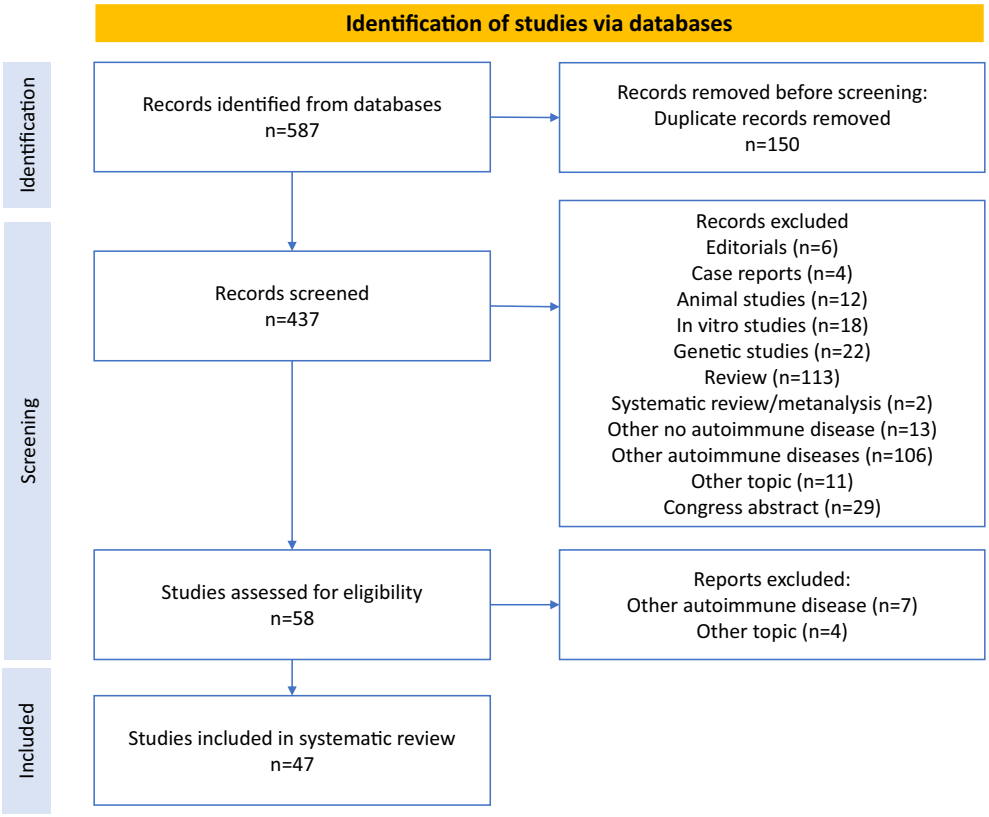

Fig. 1. PRISMA 2020 flow chart for new systematic reviews which included searches of databases, registers, and other sources.

polyarticular involvement between patients with PsO and PsA. In a UK study conducted by Korendowych et al. [17], 5.6% of patients with PsA were positive for anti-CCP antibodies compared with 0% of controls and 97% of patients with seropositive rheumatoid arthritis (RA). The presence of anti-CCP antibodies in PsA was significantly associated with the human leukocyte antigen (HLA) DRB1 shared epitope, erosive disease, number of swollen joints, and DMARD use.

Among a cohort of Japanese patients with spondyloarthritis (SpA), Yamazaki et al. identified 15.3% positivity for anti-CCP–associated arthritis of the hand and abnormal erythrocyte sedimentation rate (ESR) [18]. In addition, they reported that patients with PsA had de higher anti-CCP frequency among SpA. In another Japanese group of 16 patients, Shibata et al. identified a 13% prevalence of anti-CCP–positive PsA (2/16); as compared with patients with anti-CCP–negative PsA, these patients had higher levels of RF without other clinical skin or articular differences [19]. Similar results were reported by Maejima et al., who reported anti-CCP positivity in 20% (3/15) of patients in another Japanese group. They also reported a higher incidence of radiographic erosion, polyarticular disease, use of DMARDs, and presence of human leukocyte antigen (HLA) DRB1*04 shared epitope [20].

Among PsA patients, Inanc et al. reported 12.5% positivity for anti-CCP, and it was associated with symmetrical polyarthritis, RF positivity, and the use of corticosteroids [21]. In 1996, Behrens et al. identified 5.3% positivity for anti-CCP in patients with PsA; those patients had higher swollen joint counts and disease activity score 28 (DAS28) values, dactylitis, and a higher rate of erosive changes in multivariate analysis, with an odds ratio (OR) of 2.77 (1.63–4.69) [22]. Bogliolo et al. reported anti-CCP positivity in 15.7% of patients. Those patients presented with more involved joints and a higher frequency of erosive arthritis and positive RF. In multivariate analysis, erosive arthritis had an OR of 9.8 (1.87–51.8), and $\geq$ 10 of cases involved joints (OR 17.9; 3.6–89.2) [23]. In 2010, Tesija-Kuna et al., despite the limitations of their study, found a low frequency in patients with PsA and reported an association with a polyarticular manifestation but did not find a correlation with PsA duration, C-reactive protein (CRP), ESR, or activity index [24]. In addition, Abdel Fattah et al. identified anti-CCP positivity in 17.5% of 40 PsA patients, who had higher tender and swollen joint counts and a higher frequency of deformities in the peripheral joints, functional impairment, and radiologic changes (deformities/erosions) [25]. Finally, Caspi et al. evaluated anti-CCP and immunoglobulin A (IgA) RF in PsA, but the levels in synovial fluid (SF) were higher for RA and similar to levels for osteoarthrosis (OA) [26]. In 2006, Spadaro et al. evaluated anti-CCP in SF and serum, finding lower levels in patients with PsA compared with patients with RA, without a difference with OA. The presence or absence of anti-CCP antibodies did not discriminate against a particular clinical subset [27].

It is not only the positivity of the anti-CCP antibodies that is essential but also the serum levels measured. In a 2014 study by Payet et al. conducted in France, the authors requested anti-CCP determinations in 1162 patients. In this large cohort, 357 (30.7%) had second-generation anti-CCP (anti-CCP2) antibodies, 292 patients with RA (70% of the total RA group), 13 patients with PsA (10.7%), and 52 patients with articular diseases (of inflammatory and noninflammatory origin) [28]. The authors concluded that antibodies could help in the diagnosis of RA (70% sensitivity, 91.3% specificity). However, when the authors examined the levels of antibodies, there did not appear to be any further discriminatory power among patients who were anti-CCP2 positive.

Nine of the 31 articles mentioned specific forms of anti-CCP. The first generation of the anti-CCP test used a peptide derived from the filaggrin protein as the antigen. The second- and third-generation anti-CCP (CCP2 and CCP3, respectively) are no longer based on the filaggrin-derived native sequences but on peptides specifically designed and optimized (mimotypes) to detect ACPA. In addition, there are assays based on an entire protein different from filaggrin, such as vimentin antibodies (anti-MCV), PepA/PepB, or viral specific peptides.

Based on the use of vimentin, Dalmády et al. in 2013 evaluated the

Table 1
Overview of studies with citrullination as a posttranslational modification in PsA patients.

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
Abdel Fattah et al. [25]	2009	Egypt	40	No	PsO 40 RA 40	40	Yes	No	Serum	Anti-cyclic citrullinated peptides	Anti-CCP–positive patients with PsA had significantly higher numbers of involved, swollen, and tender joints; deformities; functional impairment of peripheral joints; and radiologic changes compared with anti-CCP–negative PsA.
AleniusGM, et al. [15]	2006	Sweden	160	No	PsO 146 RA 101	102	Yes	No	Serum	Anti-cyclic citrullinated peptides	Anti-CCP antibodies did not seem to be related to radiologic changes or deformity and functional impairment in PsA.
Anzilotti et al. [36]	2007	Italy	128	No	RA 146 AS 52 UA 19 SSc 20 MC 19 SLE 24 PMR35 SS 13	89	Yes	No	Serum	Anti-viral citrullinated peptide IgG, IgA, and IgM	No correlation was found between the isotype and the clinical manifestations or duration of the disease in PsA.
Behrens et al. [22]	2016	Germany	1996	Yes	No	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	ACPA-positive patients had significantly higher swollen joint counts and 28-joint DAS, and they also had significantly higher rates of erosive changes and dactylitis. Multiple logistic regression analysis confirmed that ACPA seropositivity was associated with a 2.8-fold increase in the risk of erosive disease.
Bogliolo L., et al. [23]	2005	Italy	102	No	No	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	Anti-CCP–positive PsA had higher rates of erosive changes and positive RF and were more frequently treated with disease-modifying antirheumatic drugs. In multiple logistic regression, anti-CCP (but not RF) was significantly associated with erosive arthritis and greater than or equal to 10 involved joints.
Candia et al. [14]	2006	Colombia	72	No	PsO 106 UA 41 RA 41 OA 41	41	Yes	No	Serum	Anti-cyclic citrullinated peptides	Most anti-CCP–positive PsA patients were female and had

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Table 1 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
											polyarticular joint involvement compared with PsO without arthritis or HC.
Caspi et al. [26]	2006	Israel	20	No	RA 29 OA 19	No	Yes	No	Sinovium	Anti-cyclic citrullinated peptides	Synovial fluid levels of anti-CCP and IgA RF were significantly higher in patients with RA compared with those with PsA and OA, whereas no significant difference was observed between patients with PsA and OA.
Dai YL, et al. [10]	2019	China	77	No	No	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	Anti-CCP–positive patients with PsA were older with higher rates of RF positivity and serum levels of fibrinogen. All patients had polyarthritis.
Dalmády S, et al. [29]	2013	Hungary	46	Yes	PsO 42	40	Yes	No	Serum	Antibodies against mutated citrullinated vimentin (anti-MCV)	Anti-MCV in PsO patients was associated with a more severe disease course and early onset of disease. Patients with PsA were associated with tender knee joints and nail psoriasis.
Damjanovska et al. [30]	2010	Netherlands	99	No	RA 566, SpA 72, ReA 38, OA 32, seronegative RA 30, CTD 21, sarcoidosis 26, paramalignant 11, gout/ pseudogout 6, Lyme 6, JIA 2, iInflammatory arthritis 8	No	Yes	No	Serum	Anti-cyclic citrullinated peptides (anti-CCP2, anti-CCP3) and antimutated citrullinated vimentin (anti-MCV)	In PsA, SpA, and other forms of arthritis, the prevalence of anti-MCV antibodies ranged from 13.9% to 19.4%. Therefore, the anti-MCV test has lower diagnostic performance in the differential diagnosis of early arthritis.
Frasca et al. [39]	2018	Switzerland	32	Yes	PsO 24 and OA 12	14	Yes	No	Synovial tissue and serum	Citrullinated-LL37	Patients with PsA had higher levels of anti-carbamylated/ citrullinated-LL37 antibodies compared with OA patients. In addition, there was a significant positive correlation between plasma anti-LL37carb antibodies and disease activity (DAS44) in PsA patients.
Gruber et al. [16]	2020	Brazil	41	Yes	PsO 48	100	Yes	No	Serum	Anti-cyclic citrullinated peptides	PsA with polyarticular forms was more likely to be anti-CCP positive compared with PsO. In the

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Table 1 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
											group of patients with PsA, those who were anti-CCP positive were more likely to suffer from polyarticular forms of arthritis.
Hagiwara et al. [9]	2020	Japan	41	Yes	No	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	In PsA patients, anti-CCP antibodies may be associated with lung involvement, elderly onset, higher RF and MMP-3 titres, and resistance to anti-TNF.
Häyrynen J, et al. [35]	2015	finland	14	No	RA 41, undifferentiated arthritis 57, ReA 8, and AS 11	No	Yes	No	Serum	Homocitrulline and citrulline containing telopeptides of type I and type II collagens	Autoantibodies binding to homocitrulline or citrulline containing telopeptides of type I and II collagen did not differ significantly in PsA compared with other types of arthritis, including seronegative RA or UA.
Hueber et al. [38]	2006	USA	21 PsA and AS	No	RA 56	19	No	No	Serum	Citrullination	Autoantibody reactivity was observed against citrullinated epitopes between patients within the high-cytokine subgroup in eRA compared with other patient groups. In addition, there was no relationship between the profile of cytokines evaluated and autoantibody reactivity against citrullinated epitopes in PsA.
Inanc et al. [21]	2007	Turkey	56	No	RA 208	39	Yes	No	Serum	Anti-cyclic citrullinated peptides	Anti-CCP positivity in PsA was significantly higher than in HC. PsA had symmetrical polyarthritis with a higher median swollen joint count. None of the PsA patients with anti-CCP antibodies had axial involvement.
Korendowych et al. [17]	2005	United Kingdom	126	No	RA 40	40	Yes	No	Serum	Anti-cyclic citrullinated peptides	PsA and being anti-CCP positive were significantly associated with the HLA-DRB1 shared epitope, erosive disease, number of swollen joints, and DMARD use.

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Table 1 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
Kruithof et al. [37]	2005	Belgium	45	No	RA, USpA	No	Yes	No	Synovial tissue	Citrullinated S100A12	There is no presence of citrullinated S100A12 in PsA, contrary to that identified in RA.
Lac et al. [34]	2017	Canada	37	Yes	RA 137 SLE 37	51	Yes	No	Serum	Anti-cyclic citrullinated peptides and homocitrullinated/ carbamylated protein/peptide (AHCPA)	Antibodies to CitJED, HomoCitJED, and CitJED were also frequently found in RA patients and were rare in other conditions.
Maejima et al. [20]	2010	Japan	15	Yes	PsO 18	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	Patients with PsA who were anti-CCP positive had a higher prevalence of polyarthritis, DMARD use, HLA-DRB1*04 shared epitopes; erosive disease counts were also significantly higher.
Martinez-Prat et al. [33]	2018	Switzerland	237	No	RA 968 AxSpA 450	No	Yes	No	Serum	Anti-cyclic citrullinated peptides CCP2 and CCP3 ELISA and CCP3 in CIA	ACPA assays showed good discrimination between RA patients and SpA, and CCP3 was found to be superior to CCP2.
Payet et al. [28]	2014	France	112	Yes	RA 1162, rheumatism 62, UCTD 28, Sjogren 33, SLE 30, SS 36, JAI 44, and no inflammatory diseases 220	No	Yes	No	Serum	Anti-cyclic citrullinated peptides–CCP2 IgG	Patients with PsA and anti-CCP2 IgG positive had peripheral joint involvement, and most also had erosions and/or joint space narrowing.
Perez-Alamino et al. [11]	2014	USA and Colombia	81	Yes	No	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	Patients with PsA who were anti-CCP positive were females and specially exhibited significantly more symmetric polyarthritis, higher frequency of erosive disease, and less nail involvement. The frequency of RF positivity was also higher in PsA anti-CCP positive patients, and these patients were on anti-TNF therapy.
Popescu et al. [13]	2013	Romania	41	Yes	RA 139	147	Yes	No	Serum	Anti-cyclic citrullinated peptides	Patients with PsA who were anti-CCP positive had a polyarticular pattern and were more frequently treated with biological therapy.
Rotondo et al. [12]	2021	Italy	113	Yes	No	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	The presence of anti-CCP in PsA patients may indicate a more

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Table 1 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
											severe disease, with shorter survival of both methotrexate monotherapy and first-line biotechnological drugs. PsA with anti-CCP was associated with a significantly shorter methotrexate monotherapy survival and shorter first-line b-DMARDs survival and a significantly higher rate of multifailure.
Sanmartí R, et al. [32]	2009	Spain	113	No	RA 322 SLE 119 hepatitis C infection 84	307	Yes	No	Serum	Antibodies to chimeric fibrin/ filaggrin citrullinated synthetic peptides (CFFCP1, CFFCP2, CFFCP3) and anti-cyclic citrullinated peptides CCP2	Anti-CFFCP or anti-CCP2 status is rare in patients with PsA, except for anti-CFFCP2 status, which was found in 9.8% of PsA patients. In general, anti-CFFCP antibodies have high sensitivity and specificity for RA.
Shibata et al. [19]	2009	Japan	16	No	PsO 15 RA 9	11	Yes	No	Serum	Anti-cyclic citrullinated peptides	PsA anti-CCP–positive patients also had high levels of serum IL-23p19, which is associated with PsA rather than RA.
Spadaro et al. [27]	2007	Italy	31	No	RA 29 OA 15	No	Yes	No	Synovial fluid and serum	Anti-cyclic citrullinated peptides	Lower levels of IgG anti-CCP antibodies were found in both the synovial fluid and serum of PsA patients compared with RA patients, and there was a higher SF/serum ratio for anti-CCP in PsA patients compared with total IgG. However, there was no difference in anti-CCP levels between PsA and OA patients.
Tesija-Kuna et al. [24]	2010	Croatia	56	No	RA 97 other autoinflammatory diseases 44	107	Yes	No	Serum	Antibodies against mutated citrullinated vimentin (anti-MCV) and anti-cyclic citrullinated peptides	In PsA patients, there was no significant difference in anti-MCV levels according to clinical subtypes of PsA.
Vander Cruyssen et al. [31]	2005	Belgium	192	No	No	No	Yes	No	Serum	Antibodies against pepA and pepB (two synthetic citrullinated peptides)	Anti-CCP–positive PsA patients were also positive for anti-pepA or pepB antibodies.

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Table 1 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
Yamazaki et al. [18]	2021	Japan	20	Yes	AS 43 SAPHO 13 uSpA 27 3 ReA 3 IBD	No	Yes	No	Serum	Anti-cyclic citrullinated peptides	PsA patients had a significantly higher prevalence rate of positive anti-CCP antibodies among SpA patients, and the positive rates in SAPHO and uSpA were also high.

presence of this immunoglobulin M (IgM) isotype anti-MCV in 90 patients, 46 with PsA and 42 with only PsO. The prevalence of this isotype was higher in those with PsA (24% vs. 8% PsO and 0% in healthy controls [HC]), with significantly higher titres [29]. Those patients had more tender knee joints and nail involvement. In 2010, Damjanovska et al. evaluated the diagnostic performance of anti-MCV in differentiating RA from other early arthritis [30]. They included 917 patients with arthritis of <2 years' evolution; 15.2% with PsA. Those authors were also able to identify the usefulness of this marker for differentiating RA from other forms of arthritis, including PsA, with greater sensitivity for anti-MVC than for anti-CCP2 and anti-CCP3 (62% vs. 56.9% and 58.1%, respectively), but with lower specificity (82% vs. 93.4 and 90%, respectively). Patients with PsA had a similar prevalence of anti-MVC to other diseases such as SpA (13.9%) and other arthritis (19.4%). Finally, in 2010, Tesija-Kuna et al. measured anti-MVC antibodies using an enzyme-linked immunosorbent assay (ELISA) kit, with a specificity of 98%. They found a significantly lower level of antibodies, with a mean of 6.5 in patients with PsA versus 120.9 for patients with RA, and only two patients were positive, both of whom had long-standing PsA [24].

Vander Cruyssen used ELISA to detect ACPA against synthetic citrullinated peptides, PepA/PepB, with a sensitivity and specificity of 63% and 98.% for the first and 54% and 98.5% for the second, respectively [31]. Only 7.8% of individuals with PsA were positive for ACPA, with an association with a greater number of joint erosions, asymmetric oligoarticular disease, and predominance in the lower limbs and no correlation with the count of swollen joints, radiologic changes in the hands, or sacroiliitis.

Because the epithelial protein filaggrin is not expressed in synovial tissue, it may not be a good target in vivo. In addition to vimentin, fibrin (or fibrinogen) can undergo citrullination. Sanmartí et al. published their results obtained after creating an ELISA using chimeric fibrin and citrullinated filaggrin peptide (CFFCP) 1 versus CFFCP2, CFFCP3, and the conventional CPP2 assay [32]. Among 133 patients with PsA, 9.8% were positive with CFFCP2, 4.5% with CFFCP1, 3% with classic CPP2, and only 1.5% with CFFCP3. However, the purpose of their study was to demonstrate the diagnostic performance of synthetic peptides against the commercial CPP2 ELISA in RA. In 2018, Martinez-Prat et al. encountered excellent and good total agreement between ELISA and chemiluminescence immunoassay (CIA) for CCP3 and between CCP2 and CCP3 by ELISA, respectively [33]. CCP3 ELISA and CIA were positive in 1.3% and 1.7% of patients with PsA, but CCP2 ELISA was positive in 13.1%, suggesting a higher specificity of the CCP3 assay compared with CCP2 in RA.

Another synthetic preparation was evaluated by Lac et al., who in 2018 evaluated the cross-reaction of immunoglobulin G (IgG)–type ACPA and homocitrullinated/carbamylated peptide (AHCPA), which they called CitJED and HomoCitJED, respectively [34]. They found that the presence of this cross-reactivity suggested that both forms of antibodies come from the same population of B cells in RA patients, but they were not positive in any of the 37 patients with PsA.

Häyrynen et al. evaluated citrullination and homocitrullination in C-telopeptides from collagen I and II, but they found no association with PsA. However, they did find a correlation among only patients with RA or undifferentiated arthritis (UA) and seropositivity for RF and anti-CCP [35].

Anzilotti et al. evaluated viral citrullinated peptides in inflammatory arthritis. In PsA, the IgG was positive in two patients (1.5%), IgM was positive in six patients (4.4%), and there were no positive results for IgA [36]. The presence of these antibodies with low affinity was uncommon in PsA patients, but they were associated with a polyarthritis profile. Kruithof et al. evaluated intracellular citrullinated peptides in SF with absence in oligoarticular or polyarticular PsA compared with RA [37]. Finally, Hueber et al., performed a proteomic analysis that did not find an association between ACPA and PsA [38]. Frasca et al., described the presence of anti-carbamylated/−citrullinated-LL37 antibodies in PsA but not in controls, as will be reported in the "Carbamylation" section below [39].

3.1.2. Carbamylation

Four articles using different approaches evaluated the association between the levels of anti-CarP antibodies and the activity, severity, and atherogenic index of PsA [39–42] (see Table 2). Evidence from the literature suggests that autoimmune processes may drive the features of PsA. These autoantibodies have been associated with a worse disease progression independent of ACPA in RA. Chimenti et al. aimed at analyzing, for the first time, the anti-CarP antibodies in the serum of patients with active PsA who were negative for ACPA [42]. They found significantly increased levels of anti-CarP antibodies compared with HC. Those findings indicate that anti-CarP antibodies are detectable with high specificity and sensibility in PsA. Anti-CarP antibodies can prove useful in improving the diagnosis of PsA and are correlated with disease activity. Ibrahim et al. [40] evaluated disease activity in PsA according to the modified DAS28 and PASI. In addition, they performed musculoskeletal ultrasound (US) of the small hand joints using gray-scale (GS) and power Doppler (PD). The authors found a significant correlation between anti-CarP antibody and DAS28, ESR, CRP, PASI, the GS and PD joint counts ($r = 0.97$, $r = 0.97$, $r = 0.97$, $r = 0.97$, $r = 0.96$, and $r = 0.9$, respectively) as well as with the US joint scores denoting severity. Therefore, anti-CarP antibody might represent a marker to predict joint damage and disease activity in patients with PsA.

With a different goal, Tecer et al. in 2019 investigated the associated between carbamylated low-density lipoprotein (ca-LDL), the atherogenic index of plasma (AIP), atherogenic coefficient, Castelli's risk indices I and II, and subclinical atherosclerosis in PsA [41]. Carotid intima-media thickness (CIMT) was measured at both common carotid arteries, and the mean CIMT was calculated. The results showed a significant increase in CIMT in patients with PsA without clinically evident cardiovascular disease or any traditional atherosclerosis risk factors. CIMT was correlated with the Homeostatic Model Assessment for Insulin Resistance, triglycerides/high-density lipoprotein, and AIP. Finally, it has been reported that the LL37 protein becomes an autoantigen for psoriatic Th1-Th17/CD8 T cells. Frasca et al. analyzed inflammatory factors, including LL37, in PsA and PsO plasma and PsA SF/biopsies. They showed that LL37 and autoantibodies to LL37 are elevated in PsA

Table 2
Overview of studies with phosphorylation, carbamylation, glycosylation, acetylation, methylation, and oxidative stress as a posttranslational modification in PsA patients.

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
Phosphorylation											
Lories et al. [47]	2008	Belgium	9	No	No	No	Yes	No	Sinovium	Phosphorylated ERK, p38, JNK or IBκ α	The effects of etanercept therapy showed a significant decrease in NFκB, ERK, and JNK activation but not in p38 activation. But no correlation was found between pre- and posttreatment measurements of NFκB and MAPK activation and disease activity.
Macaubas et al. [48]	2021	Israel	15	Yes	PsA inactive 12, RA 14	No	No	Yes	Peripheral blood mononuclear cells (PBMCs)	Phosphorylated pSTAT1, pSTAT3, and pSrc	An analysis confirmed that levels of pSTAT3 in Th1 and Tfh CD4+ T cells, as well as in CD14 + CD16− monocytes, remained significantly higher in active PsA patients after correction for confounding variables. There was no significant difference in cell frequency for 16 immune subpopulations between active PsA and active RA.
Mitra et al. [49]	2012	USA	5	Yes	RA 5 OA 5	10	Yes	Yes	Skin and sinovium	Phosphorylated Akt/ mTOR	A significant increase was observed in phosphorylated Akt (pAkt) in both cell types when exposed to IL-22 as well as in the upregulation of AKT1 and MTOR expression.
O'Brien et al. [50]	2021	Ireland	14	Yes	PsA 14 without iJAK	No	Yes	Yes	Sinovium	Phosphorylated pSTAT3	JAKi treatment suppressed PsAFLS cell invasion, migratory capacity, and MMP1, 3, and 9 expressions, with peficitinib demonstrating the greatest effect.
			8	Yes	PsO 8	5	No	Yes	Peripheral blood mononuclear cells (PBMCs)	Phosphorylated p38MAPK	SIRT2 expression is increased in PsA compared with PsO and in healthy controls, and its expression levels are negatively correlated with p38MAPK phosphorylation.
Zhu et al. [51]	2021	China	4	Yes	PsO 4	4	No	Yes	Peripheral blood mononuclear cells (PBMCs)	Phosphorylated p38MAPK	PBMC protein expression profiling of PsA and PsO significantly changed. Among these biomarkers, SIRT2 was confirmed to have higher expression in PsA.
Carbamylation											
Chimenti et al. [42]	2015	Italy	30	Yes	No	40	Yes	No	Serum	Carbamylated protein (anti-CarP) antibodies	Anti-CarP antibodies are detectable in active PsA. Positive correlations were identified between anti-CarP levels and age, disease duration, ESR levels, and VAS. A negative correlation was found between anti-CarP levels and GH (global health status).

(*continued on next page*)

Table 2 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
Frasca et al. [39]	2018	Switzerland	32	Yes	PsO 24 and OA 12	14	Yes	No	Synovial tissue and serum	Carbamylated LL37	Anti-LL37cit and anti-LL37carb antibodies were higher in the synovial fluid of PsA compared with OA patients and in the plasma of PsA patients compared with HC. Anti-LL37carb antibodies in plasma showed a significant positive correlation with disease activity (DAS44).
Ibrahim et al. [40]	2017	Egypt	45	Yes	No	45	No	No	Serum	Carbamylation	Significant correlation between anti-CarP antibody and clinical measures of disease activity (DAS28, ESR, CRP) as well as skin involvement (PASI) suggests that it may serve as a useful biomarker for predicting joint damage and disease activity in PsA.
Tecer et al. [41]	2019	Turkey	39	Yes	No	19	Yes	No	Serum	Carbamylated low-density lipoprotein (ca-LDL)	The positive correlation between ca-LDL and serum amyloid A protein level may indicate a link between lipid metabolism and systemic inflammation in PsA.
Oxidative stress											
Firuzi et al. [53]	2006	Italy	10	No	RA 9, SSc 17	22	No	No	Serum	Oxidative stress	PsA patients had significantly increased levels of hydroperoxides and significantly lower levels of sulfhydryls compared with the control group. These findings suggest that there is increased free radical–mediated injury in PsA.
Firuzi et al. [54]	2008	Italy	16	No	RA 18 and OA 15	No	No	No	Synovial fluid and serum	Oxidative stress	The levels in the sulfhydryl group were lower in both the serum and synovial fluid of PsA compared with controls and OA, and the serum sulfhydryl levels were higher than in RA.
Wójcik P, et al. [55]	2020	Poland	16	Yes	PsO 32	16	No	Yes	Peripheral blood mononuclear cells (PBMCs)	Oxidative stress and lipid peroxidation	The results suggest that patients with PsO and PsA have increased oxidative stress levels. The Nrf2 pathway may play a role in the differential levels of redox imbalance between PsO and PsA. In addition, the study found an increase in proteins forming adducts with 4-ONE and MDA.
Glycosylation											
Collins et al. [43]	2013	Ireland	25	No	RA 29	No	No	No	Serum	Glycosylation of immunoglobulin G	Glycosylation patterns of IgG were observed in the serum of RA and PsA patients after anti-TNF therapy. Also seen was an increase in galactosylated glycans from IgG, as well

(*continued on next page*)

Table 2 (*continued*)

Author	Year	Country	PsA	CASPAR criteria	Disease control	Healthy control	Tissue	Cells	Type tissue/ cells	Posttranslational modification	Results
											as an increase in core-fucosylated biantennary galactosylated glycans and a decrease in sialylated triantennary glycans with and without outer arm fucose after treatment.
Saso et al. [44]	1998	Italia	18	No	No	15	Yes	No	Serum	Glycosylation of serum proteins	The total reactivity of Con A (a lectin) with serum glycosylated proteins was higher in PsA compared with the control group. A correlation between this increased reactivity and inflammatory markers.
Triolo et al. [45]	2003	Italia	50	No	PsO 8	24	No	Yes	Erythrocytes	Glycosyl-phosphatidylinositol-anchored membrane CD59	In PsA patients, the expression of CD59 was found to be significantly reduced compared with HC. In addition, a significant inverse correlation was observed between levels of SC5b-9 and erythrocyte surface CD59 levels in patients with active arthritis.
Watson et al. [46]	1999	United Kingdom	9	No	SLE 10 AS 10 SS 6 AIJ 13 RA 5	19	Yes	No	Serum	Glycosylation of Immunoglobulin G	Agalactosyl and monogalactosyl structures were present in a characteristic pattern in PsA patients. Furthermore, there was a correlation between the oligosaccharide structure of g0b/neutral and the disease.
Acetylation and methylation											
Ovejero-Benito et al. [52]	2018	Spain	11	No	PsO 28	42	No	Yes	Peripheral blood mononuclear cells (PBMCs)	Histone H3/H4 acetylation and methylation	The study found significant differences only in global histone H4 acetylation between PsA patients and HC and the percentage of H3K4 methylation was significantly increased in patients with PsA.

but not in OA SF [39]. Anti-LL37 antibodies correlate with clinical inflammatory markers. Carbamylated/citrullinated-LL37 antibodies are present in PsA SF/plasma and, to a lesser extent, in PsO plasma but not in controls. Plasma anti-carbamylated–LL37 antibodies correlate with disease activity score 44 (DAS44) but not PASI. Thus, we uncovered a role for LL37 as a novel PsA autoantibody target, and correlation studies suggest participation of anti-LL37 antibodies in the pathogenesis of PsA. Notably, plasma antibodies to carbamylated-LL37, which correlate with DAS44, suggest their use as new disease activity markers.

3.1.3. Glycosylation

Four articles described glycosylation as posttranslational modifications [43–46] (see Table 2). Watson et al. evaluated oligosaccharides in IgG among different rheumatic diseases [46]. Patients with PsA had a variety of associations with agalactosyl structures (100% of patients) and monogalactosyl structures (86% of patients) as sugar prints. In addition, the authors described the association with monosialylated structures. Saso et al. identified higher reactivity using concanavalin A for glycosylation changes in PsA compared with HC. This finding was correlated with ESR, CRP, and IL-6; meanwhile, the alpha-1 antitrypsin glycosylation changes were correlated with ESR and soluble IL-2 receptors [44]. Triolo et al. compared the expression of glycosyl-phosphatidylinositol–anchored membrane CD59 in erythrocytes among patients with PsA, patients with PsO, and HC. They described an impaired expression in patients with PsA, with the lowest level in patients with active disease [45]. Finally, Collins et al. evaluated glycosylation levels based on the use of anti-TNF therapy in inflammatory arthritis, including patients with PsA and RA, using hydrophilic interaction liquid chromatography for N-glycans in serum. Measurements were obtained at baseline, 1 month, and a 1 year after treatment, with an increase observed in galactosylated glycans from IgG and in core-fucosylated biantennary galactosylated glycans and a decrease in sialylated triantennary glycans with and without outer arm fucose. In addition, a correlation was detected with decreasing CRP over the course of treatment, and these changes were concomitant with changes in glycosylation [43]. Otherwise, there were no differences based on the type of inflammatory arthritis or between responders and nonresponders. When disease activity was measured, a correlation was found with CRP; however, after 1 year of treatment, some glycans were correlated with disease activity score without CRP, but the correlations were stronger with CRP than disease activity score.

3.1.4. Phosphorylation

Five studies evaluated phosphorylation with different proteins [47–51] (see Table 2). Zhu et al. evaluated the presence of biomarkers in peripheral blood mononuclear cells (PBMCs) from patients with PsO, patients with PsA, and HC. Subsequently, using bioinformatic analysis, based on proteome and Western blotting analysis, they validated the presence of 14 protein candidates for differentiation of PsA [51]. Among the former proteins, a higher expression of NAD-dependent protein deacetylase sirtuin-2 (SIRT2) was observed in PsA versus HC and PsO and a negative correlation with the phosphorylation of p38 and the mitogen-activated protein kinases (MAPK).

Using high-dimensional mass cytometry, Macaubas et al. identified elevated expression of phosphorylated transducer and activator of transcription-3-pSTAT3 in circulating Th1 and T follicular CD4+ T cells and CD14 + CD16− from active PsA patients compared with inactive patients, which might contribute to the pathophysiology of PsA [48].

PsA is a chronic inflammatory disease characterized by proliferation of keratinocyte and fibroblast-like synoviocytes through the signaling pathway activation: the phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) target of rapamycin (mTOR)– PI3K/Akt/mTOR. Mitra et al. observed that this proliferation is induced by Th17 cytokines, such as IL-22, which regulates the signaling cascade (PI3K/Akt/mTOR) [49]. This finding suggests this signaling pathway as a new therapeutic target.

3.1.5. Acetylation and methylation

One study evaluated histone acetylation and methylation in PBMC (see Table 2). Ovejero-Benito et al. evaluated 39 patients with PsO (11 with PsA). They identified a significantly reduced histone H4 acetylation in both PsA and PsO as compared with HC, and both had no differences in H3 acetylation [52]. In addition, the percentage of H3K4 methylation was significantly increased in patients with PsA. Unfortunately, the small sample size and impact of drug response could not be evaluated in the PsA group, whereas they reported that in the PsO group, responders had changes in methylated H3K4.

3.1.6. Oxidative stress

The presence of oxidative stress in PsA was evaluated in three articles [53–55] (see Table 2). Firuzi et al. initially described the presence of different oxidative stress parameters from peripheral blood in their comparison of patients with PsA, systemic sclerosis, and RA with HC. They identified a significant increase in hydroperoxides in patients with PsA, and sulfhydryls were significantly lower compared with HC [53]. In an additional study, Firuzi et al. described the presence of oxidative stress in serum and SF in comparing patients with PsA, RA, and OA [54]. Serum sulfhydryl levels were inversely correlated with ESR and CRP and were lower in PsA than in OA and higher than in RA. The sulfhydryl levels in SF were lower in PsA compared with OA ($p < 0.02$). The serum and synovial levels of the carbonyl groups were not significantly different among the groups. Wojcik et al. described the redox imbalance in patients with PsO and PsA as compared with HC. They demonstrated pro-oxidative conditions and protein modifications in lymphocytes by lipid peroxidation products 4-oxononenal (4-ONE) in binding proteins and malondialdehyde (MDA) in catalytic proteins with redox activity [55]. The level of proteins forming adducts with 4-ONE and MDA was enhanced in lymphocytes from patients with PsO and PsA by approximately 40% and 70%, respectively, which was manifested by enhanced expression of proapoptotic caspases, particularly caspase 3.

3.2. Quality appraisal

The overall mean quality score revealed that all studies consisted of observational cohort and cross-sectional studies. According to the NIH tool, 14.9% had a good-quality rating, the other studies were of fair quality, and none were considered poor (more details about the items are presented in Supplementary Table 2).

4. Discussion

There has been difficulty in identifying a valuable diagnostic/prognostic biomarker in PsA [56,57]. In recent years, PTMs have been critical in the pathogenic development of multiple diseases, with particular interest in their application as biomarkers in different autoimmune diseases [58]. Otherwise, PTMs have received less attention, as there are many technical challenges related to their measurement [58]. The present systematic literature review attempted to summarize scientific information on PTMs in patients with PsA (Fig. 2).

Although PsA and RA share similar pathophysiological mechanisms, their pathogenesis pathways differ, for example, in the predominance of lymphocyte T phenotypes. In RA disease, citrullination induces autoantibodies such as anti-CCP or ACPA with valuable diagnostic power [59], which is why they have been included in the current classification criteria [60] and are considered preclinical markers [61,62]. However, it may also be present in others joint conditions, particularly autoimmune diseases [63]. Despite being found more frequently in patients with PsA than in PsO, citrullination occurs in a small percentage of patients, unlike in RA (0%–20% in individuals diagnosed with PsA), which limits its diagnostic performance. However, it is the second etiology (after RA) in terms of frequency of positive ACPA, which makes it possible to identify different clinical subsets, as it has a tendency to be related to peripheral joint involvement (symmetric polyarticular or asymmetric oligoarticular), the concomitant presence of RF, and an association with the shared epitope (HLA DRB1*04) [64]. Although older age and a higher frequency of lung involvement have been associated with citrullination, those patients interestingly influence methotrexate monotherapy survival and response to anti-TNF therapy. The results against erosive disease and other traditional radiologic findings are contradictory, whereas in RA, this association has been described historically [65]. In addition, the study of anti-CCP in SF does not have diagnostic or clinical importance in scenarios of PsA compared with RA [66].

Other models of antibodies against citrullinated proteins such as vimentin [29,30] or fibrin [32] showed low frequencies—between 15.2%–24.0% and 9.8%, respectively—without clinically characterizing a subtype of patients in an important way.

Another serological PTM is carbamylation, which also induces the formation of autoantibodies carbamylated peptides (anti-Carp). Anti-Carp had been also studied in RA patients, with a lower diagnostic power than those classically described for ACPA and RF, associated with disease activity and severe joint damage [67]. However, Anti-Carp is also present in other arthritis conditions. More recently, in the hope of expanding this evidence, researchers have sought to identify the association between anti-CarP and PsA, and they have found this same association with more significant disease activity and severe joint damage, independent of the presence of ACPA, with good sensitivity and specificity values [68].

Phosphorylation as PTM has been reported in systemic lupus erythematosus (SLE), celiac disease, and inflammatory bowel disease [69–73]. In this systematic literature review, five studies evaluated the phosphorylation of p38, MAPK, signal transducer and activator of transcription (STAT) 1, STAT3, Ibκα, and Akt/mTOR, identifying an impact in cellular activation or regulation pathways influencing inflammation and possible treatment target or treatment response [47–51].

Oxidative stress has been evaluated in rheumatic diseases. Dysfunction in oxygen reduction enzymes such as superoxide dismutase, catalase, glutathione peroxidase, peroxiredoxins, thioredoxins, and thioredoxin reductases has been shown to promote apoptosis, inflammation, and formation of autoantibodies in SLE and RA [74–78]. In the case of PsA, studies identified in synovium and PMBCs an imbalance in redox and an inflammatory profile supporting previous results [53,55]. On the other hand, glycosylation of immunoglobulins has been reported to influence effector function. One study used the galactosylation ratio

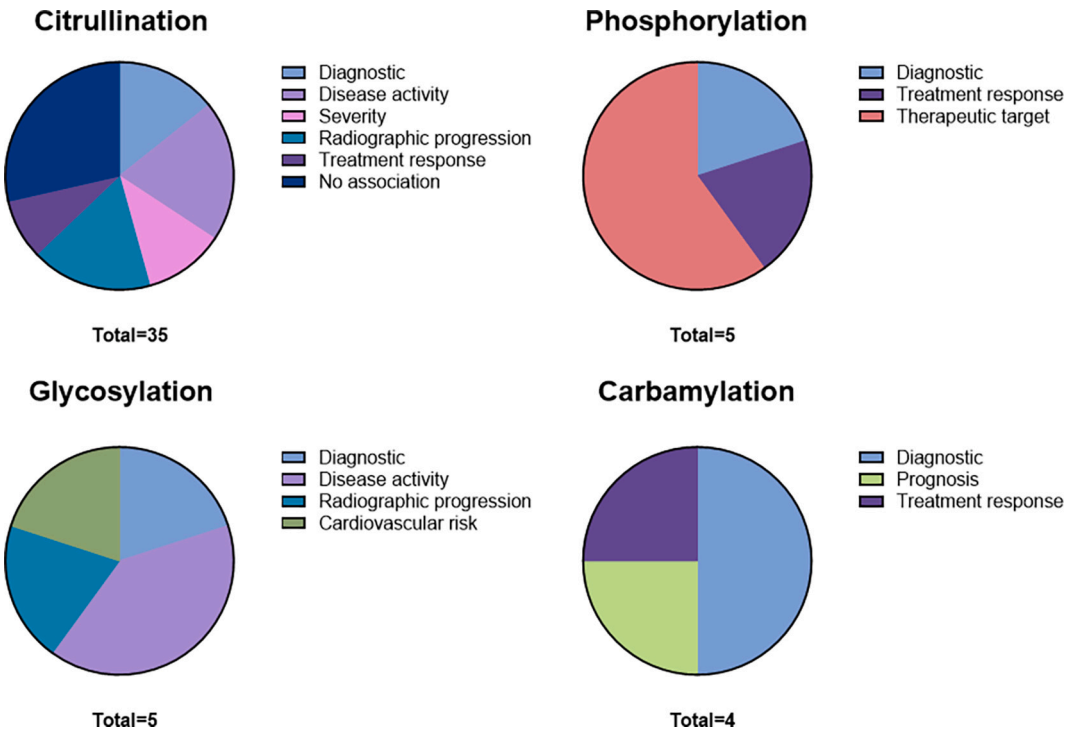

Fig. 2. Posttranslational modifications and possible clinical applications.

as a discriminatory tool in RA as compared with OA [79]; galactosylated glycans from IgG were evaluated in PsA in two different works with diagnostic and treatment response utility [43,46]. Acetylation of histones in seronegative RA has been evaluated with evidence of cross-reactivity with ACPA [80]. In their 2018 study conducted in patients with PsA, Ovejero-Benito et al. reported an increase in histone methylation and also found that PsO and PsA reduced histone acetylation. However, no clinical association was evident, possibly due to the small sample size [52].

The main limitations of the included studies were their high heterogeneity, including differences in the PsA population, diagnostic criteria, geographical regions, and ethnicity, as well as different types of samples and procedure reproducibility. Multiple measurement techniques were used with highly mixed results; different control groups were considered within the studies, and differences in the investigated outcome were reported, some focusing on diagnostic utility, others on prognosis, and a fraction on treatment response. For instance, pooling the data of the original articles would be highly difficult due to the heterogeneity of study design and reported outcomes, and the heterogeneity in disease severity could affect the treatment output.

Despite the heterogeneity and methodological challenges, the importance of PTMs in rheumatology and, significantly, PsA is growing. Validation of biomarkers in different populations is needed to confirm the reports included in the present systematic literature review for future research and clinical practice implementation.

5. Conclusions

Evidence from the information collected show that the main PTM were citrullination, phosphorylation, carbamylation, and glycosylation in PsA. The latter is useful for defining patient subtype. Our study further highlighted the importance of conducting quality studies so that the results can be trusted with more certainty.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study protocol design, execution, acquisition of data, analysis, and interpretation or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that the research was conducted in the absence of any AI-assisted technologies in the writing process.

Declaration of Competing 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.

Data availability

Data will be made available on request.

Acknowledgements

The authors thank Universidad El Bosque for financial support in English language edition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2023.103393.

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