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REVIEW ARTICLE

Reactive arthritis before and after the onset of the COVID-19 pandemic

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Abstract

Most accepted definitions of reactive arthritis (ReA) consider it a type of spondyloarthritis (SpA) precipitated by a gut or urogenital infection. A wider definition considers any arthritis that occurs after a mucosal surface infection as ReA. There is limited consensus regarding a working definition, status of HLA-B27, or even classification criteria for ReA. This may also contribute to a lack of systemic studies or clinical trials for ReA, thereby reducing further treatment recommendations to expert opinions only. The emergence of post-COVID-19 ReA has brought the focus back on this enigmatic entity. Post-COVID-19 ReA can present at extremes of age, appears to affect both sexes equally and can have different presentations. Some present with small joint arthritis, others with SpA phenotype-either with peripheral or axial involvement, while a few have only tenosynovitis or dactylitis. The emergence of post-vaccination inflammatory arthritis hints at similar pathophysiology involved. There needs to be a global consensus on whether or not to include all such conditions under the umbrella of ReA. Doing so will enable studies on uniform groups on how infections precipitate arthritis and what predicts chronicity. These have implications beyond ReA and might be extrapolated to other inflammatory arthritides.

Key Points

- *Classical reactive arthritis (ReA) has a spondyloarthritis phenotype and is preceded by symptomatic gut or urogenital infection*
- *The demonstration of antigen and nucleic acid sequences of pathogens in synovium has blurred the difference between invasive arthritis and reactive arthritis*
- *Post-COVID-19 ReA has a transient phenotype and can have different presentations. All reported cases are self-limiting*
- *The large amount of literature reporting post-COVID-19 ReA calls for introspection if the existing definitions of ReA need to be updated.*

Keywords Infection-induced arthritis · Reactive arthritis · SARS-CoV-2 arthritis · Spondyloarthritis

Introduction

Reactive arthritis (ReA) is classically considered a sub-type of spondyloarthritis (SpA) that is precipitated after a gastrointestinal or genitourinary infection [1]. The usual presentation is monoarticular or oligoarticular arthritis involving large joints that occurs around 2–4 weeks after an infection [2]. However, the term has been used in a wider context of an immune-mediated arthritis that may occur after any infection. The primary concept is that there is no direct invasion of the joints by any pathogen but the arthritis occurs as a result of induced changes in the immune system.

The proposed definitions of ReA have under the umbrella of SpA, be it under the Amor or the European Spondyloarthropathy Study Group (ESSG) proposed criteria for "Spondyloarthropathy" [3] or the currently used ASAS (ASsessment in Ankylosing Spondylitis working group) criteria for peripheral SpA [4]. According to these definitions, the pathognomic features of SpA are required to label a patient as having ReA. These include sacroiliitis, uveitis, dactylitis, enthesitis, and HLA-B27 or family history of SpA, psoriasis, or uveitis [4, 5].

ReA allows us a distinctive opportunity to scrutinize and learn how an infective trigger precipitates an autoimmune phenomenon. A majority of ReA resolves within a

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few weeks to a few months. The rest assume a chronic form indistinguishable from other chronic autoimmune arthritides [6]. Thus, it also provides an opening to understand how the autoimmune process becomes self-sustaining and chronic.

ReA is a predominant problem of low-to-middle income countries where gut and urinary tract infections abound. Though it is reported from high-income countries, the phenotype is usually limited to arthralgia, tenosynovitis, dactylitis or often not-so-severe arthritis. The phenotype seen in the tropics is much different with the rapid development of secondary osteoarthritis or even evolution into ankylosing spondylitis [7]. However, with the COVID-19 pandemic, there are a lot of reports of post-COVID-19 ReA, re-igniting interest in this entity worldwide.

This perspective aims to explore how the concept of ReA has evolved over the last century, touching upon similar entities and finally how the COVID-19 pandemic is coercing us to re-look into the definitions of this enigmatic malady.

Search strategy

We have adhered to recommendations for narrative review searches [8]. We searched through Scopus and LitCovid/PubMed databases [9]. Non-English sources have not been consulted. Conference abstracts or non-peer reviewed sources were not included. To avoid confusion, we used the MeSH keyword "reactive arthritis" that includes "post infectious arthritis" for searches through LitCovid/PubMed. For Scopus, we used "reactive arthritis" OR "post infectious arthritis" in the search string.

History of ReA

The first descriptions of a post-infectious arthritis were made during the time of the First World war by Fiessinger and Leroy [10]. However, it was more commonly known with the eponym from a Nazi doctor who had first described a triad of urethritis, conjunctivitis, and arthritis. However, since he was convicted of war crimes, the eponym is not encouraged [11]. Also, a similar triad had already been described almost a century ago by Sir Benjamin Brodie in five cases [12].

More than half a century after the First World War, the concept of ReA was established as a non-purulent arthritis that occurred after a gastrointestinal infection without the direct invasion of the bacteria into the joints [13]. This concept was first contradicted by the finding of Chlamydia elementary bodies in the synovial cells of patients with ReA [14]. The tug of war over this concept has kept on going for a few decades. Now, it is clear that the entire live organism is not found in the joint but some antigen or genetic material, possibly carried by endosomes, may persist in the joint and lead to a sustained inflammatory reaction [15].

Current definitions and limitations

As the definition of ReA evolved, more and more entities were proposed for inclusion such as Lyme disease, gonococcal arthritis, post-streptococcal reactive arthritis, and rheumatic fever [16]. While it is true that Lyme disease and gonococcal arthritis may not fulfil the classical Koch's postulates to be defined as an "infection," both have unique characteristics clinical features. Clubbing them with ReA will neither help in the management nor further research. Similarly, the differences between ReA and post-streptococcal reactive arthritis are elaborated elsewhere [17].

The most commonly used definition of ReA has been provided by Braun and associates [18, 19]. This definition requires monoarthritis or oligoarthritis preceded by symptomatic diarrhoea or urethritis. For "definite" ReA to be diagnosed by the Braun criteria, an organism with known association with ReA needs to be demonstrated by culture or PCR. Even while these classification criteria were formulated, there was a lack of agreement on various points like the relationship of HLA-B27 with ReA, the existence of ReA without arthritis, or whether it should include only spondyloarthritis presentations or any arthritis [18]. More and more organisms are being added to the list of potential precipitants of ReA [20]. Also, the definition by Braun et al. does not consider the entity of "post-vaccination ReA."

The American College of Rheumatology (ACR) or the European Alliance of Associations for Rheumatology(EULAR) do not have separate practice guidelines pertaining to ReA as possibly the rheumatologists in Europe or the United States do not see severe cases of ReA[21–23]. The incidence is apparently declining in most high-income countries [24]. However, the rest of the world that depend on the ACR and EULAR recommendations may find this gap challenging. For example, Latin America had the largest proportion of patients with "peripheral spondyloarthritis" [25]. ReA from India has arthritis as the predominant feature in 95% of patients [26] while a report from Finland showed only arthralgia in two and arthritis in none of 17 patients with post-*Escherichia coli* musculoskeletal conditions [23]. Thus, there seem to be great differences in how clinicians from different parts of the world view ReA.

Only a small percentage of patients who have infections with organisms such as *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia* develop ReA [27]. Similarly, amongst millions who have developed SARS-CoV-2 infection, only a minor proportion develops arthritis. Understanding this may help unearth new verities about the immune system and tolerance mechanisms.

Clinical phenotype of post-COVID-19 ReA

Phenotype

Post COVID-19 arthritis more commonly has a rheumatoid like phenotype affecting the wrists, ankles, and small

joints of hands and feet. However, a spondyloarthritis-like presentation with axial involvement has also been reported [28]. It can also present as classical ReA with lower limb predominant oligoarthritis [29]. Isolate monoarthritis of a single metacarpophalangeal joint has also been reported [30]. Table 1 summarizes the different phenotypes, treatments given, and outcomes in various case reports of post-COVID-19 reactive arthritis from across the world.

Age and gender

The initial reports of post-COVID-19 ReA were in men past 50 years of age [31–33, 35]. This is in contrast to the classical ReA that is most common between 15 and 40 years of age. Again, at least three cases of post-COVID-19 ReA have also been reported in the paediatric age group [41, 45]. Unlike classical ReA, gender distribution appears equal between males and females. However, the total number of reported cases is too small for conclusive comments.

Treatment and outcome

The majority of the patients had responded to non-steroidal anti-inflammatory drugs (NSAIDs) while some received intra-articular steroids or rapidly tapered oral steroids (Table 2). Where outcomes are reported, usually, there was a response within the first week and the steroids /NSAIDs could be tapered down after 4 weeks. Only patients with rheumatoid arthritis-like phenotype with anti-citrullinated peptide antibodies had a chronic course and had to be given methotrexate [48–50].

Thus, the phenotype and outcomes of post-COVID-19 ReA appear to be different from those of classical ReA. These differences are summarized in Table 2.

Reactive arthritis after COVID-19 vaccination

Vaccination-induced autoimmunity is a concern since vaccines stimulate the immune system [51]. The first published case of ReA post-COVID-19 vaccination was reported in a 23-year-old woman after the inactivated Sinovac-CoronaVac vaccine [52]. We could identify a total of seven cases of inflammatory arthritis reported post-vaccination (Table 3).

Other post-COVID-19 inflammatory arthritis

We have reviewed post-COVID-19 rheumatic diseases at an earlier stage of the pandemic [57]. Post-COVID-19 peripheral nerve entrapment syndromes like carpal tunnel or tarsal tunnel syndromes have been hypothesized to be either due to localized demyelination, microangiopathy involving the vasa nervosum or an immune phenomenon targeting the adjacent synovial sheath [58]. An interesting group is the patients who have clinical phenotype and antibodies suggestive of rheumatoid arthritis developing post-COVID-19. These patients developed anti-cyclic citrullinated peptide antibody-positive arthritis after documented COVID-19 infection [48–50].

One concern was whether vaccination would cause a flare in persons with pre-existing autoimmune diseases [51]. Cases with flares of RA temporarily related to vaccination have been reported [59]. However, in a cohort of 724 patients with autoimmune rheumatic disease, only 4 patients had complained of a flare in joint pain. This was managed with NSAIDs and lasted less than a week [60].

In a cohort of 5493 RA patients from Hong Kong, a propensity-score weighted multivariate analysis did not show any association with COVID-19 vaccination and flare of RA [61].

Chronic arthritis after other viral infections

Several viruses are associated with acute polyarthritis that lasts less than 6–8 weeks [62]. In a small proportion of cases, such viral arthritis may become chronic such as in the case of HIV (Human Immunodeficiency Virus), Hepatitis B and C viruses [63, 64], parvovirus B19, and Chikungunya [65]. Some authors have argued that it may be better to label "COVID-19 associated arthritis" rather than "COVID-19 ReA" [66]. COVID-19 can also possibly precipitate arthritis in a susceptible individual. There is a case report of a lady with psoriasis and inflammatory bowel disease who developed arthritis post-COVID-19 infection [67].

Post-chikungunya or Parvovirus B-19 there can be an onset of arthritis indistinguishable from rheumatoid arthritis [68, 69]. A similar phenomenon has been reported post-COVID-19 too [48–50]. However, such anti-citrullinated antibody-positive RA has been reported only in 3 cases to date. The possibility of a coincidence cannot be excluded looking at the high incidence of COVID-19 infections and the not uncommon incidence of RA, but the point in support of a "reactive" arthritis is that the arthritis is seen after the acute COVID-19 infection. It is self-limiting. Had it been a direct viral arthritis, the synovitis should have occurred during the seroconversion phase. In acute COVID-19 infection, though arthralgia is common, documented arthritis has been rarely reported.

Possible pathogenic mechanisms

Viruses have been long implicated in the breakdown of immune tolerance and precipitation of autoimmune disease [70]. SARS-CoV-2 activates CD14 + monocytes and PD-L1 + neutrophils via the Osteopontin-mediated inhibition of Interleukin-10. This pathway is involved in rheumatoid arthritis and thus provides a common pathway for the

Table 1 Summary of case reports and case series on post-COVID-19 ReA

First author	Age/sex	Joint pattern	Axial involvement	Other features	Autoantibodies	Treatment	Outcome	Sacroiliitis on radiography	HLAB27 positivity	Family history of SpA	Uveitis	Dactylitis	Enthesopathy
[31]	73/M	Left first metatarsophalangeal, proximal and distal interphalangeal joints	No	None	ANA, RF, anti-CCP negative	NSAID	Resolved in 21 days	NA	NA	NA	NA	NA	NA
[32]	47/M	Knee monoarthritis	No	Balanitis	NA	Etoricoxib and administered intra-articular triamcinolone	Not mentioned	NA	NA	NA	NA	NA	NA
[33]	50/M	Ankle arthritis	No	None	ANA, RF, anti-CCP,	NSAID, intra-articular	"Moderate improvement"	NA	Negative	NA	NA	NA	Achilles tendon enthesitis
[34]	45/M	Acute symmetric polyarthritis of wrists and proximal interphalangeal joints	No	Diffuse myalgia	NA	Methylprednisolone tapering dose	Complete remission in 3 months	NA	NA	NA	NA	NA	NA
[35]	60/M	Right knee arthritis	No	None	ANA, RF, anti-CCP, antibodies to extractable nuclear antigens negative	NSAIDs	Improved in 3 weeks; no relapse until 6 months	NA	Negative	NA	NA	NA	NA
[36]	53/F 58/F	Nil	Sacroiliitis	None	HLA-B8 and B57 positive Autoantibodies negative	NSAIDs	Intermittent NSAID use at 6 months	NA	Negative	NA	NA	NA	NA

Table 1 (continued)

First author	Age/sex	Joint pattern	Axial involvement	Other features	Autoantibodies	Treatment	Outcome	Sacroiliitis on radiography	HLAB27 positivity	Family history of SpA	Uveitis	Dactylitis	Enthesopathy
[37]	16/F	Nil	No	None	ANA, RF negative	Naproxen	Resolved in 5 days	NA	Negative	NA	NA	Dactylitis of three toes	NA
[30]	27/F	First metacarpophalangeal	No	None	NA	NSAIDs plus steroids	Resolved	NA	NA	NA	NA	NA	NA
[38]	57/M	Left wrist, the right shoulder and the bilateral knees	No	None	ANA, RF, anti-CCP negative	Not mentioned	Resolved spontaneously	NA	NA	NA	NA	NA	NA
[39]	37/F	Nil	No	Extensor tendosynovitis	ANA, RF negative	Hydromorphone	80% improvement at 2 weeks	NA	NA	No	NA	NA	NA
[40]	65/F	Symmetric polyarthritis of ankles, wrists and knee joints;	No	Palpable purpura on calves	Autoantibodies negative	Not mentioned	Not mentioned	NA	Positive	NA	NA	NA	NA
[41]	10/M	Both knees and his right elbow	No	Urticaria	ANA, RF negative	Antihistamines and acetaminophen	Improved in 72 h	NA	NA	No	NA	NA	NA
[42]	39/F	Distal interphalangeal and proximal interphalangeal joints	No	None	ANA, RF, anti-CCP negative	Celecoxib for two weeks	Doing well two weeks after stopping NSAIDs	NA	NA		NA	NA	NA
[28]	53/M	Nil	Bilateral sacroiliitis	None	NA	Intramuscular methylprednisolone and oral diclofenac	Resolved in 3 months	NA	Positive	NA	NA	NA	NA

Table 1 (continued)

First author	Age/sex	Joint pattern	Axial involvement	Other features	Autoantibodies	Treatment	Outcome	Sacroiliitis on radiography	HLAB27 positivity	Family history of SpA	Uveitis	Dactylitis	Enthesopathy
[43]	55/M	Right ankle	No	Tenosynovitis of the posterior tibial tendon sheath	NA	Oral methylprednisolone	Controlled on 4 mg methylprednisolone	NA	Negative	No	NA	NA	NA
[44]	53/M	Right knee, both ankles and the lateral side of the left foot	No	None	ANA negative	Ibuprofen and prednisolone	Maintaining on Ibuprofen	NA	Negative	NA	NA	NA	NA
[45]	8/M 6/F	Left hip arthritis in both patients	No	None	NA	Naproxen Ibuprofen	Recovered within a week	NA	NA	NA	NA	NA	NA
[29]	27/F	Bilateral knee, ankle and midfoot joints and small joints of hands	No	None	RF was positive in low titres. Anti-CPA, and ANA negative	NSAIDs plus steroids plus opioid analgesics	Resolved in 4 weeks	NA	Negative	NA	NA	NA	NA
[46]	58/F	Right hip	Right sacroiliitis	None	NA	Indomethacin and 80 mg IM depot prednisolone	Remission in 14 days	NA	NA	No	NA	NA	NA
[47]	53/F	Left knee	No	None	RF, anti-CCP, and ANA all negative	Diclofenac 150 mg/day; tapered by 6th Week	No relapse until 6 weeks	NA	Negative	No	NA	NA	Not available

Anti-CCP, anti-cyclic citrullinated peptide; *ANA*, antinuclear antibody; *NA*, not available; *NSAID*, non-steroidal anti-inflammatory drug; *RF*, rheumatoid factor

evolution of inflammatory arthritis [71]. In Chikungunya viral infection, a prominent role of monocytes and anti-viral responses such as interferons has been postulated [72].

Interferon (IFN)-related pathways have been implicated in COVID-19 [73, 74] and these have a role in the initiation of rheumatoid arthritis. The TNF (Tumor Necrosis Factor)-induced animal models of rheumatoid arthritis are dependent on IFN and IFN response elements such as the IRF1 (interferon regulatory factor 1) transcription factor [75].

Also, various autoantibodies have been reported in COVID-19 [76]. Some of these might have pathological potential and if they persist after the infection, they may lead to rheumatic manifestations like arthritis. At least 15 different autoantibodies have been described in COVID-19 and 34 human peptides have similarities with SARS-CoV-2 proteins [77]. This may have implications for molecular mimicry in COVID-19.

Timelines of classic and post-COVID-19 reactive arthritides

Classical ReA is self-limiting in two-thirds of cases, but can damage the joints even in such a short period. Chronic ReA can have much worse sequelae. In the case of post-COVID-19 ReA, the manifestations appear more transient and self-limiting. This appears more similar to post-streptococcal ReA rather than classical ReA [17]. Also, some cases of post-COVID-19 ReA have different antibodies. There is a possibility that these may evolve into classifiable rheumatic diseases such as rheumatoid arthritis or lupus [57].

It is not necessary that all arthritis occurring post-COVID-19 should be reactive arthritis. The alternative is that it may be late-onset viral arthritis with actual invasion of the synovial space with the virus [78]. We could identify one study that reported the detection of SARS-CoV-2 RNA in a patient with wrist arthritis that had appeared 15 days after diarrhoea and upper respiratory tract symptoms [79]. However, other cases have not found such evidence [80]. Moreover, a post-mortem study also failed to find any viral RNA in synovial fluid or bone tissue in five patients who had died of COVID-19 [81].

Limitations

One limitation of this review is that the search strategy could miss cases of SARS-CoV-2 associated arthritis if the words "reactive" or "post-infectious" were not used. However, the main focus of the review was to assess how clinicians perceive and use the concept of reactive arthritis rather than only assessing SARS-CoV-2 associated arthritis.

Refining definitions for ReA

The definitions of ReA have been evolving gradually over the last half-century. Nevertheless, an ideal working definition still eludes us. Since this entity is not very common in high-income countries, there are possibly limited guidelines for this entity. The evidence base for treatment is also weak. The first and foremost requirement to fill in these deficiencies is a strong and universal definition of ReA.

Table 2 Differences between classical and post-COVID-19 reactive arthritis

	"Classical" reactive arthritis	Post-COVID-19 reactive arthritis
Age	15–40 years predominantly	Above 45 years predominantly, but reported in all ages
Gender	Male preponderance	Equal male–female distribution
Precipitating factor	Gut or urogenital infection	Respiratory tract infection
Inciting agent	Bacteria	Virus
Phenotype	Spondyloarthritis-like	Multiple phenotypes
	-Axial involvement	
	-Lower limb predominant oligoarthritis	
Joint predilection	Large joints	Small joints
Chronicity	1/3rd become chronic (lasts beyond 3 months)	Most resolve within 2 weeks to 3 months
Management	Treated as other spondyloarthritis (limited evidence base)	Usually, low dose steroids with or without NSAIDs is sufficient (limited evidence base)
Extra-articular manifestations	Dactylitis	Unknown/limited
	Enthesitis	
	Skin	
	Uveitis	
	Inflammatory bowel disease	

Table 3 Post-vaccination inflammatory arthritis

Reference	Age/sex	Vaccine	Temporal gap	Clinical features	Treatment	Outcome
[52]	23/F	CoronaVac	3 days after 1st dose; Again after the 2nd dose	Left knee monoarthritis	Celecoxib orally and intraarticular corticosteroid injections	Normal at 1-month follow-up
[53]	74/F	Sinovac	2 days after 2nd dose	Arthritis in the right wrist, 2nd–4th metacarpophalangeal and 2nd–4th proximal IP joints	10 mg/day prednisolone with tapering	No recurrence
[53]	76/M	Sinovac	1 week after 2nd dose	Arthritis in left hand all distal IP joints; hip; entire spine (previously diagnosed as ankylosing spondylitis)	10 mg/day prednisolone with tapering	No recurrence
[54]	72/F	Sinovac	3 weeks after vaccination	Arthritis in the left elbow, bilateral knees and right ankle	Prednisolone	Arthritis regressed in 2 weeks
[54]	79/F	Sinovac	5 days after the 2nd dose	Arthritis in both wrists, hand joints, and left ankle	Methylprednisolone	Had residual pain and swelling at 1-week follow-up
[55]	58/M	SPUTNIK-V	5 days after the 2nd dose	Left elbow	Non-steroidal anti-inflammatory drugs, physiotherapy, and intra-articular injection	Pain on active motion persisted at 1 month
[56]	38/F	SPUTNIK-V	20 days after the first dose with worsening after the 2nd dose	Arthritis in both shoulders and both knees initially. Involved small joints of hand and feet after the second dose	methotrexate, non-steroidal anti-inflammatory drugs, and methylprednisolone	Improved at 3 months follow-up

IP, interphalangeal joint

Though there is a definite association between COVID-19 and arthritis, the scientific rigor to establish causality is incomplete yet. Thus, any new definition should allow for reasonable doubt, but still be sufficiently solid to further studies in the field.

The advent of ultrasound in the detection of enthesitis can enable a more objective definition [82]. Also, radiographic features such as new bone formation at the site of enthesitis can be a possible marker [83]. Radiographic changes are late but ultrasound diagnosis can be early with validated OMERACT (Outcome Measures in Rheumatology Clinical Trials) definitions available [84].

Conclusion

The emergence of post-COVID-19 ReA and possibly post-vaccination ReA is forcing a paradigm shift in how we perceive this entity. Post-vaccination autoimmune diseases are being reported [85]. This leads to the question of whether individuals with genetic predisposition such as HLA-B27 positivity need to be segregated for different vaccines [52].

As the SARS-CoV-2 pandemic is transformed into an endemic due to wide-spread vaccination and emergence of less virulent strains, it will be interesting to study how this affects emergence of COVID-19 associated autoimmune conditions including ReA.

Finally, post-infectious arthritis may hold the key to understanding how the chronicity of arthritis develops. This may help in future preventive strategies. The first step has to be a coordinated effort across nations and various rheumatology societies to set up working definitions and enumerate thrust areas of research for ReA.

Author contribution All co-authors contributed substantially to the concept formulation, searches of relevant articles, and revisions. They approve the final version of the manuscript and take full responsibility for all aspects of the work.

Declarations

Conflict of interest SA has received honorarium as speaker from Pfizer, DrReddy's, Cipla, and Novartis (outside of the current work). All other authors declare no competing interests.

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Knowledge and Perceptions of Reactive Arthritis Diagnosis and Management Among Healthcare Workers During the COVID-19 Pandemic: Online Survey

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ABSTRACT

Background: Reactive arthritis (ReA) is an often neglected disease that received some attention during the coronavirus disease 2019 (COVID-19) pandemic. There is some evidence that infection with severe acute respiratory syndrome coronavirus 2 can lead to "reactive" arthritis. However, this does not follow the classical definition of ReA that limits the organisms leading to this condition. Also, there is no recommendation by any international society on the management of ReA during the current pandemic. Thus, a survey was conducted to gather information about how modern clinicians across the world approach ReA.
Methods: An e-survey was carried out based on convenient sampling via social media platforms. Twenty questions were validated on the pathogenesis, clinical presentation, and management of ReA. These also included information on post-COVID-19 arthritis. Duplicate entries were prevented and standard guidelines were followed for reporting internet-based surveys.
Results: There were 193 respondents from 24 countries. Around one-fifth knew the classical definition of ReA. Nearly half considered the triad of conjunctivitis, urethritis and asymmetric oligoarthritis a "must" for diagnosis of ReA. Other common manifestations reported include enthesitis, dermatitis, dactylitis, uveitis, and oral or genital ulcers. Three-fourths opined that no test was specific for ReA. Drugs for ReA were non-steroidal anti-inflammatory drugs, intra-articular injections, and conventional disease-modifying agents with less than 10% supporting biological use.

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Conclusion: The survey brought out the gap in existing concepts of ReA. The current definition needs to be updated. There is an unmet need for consensus recommendations for the management of ReA, including the use of biologicals.

Keywords: Reactive Arthritis; Post-Infectious Arthritis; COVID-19; Definition; Treatment; Surveys and Questionnaires

INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) has set up new challenges in the management of persons with chronic diseases such as rheumatological disorders.[1,2] Various registries and surveys have helped provide real-world data on patients with rheumatic diseases. Analysis of data from electronic record databases and other registries has shown that COVID-19 outcomes are usually poorer in patients with rheumatic diseases.[3-7] However, the bulk of this data is limited to patients having common rheumatic diseases like rheumatoid arthritis, spondyloarthritis (SpA), systemic lupus erythematosus, or psoriatic arthritis. There is some evidence that patients with SpA may have better outcomes with COVID-19.[8] However, limited information is available about reactive arthritis (ReA) during the pandemic.

The classical definition of ReA encompasses arthritis that occurs around 2–4 weeks after a genitourinary or enteric infection and with no direct infection in the primary joint structures.[9-11] It is a sub-type of SpA. Arthritis occurs as a result of immune-mediated changes rather than the direct invasion of the joints by any pathogen.[12] Several pathognomonic features are sacroiliitis, uveitis, dactylitis or enthesitis. The presence of the HLA-B27 gene or a family history of SpA, psoriasis, or uveitis helps to categorize a patient as having ReA.[13] In countries where ReA is not commonly diagnosed, it may be misclassified as peripheral oligoarthritis or even psoriatic arthritis.[14]

ReA is prevalent in lower-income countries. In contrast, it is not so much known in Eastern Europe and Central Asia. Worldwide it is thought that the incidence of ReA is declining. However, it is still encountered in developing countries where infections are common. Several questions remain unanswered about the patterns of ReA worldwide, in the background of wider antibiotic use and immunosuppressants. HIV-related infections are on the rise globally and these also seem to play a role in the pathogenesis of ReA as a direct arthritogenic agent or causing immune dysfunction and deregulation in the production of cytokines predisposing to infection by other arthritogenic pathogens.[15,16]

Generally, COVID-19 presents with mild to modest musculoskeletal symptoms such as arthralgia and myalgia. It does not typically cause clinical arthritis. The pattern of profound inflammation and generation of pro-inflammatory cytokines is similar between COVID-19 and ReA.[17] The introduction of the term "post-COVID ReA" has led to many new questions.[10] Also, ReA after COVID-19 vaccination has been reported.[18] After the COVID-19 pandemic, the emergence of this "post-COVID-19 ReA" has raised an important question of whether we must persist with the traditional definitions of ReA or update it to include more diverse entities. There is a burning need to allow or disallow arthritides occurring after emerging infections to be called ReA. The controversies brought forth in ReA by the pandemic are best summarized elsewhere.[19]

The focus is particularly on therapeutic cytokine inhibition to counteract the pathological hyper-inflammatory disease state. However, none of the rheumatology societies or such international organizations has advised on the management of ReA during the current pandemic. Therefore, this survey was conducted to look at the patterns of ReA encountered by rheumatology practitioners and understand their choices, especially in the context of the COVID-19 pandemic.

METHODS

This survey was devised to cover the current knowledge and perceptions of healthcare workers (HCWs) regarding ReA diagnosis and management amidst the COVID-19 pandemic. An online platform (SurveyMonkey.com) was used to carry out the survey.

Survey design

The survey was designed to obtain information about the understanding of pathogenesis and specific features of ReA (arthritis, dactylitis, enthesitis, conjunctivitis, uveitis, oral and/or genital ulcers, sacroiliitis), clinical presentation, common test practices used for diagnosis, presence of preceding infection (urogenital, gastrointestinal and respiratory), the time interval between triggering infection and onset of arthritis and commonly used management strategies in ReA patients. The survey also obtained information regarding arthralgia and/or arthritis cases post COVID-19 infection and changes in ReA incidence over time as experienced by HCWs in their practice.

Three experts reviewed the questions over three rounds of discussion to finalize the wording and ensure content validity. The third round included dummy fill-ups of the online form to have a real feel. After finalization, the survey included 20 questions, of which 18 were multiple choice questions with a single answer to be chosen for 13 and multiple answers allowed for five questions. The two remaining questions needed numerical value entry only.

The respondents could change the answers before submission but not after it. All questions were made mandatory, such that partial responses were automatically discarded by the SurveyMonkey platform.

Sampling strategy

We employed a convenient sampling strategy. The questionnaire was circulated on social media platforms like Twitter and Facebook between 6th October 2021 and 23rd January 2022. The survey began with an informed consent document with all information pertaining to the survey mentioned therewith.

The survey link was open from the time the survey link was circulated on social media. The cover letter included details on the background and purpose of the study. Informed consent was taken at the beginning of the survey and no incentives were offered for survey completion.

Statistical analysis

The normality of data was checked by the Shapiro-Wilk test. Mostly descriptive statistics are presented. For graphical representations, Microsoft Excel (Microsoft, Redmond, WA, USA) was used to build figures. Chi-square tests were used to compare responses between groups.

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Results were considered to be significant at a *P* value of < 0.05. Statistical analysis was performed also using Microsoft Excel.

Confidentiality

The survey was partly anonymised with Internet Protocol (IP) addresses and emails of respondents being the only linked identifiers. These identifiers were used to ensure unique entries from each individual. Data handling was completely anonymous, with the IP addresses and email lists remaining with the first and corresponding author. Other authors had access to the synthesized data in tables without linked identifiers.

Ethics statement

Full ethics review was exempted by the Institutional Ethics Committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow (protocol number 2021-299-IMP-EXP-44). We adhered to our recommendations on online surveys during the COVID-19 pandemic[20] and the Checklist for Reporting Results of Internet E-surveys to report the data.[21]

RESULTS

Out of a total of 193 respondents, nearly half (88, 45.6%) were adult rheumatologists followed by general practitioners (24, 12.4%). Nearly one-third lived in Kazakhstan (59, 30.6%) followed by Turkey (41, 21.2%). There were responses from 22 other countries also. A detailed description of the demographics of the respondents is presented in **Table 1**.

Presenting features of ReA

More than half (123, 63.7%) of the respondents were aware of the definition of ReA along with its origin, with nearly one-third (42, 21.8%) knowing the definition. Based on observations in clinical practice, the period between contracting the infection and presenting with ReA was reported to be more than two weeks in nearly half the cases (99, 51.3%) (**Fig. 1**). Urogenital (140, 72.5%) and gastrointestinal (121, 62.7%) system infections were among the majority to precede ReA (**Fig. 2**). Nearly half of the respondents reported that the triad of conjunctivitis (81, 42.0%), urethritis (87, 45.1%), and asymmetric oligoarthritis (108, 56.0%) were the classic clinical presentation signs of ReA. More than one-third (76, 39.4%) reported dermatitis in addition to the classical triad (**Fig. 3**). Among the specific features of ReA, nearly three-fourths (141, 73.1%) reported mono or oligoarthritis predominantly in the lower limbs, followed by asymmetric oligoarthritis (136, 70.5%), conjunctivitis (122, 63.2%) and enthesitis (pain or tenderness at the insertion of the Achilles tendon or plantar fascia) (97, 50.3%) (**Fig. 4**).

Diagnosis of ReA

Among the tests employed to examine ReA patients in order to reach a diagnosis, C-reactive protein (132, 68.4%) was the most commonly used modality followed by a test for Chlamydia trachomatis (120, 62.2%), Joints imaging/ultrasonography (affected joints and sacroiliac joints) (118, 61.1%), HLA-B27 (116, 60.1%) and others. However, nearly three-fourths (138, 71.5%) reported that there are no specific tests for the diagnosis of ReA.

Treatment of ReA

Non-steroidal anti-inflammatory drugs were the most commonly (162, 83.9%) used drug for the management of ReA in practice settings, followed by Intraarticular corticosteroid injections (79, 40.9%), Methotrexate and other disease-modifying antirheumatic drugs (78, 40.4%) and others.

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Table 1. Baseline demographics

Variables	Response
Specialty	
Adult rheumatologist	88 (45.6)
Paediatric rheumatologist	6 (3.1)
Rheumatology nurse specialist	3 (1.6)
Resident	23 (11.9)
Intern	6 (3.1)
General practitioner	24 (12.4)
Internal medicine specialist	12 (6.2)
Other	31 (16.1)
Years in medical practice after graduation	
0–10	89 (46.1)
11–20	57 (29.5)
21–30	23 (11.9)
31–40	14 (7.3)
> 40	10 (5.2)
Practice setting	
Private clinic	36 (18.7)
Public clinic	65 (33.7)
Both private and public clinics	18 (9.3)
Teaching hospital/outpatient setting	74 (38.3)
Country	
Kazakhstan	59 (30.6)
Turkey	41 (21.2)
India	14 (7.6)
Morocco	13 (6.7)
Croatia	11 (5.7)
Age	
18–25	29 (15.0)
26–35	67 (34.7)
36–45	54 (28.0)
46–55	27 (14.0)
56–65	14 (7.3)
> 65	2 (1.0)
Gender	
Female	77 (39.9)
Male	78 (40.4)
Not specified	38 (19.7)

Values are presented as number (%).

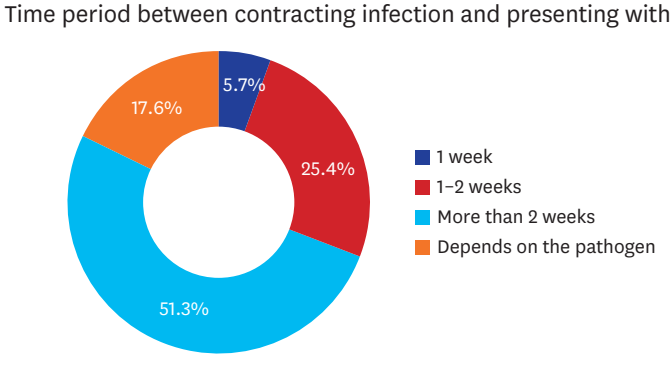

Fig. 1. Time period between contracting infection and presenting with ReA.
ReA = reactive arthritis.

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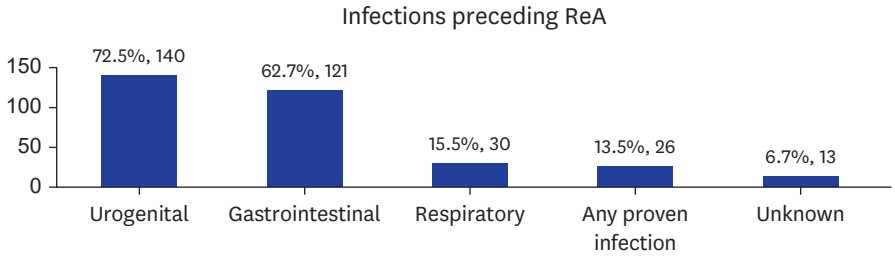

Fig. 2. Infections preceding ReA. Y axis depicts the number of respondents.
ReA = reactive arthritis.

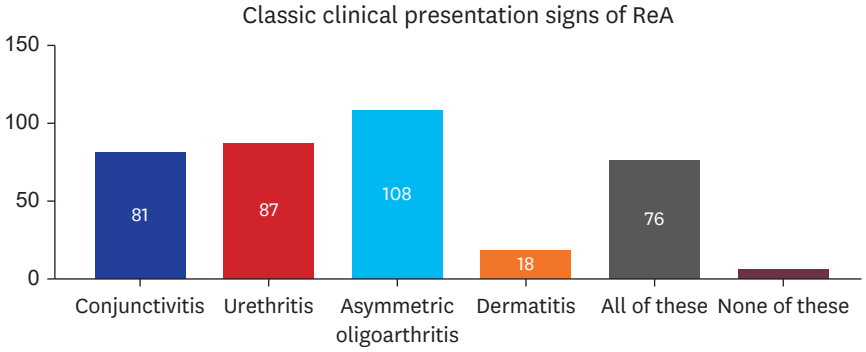

Fig. 3. Classic clinical presentation signs of ReA. Y axis depicts the number of respondents.
ReA = reactive arthritis.

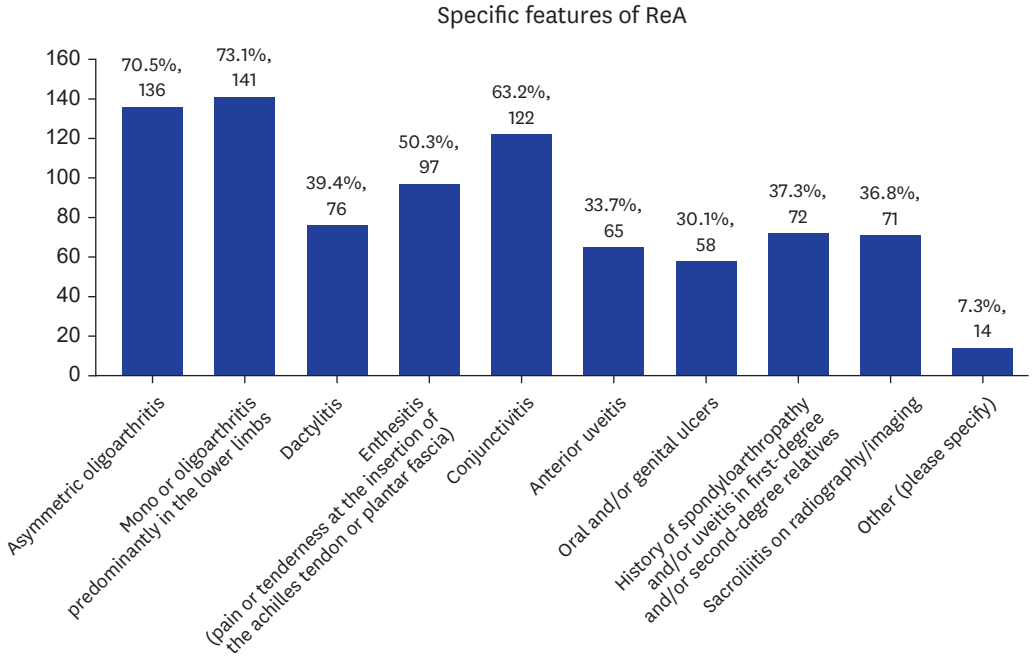

Fig. 4. Specific features of ReA. Y axis depicts the number of respondents.
ReA = reactive arthritis.

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Table 2 gives a detailed description of the Knowledge and perceptions of ReA diagnosis and management amidst the COVID-19 pandemic. **Table 3** gives a detailed description of the Knowledge and perceptions of ReA diagnosis and management in Kazakhstan and Turkey.

Table 2. Knowledge and perceptions of ReA diagnosis and management amidst the COVID-19 pandemic

Variables	Values
Presenting features	
Incubation period, wk	
1	11 (5.7)
1–2	49 (25.4)
≥ 2	99 (51.3)
Depends on the pathogen	34 (17.6)
Infections preceding ReA	
Urogenital	140 (72.5)
Gastrointestinal	121 (62.7)
Respiratory	30 (15.5)
Any proven infection	26 (13.5)
Unknown	13 (6.7)
Classic clinical presentation signs of ReA	
Conjunctivitis	81 (42.0)
Urethritis	87 (45.1)
Asymmetric oligoarthritis	108 (56.0)
Dermatitis	18 (9.3)
All of these	76 (39.4)
None of these	6 (3.1)
Other	3 (1.6)
Specific features of ReA	
Asymmetric oligoarthritis	136 (70.5)
Mono or oligoarthritis predominantly in the lower limbs	141 (73.1)
Dactylitis	76 (39.4)
Enthesitis (pain or tenderness at the insertion of the Achilles tendon or plantar fascia)	97 (50.3)
Conjunctivitis	122 (63.2)
Anterior uveitis	65 (33.7)
Oral and/or genital ulcers	58 (30.1)
History of spondyloarthropathy and/or uveitis in first-degree and/or second-degree relatives	72 (37.3)
Sacroiliitis on radiography/imaging	71 (36.8)
Other	14 (7.3)
Diagnosis of ReA	
Tests employed to examine ReA patients	
Clinical history and examination only	97 (50.3)
CRP	132 (68.4)
Uric acid in serum	59 (30.6)
Rheumatoid factor	89 (46.1)
Antinuclear antibodies	60 (31.1)
Antineutrophil cytoplasmic antibodies	37 (19.2)
HLA-B27	116 (60.1)
Test for anti-streptolysin O	63 (32.6)
Test for *Chlamydia trachomatis*	120 (62.2)
Test for *Mycoplasma*	62 (32.1)
Test for syphilis	62 (32.1)
Test for gonococcal infection	87 (45.1)
Test for HIV	59 (30.6)
Joints imaging/ultrasonography (affected joints and sacroilial joints)	118 (61.1)
Joint aspirate analysis	78 (40.4)
Other	8 (4.2)
Specific diagnostic tests employed	
Not sure	39 (20.2)
There are not any specific tests	138 (71.5)
Others	16 (8.3)

(continued to the next page)

Table 2. (Continued) Knowledge and perceptions of ReA diagnosis and management amidst the COVID-19 pandemic

Variables	Values
Treatment	
Commonly used treatment options for the management of ReA	
NSAIDs	162 (83.9)
Intraarticular corticosteroid injections	79 (40.9)
Oral corticosteroids	58 (30.1)
Intravenous (systemic) corticosteroids	21 (10.9)
Methotrexate and other disease-modifying antirheumatic drugs	78 (40.4)
Anti-TNF-alpha agents	15 (7.8)
Topical drug treatment	15 (7.8)
Joint support brace or tape	4 (2.1)
Other biologic agents	1 (0.5)
HCWs first preference as first line treatment for ReA	
NSAIDs	108 (56.0)
Intra-articular injections	6 (3.1)
A + B	51 (26.4)
Non-pharmacological only	2 (1.0)
Conventional synthetic disease-modifying antirheumatic drug (e.g., methotrexate, leflunomide, sulfasalazine, etc.)	17 (8.8)
Anti-TNF	4 (2.07)
Other	5 (2.6)
Subjects with persistent arthralgia and/or arthritis after recovering from COVID-19	
Yes	124 (64.3)
No	69 (35.8)
Online follow-up consultations/clinics for ReA patients	
Yes	64
No	129

Values are presented as number (%).
ReA = reactive arthritis, COVID-19 = coronavirus disease 2019, HIV = human immunodeficiency virus, CRP = C-reactive protein, NSAID = non-steroidal anti-inflammatory drug, TNF = tumor necrosis factor, HCW = healthcare worker.

DISCUSSION

This study aimed to identify the current knowledge and perceptions of HCWs regarding ReA diagnosis and management amidst the COVID-19 pandemic. The epidemiology of ReA has been evolving[15]and the COVID-19 pandemic has made it evolve further.

Nearly half of the survey respondents (88, 45.6%) were adult rheumatologists with up to 10 years of experience in medical practice after graduation (89, 46.1%). Nearly one-third of the respondents practised at a public clinic (65, 33.7%) and a teaching hospital/ outpatient setting respectively (74, 38.3%). The majority of the responses were from Kazakhstan (59, 30.6%) and Turkey (41, 21.2%).

ReA is inflammatory arthritis which manifests after several days to weeks after a genitourinary or gastrointestinal infection.[22] When the findings from Kazakhstan and Turkey are compared, we note that there is a significant difference in the percentage of respiratory infections preceding ReA, with the number of cases encountered being higher in Kazakhstan. It may point to the changing pattern in pathogens preceding ReA which could be a consequence of COVID-19 infection and its effects on individuals. Respondents from different parts of the world may be using different concepts or definitions of ReA.[23]

This perception of ReA occurring after respiratory infections is possibly the effect of the COVID-19 pandemic. ReA is often an orphan disease that may be neglected by physicians. However, the COVID-19 pandemic has brought it to the forefront.[24] Before this interest is lost, it

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Table 3. Knowledge and perceptions of ReA diagnosis and management in Kazakhstan and Turkey

Variables	Kazakhstan (n = 59)	Turkey (n = 41)	*P* value
Incubation period, wk			
1	10 (17.0)	0 (0)	0.002
1–2	11 (18.6)	10 (24.4)	0.827
≥ 2	19 (32.2)	27 (65.9)	0.238
Depends on the pathogen	19 (32.2)	4 (9.8)	0.002
Infections preceding ReA			
Urogenital	31 (52.5)	34 (82.9)	0.710
Gastrointestinal	20 (33.9)	34 (82.9)	0.057
Respiratory	13 (22.0)	4 (9.8)	0.029
Any proven infection	11 (18.6)	3 (7.3)	0.033
Unknown	7 (11.9)	0 (0)	0.008
Tests employed to examine ReA patients			
CRP	21 (35.6)	32 (78.1)	0.131
Uric acid in serum	22 (37.3)	9 (22.0)	0.020
Rheumatoid factor	32 (54.2)	18 (43.9)	0.048
Antinuclear antibodies	22 (37.3)	12 (29.3)	0.086
Antineutrophil cytoplasmic antibodies	21 (35.6)	5 (12.2)	0.002
HLA-B27	20 (33.9)	24 (58.5)	0.546
Test for anti-streptolysin O	27 (45.8)	9 (22.0)	0.003
Test for *Chlamydia trachomatis*	26 (44.1)	24 (58.5)	0.777
Test for *Mycoplasma*	19 (32.2)	9 (22.0)	0.059
Test for syphilis	23 (39.0)	8 (19.5)	0.007
Test for gonococcal infection	25 (42.4)	16 (39.0)	0.160
Test for HIV	12 (20.3)	10 (24.4)	0.670
Joints imaging/ultrasonography (affected joints and sacroiliac joints)	28 (47.5)	23 (56.1)	0.484
Joint aspirate analysis	14 (23.7)	21 (51.2)	0.237
Other	1 (1.7)	3 (7.3)	0.317
Commonly used treatment options for the management of ReA			
Non-steroidal anti-inflammatory drugs	38 (64.4)	38 (92.7)	1.000
Intraarticular corticosteroid injections	16 (27.1)	19 (46.3)	0.612
Oral corticosteroids	15 (25.4)	14 (34.2)	0.853
Intravenous (systemic) corticosteroids	19 (32.2)	1 (2.4)	-
Methotrexate and other disease-modifying antirheumatic drugs	18 (30.5)	16 (39.0)	0.732
Anti-TNF-alpha agents	3 (5.1)	1 (2.4)	0.317
Topical drug treatment	6 (10.2)	2 (4.9)	0.157
Joint support brace or tape	1 (1.7)	3 (7.3)	0.317
Other biologic agents	0 (0)	0 (0)	-
Subjects with persistent arthralgia and/or arthritis after recovering from COVID-19			0.115
Yes	28 (47.5)	26 (63.4)	
No	31 (52.5)	15 (36.6)	
Online follow-up consultations/clinics for ReA patients			0.641
Yes	18 (30.5)	8 (19.5)	
No	41 (69.5)	33 (80.5)	

Values are presented as number (%).
ReA = reactive arthritis, COVID-19 = coronavirus disease 2019, HIV = human immunodeficiency virus, CRP = C-reactive protein, TNF = tumor necrosis factor.

is imperative to update the definitions of ReA so that physicians worldwide recognise this entity in the same conceptual framework. Several newer pathogens beyond severe acute respiratory syndrome coronavirus 2 are being implicated in the pathogenesis of ReA.[25] Nevertheless, there is no consensus on how to include newer pathogens in the definition of ReA.[13]

Among the tests employed to examine ReA patients, there was a significant difference between Kazakhstan and Turkey when it came to the following tests: serum urate levels, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, test for anti-streptolysin O and test for syphilis, all of which is used in higher numbers in Kazakhstan. This may suggest the change in aetiology and origin of ReA over the years. However, regardless of the infectious agent and diagnostic modality, there has been no difference observed in the treatment

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of ReA.[26] The management goals of ReA in terms of providing symptomatic relief and preventing chronic complications are still prevalent.

This study also highlights the lack of clarity and consensus regarding the diagnosis and care of ReA. This is not new and has been acknowledged even whenever attempts have been made to structure working definitions.[19,27] Expanding the definition of ReA requires input from all parts of the world and this survey contains perspectives from central Asia that are often missing in the literature.[28] Since it is a relatively uncommon disease, it requires well-defined hypotheses and planning to establish clinically relevant case definitions.[29]

The limitations of the study include the snapshot picture of the data captured during the pandemic period. The pattern and chronicity may change in the future. It is also limited by the fact that the relationship between COVID-19 and ReA was not studied in great detail.

This survey highlights the varied interpretations of ReA by different respondents and the lack of consensus in management, especially during the COVID-19 pandemic. This calls for a united international effort for experts in the field to get together and formulate and update current definitions of ReA.

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Trends in the incidence of musculoskeletal diseases in Kazakhstan in 2011–2020: an information-analytical study

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Abstract

According to the World Health Organization, there is an increase in the incidence of musculoskeletal diseases worldwide. The problem of this group of diseases is that they are associated with the onset of temporary and permanent disability. A number of studies have demonstrated an increase in the incidence of musculoskeletal diseases in the US, Canada, Australia, and European countries. The current informational and analytical study was aimed to reflect on related morbidity trends in Kazakhstan. We analyzed data on the incidence of diseases of the musculoskeletal system in 2011–2020. Ten annual statistical yearbooks of the Ministry of Health of Kazakhstan were used to obtain data. The results showed an increase in the total incidence of musculoskeletal diseases of 304,492 cases between 2011 and 2020. Primary incidence of musculoskeletal disorders in the whole population increased by a factor of 1.5. The incidence rate of musculoskeletal diseases increased in the age group over 18 years and in the 0–14 years' child group. A comparative analysis of morbidity figures for rural and urban populations was also presented. An increase in the incidence of musculoskeletal diseases in both populations was observed. Finally, comparative data analysis on morbidity across Central Asian countries was provided. This information-analytical study shows that the incidence of musculoskeletal disorders is steadily increasing in Kazakhstan. The scientific community should pay attention to this trend to prevent further increases in the incidence of musculoskeletal disorders.

Keywords Musculoskeletal diseases · Incidence · Morbidity · Statistical yearbook · Kazakhstan

Introduction

The number of people suffering from musculoskeletal disorders is steadily increasing worldwide [1]. Factors influencing this growth are not only related to the global population growth, but are also associated with increased life expectancy and global spread of rheumatic diseases and injuries [2]. According to the World Health Organization data as of February 8, 2021, musculoskeletal disorders comprise an average of 150 different pathologies [3]. This broad group of clinical conditions and diseases includes osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gouty arthritis, ankylosing spondylitis, systemic lupus erythematosus, osteoporosis, fractures, dislocations, and many other entities [3]. Although musculoskeletal disorders are highly prevalent among the elderly, younger adults are also increasingly affected by the same diseases [4, 5]. The absolute number of subjects with musculoskeletal disorders is predicted to increase annually, particularly in developing countries [6].

Steadily increasing rate of temporary and permanent disabilities is a consequence of the global spread of musculoskeletal disorders [7]. Premature disabilities overburden societies with physical and psychological issues and result in economic hardships for individuals, their families, and societies. There are 1.71 billion people worldwide with musculoskeletal disorders [3]. A large number of them suffer from lumbago syndrome (568 million) [3]. The 2nd largest disease group presents with fractures (436 million) [3]. And the 3rd group is represented by subjects with osteoarthritis (343 million) [3].

Rheumatoid arthritis, one of the main autoimmune rheumatic diseases, affects 14 million people worldwide [8]. Overall, rheumatic diseases are spread across countries. In India, rheumatic diseases affect up to 24% of the population [9]. These diseases are among the most common

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chronic conditions leading to disability in Australia, Canada, Europe, and the US [10]. Joint pain is the most common reason of specialist referrals. At least 47.8 million people in the US suffer from arthritis, with a predicted increase to 60 million by 2020 [11]. Arthritis affects 8 million people in the UK and 108 million people across the European continent [12]. According to official data in Eastern European countries such as Ukraine, the percentage of rheumatic diseases increased by 40% in 1988–1993 [13]. In Bulgaria as of 2016, the number of patients with rheumatic diseases was 1712.1 per 100,000 population [14]. Musculoskeletal diseases are also supposedly a pressing issue in Kazakhstan. Therefore, the aim of this study was to explore related trends in Kazakhstan. We aimed to present the dynamics of musculoskeletal diseases in Kazakhstan in 2011–2020.

Methods

This study is informational and analytical in nature. For the analysis of epidemiological features of diseases of musculoskeletal system in Kazakhstan, we analyzed 10-year statistical data based on statistical yearbooks of the Ministry of Health of Kazakhstan titled—"Population health of the Republic of Kazakhstan and activity of public health organizations" (2011–2020 years) [15]. Statistics on the activities of health care organisations and health indicators in the Republic of Kazakhstan for each year are presented in each compendium. All yearbooks contain 20 sections each of which reflects numerical data of the activities of health-care organizations and health indicators. The indicators in the sections are divided into public, private, and departmental. All the numerical data in these compilations are generated by the Statistics tool of the Republican State Enterprise for "Republican e-Health Centre". All morbidity indicators for the period 2011–2020 belonging to the category 'musculoskeletal and connective tissue diseases' are included in the inclusion criteria. The exclusion criteria are morbidity rates from other disease categories that are not relevant for the period 2011–2020. Two tables, each with a 10-year summary, are generated to group the information obtained from the ten collections into a separate Word document. All the data are presented in Table 1. Morbidity per 100,000 population by sex and place of residence is reported. Morbidity per 100,000 is divided into age groups in Table 2. All statistical data are presented in absolute and relative numbers.

Results

Morbidity of total population of Kazakhstan has increased almost 1.4-fold from 682,585 to 987,077 in 2011–2020. During the same period, the level of overall morbidity in subjects above 18 years has increased from 563,226 to 861,178. An increase in the overall incidence is also noted in 0–14 age group, with an increase of 16,019 cases by 2020. In contrast, in 15–17 age group, the total incidence decreased over the decade from 45,821 to 36,342 cases. Alongside the increase in general morbidity, there has been an increase in primary morbidity by 122,052 since 2012. The dynamic of general and primary morbidity in the population is shown in Fig. 1.

The relative incidence rate per 100,000 has increased from 1,616 to 2,086.5 over the study period. At the same time, morbidity of females has increased from 1,619.4 to 2,336.9 per 100,000 over the same period.

The following incidence data are available for urban population: in 2011, the rate is 2006.7 per 100,000; there is a gradual decrease in the incidence rate from 1965.5 to 1834.6

Table 1 Gender- and residence-based distribution of the incidence of musculoskeletal diseases in Kazakhstan in 2011–2020 (per 100,000 inhabitants)

	Dynamic in 2011–2020									
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
The entire population of the country	1616.0	1603.7	1549.0	1503.4	1631.7	1884.3	2022.2	2117.3	2098.5	2086.5
Female population	1619.4	1661.7	1663.7	1640.8	1807.2	2094.7	2290.1	2408.3	2308.8	2336.9
Urban population	2006.7	1965.5	1905.0	1834.6	1974.3	2231.1	2413.3	2594.6	2531.8	2605.6
Rural population	1146.4	1165.1	1114.5	1073.1	1181.0	1421.4	1497.1	1457.8	1450.2	1342.9

Table 2 Age-related incidence of musculoskeletal diseases in 2011–2020 in Kazakhstan (per 100,000 inhabitants)

	Dynamic in 2011–2020									
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
0 to 14 years	1002.2	966.6	817.0	757.0	752.9	927.3	1078.4	1165.7	1135.7	978.1
15 to 17 years	2895.2	2893.1	2882.1	2796.7	2787.0	3022.3	3032.3	2952.7	2838.0	2317.7
Above 18 years	1743.5	1749.6	1738.2	1711.8	1908.9	2203.8	2352.9	2468.4	2465.7	2553.6

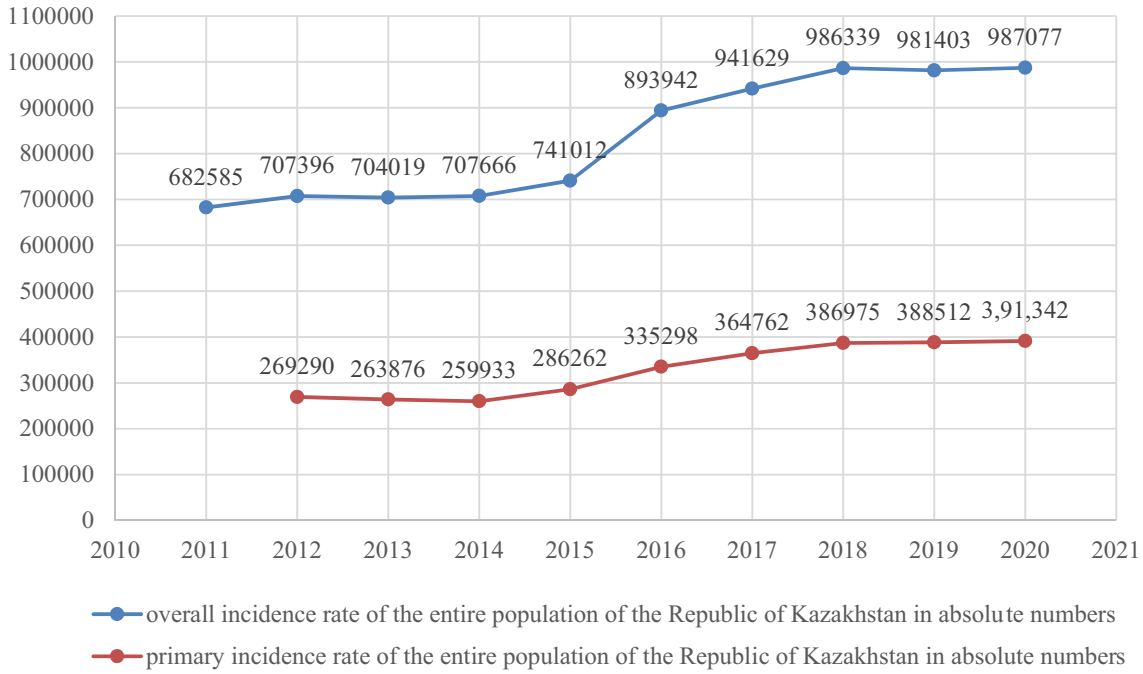

Fig. 1 Dynamics of general and primary incidence of musculoskeletal disorders in the population of Kazakhstan. *Statistical data on diseases of the musculoskeletal system according to statistical yearbooks of the Ministry of Health of Kazakhstan titled—"Population health of the Republic of Kazakhstan and activity of public health organizations" (2011–2020 years). *The graphs were made using Excel

per 100,000 in 2012–2014; a gradual increase from 1974.3 to 2594.6 per 100,000 in 2015–2018; however, there is a slight decline in the incidence are to 2531.8 in 2018–2019 and a further gradual increase to 2605.6 per 100,000 by 2020.

A fluctuating morbidity trend has been identified among rural subjects: from 2011 to 2012–from 1146.4 to 1165.1 per 100,000, from 2013 to 2014—1073.1 per 100,000, from 2015 to 2017—again an increase to 1497.1 per 100,000, and from 2018 a gradual decrease that reached 1342.9 per 100,000 by 2020. The rural and urban morbidity dynamic is presented in Fig. 2.

In comparative terms, the urban incidence rate is 2006.7 per 100,000 in 2011 and rural morbidity is 1,146.4 per 100,000. After a 10-year interval, the urban incidence rate is already 2,605.6 per 100,000 and rural incidence rate 1,342.9 per 100,000. The distribution of morbidity among the urban and rural subjects is shown in Table 1.

The incidence rate of diseases of musculoskeletal system in the age group above 18 years is as follows: 1743.5 per 100,000 in 2011 and 2553.6 per 100,000 in 2020. In the age group 0–14 years, there has been a decrease in the incidence rate during the study period, from 1,002.2 to 978.1 per 100,000 inhabitants. During the same period, the age group 15–17 showed a similar trend, with the incidence rate declining from 2,895.2 to 2,317.7 per 100,000 inhabitants. Data by age group are presented in Table 2.

Discussion

Musculoskeletal diseases are an urgent issue in Kazakhstan. According to the annual statistical yearbooks titled "On the state of health of the population of the Republic of Kazakhstan and the activities of health care organizations" (Ministry of Health of Kazakhstan), there is an increase in morbidity throughout the country. The predominant majority in the age structure are people older than 18 years. This is particularly important for the whole society whose work activities may be associated with increased strain, triggering—work-related musculoskeletal disorders [16]. Based on our results, the overall morbidity incidence rate in Kazakhstan has increased 1.4 times. The primary morbidity rate for the entire population of the country has risen 1.5-fold. In the 10-year timespan, the incidence rate increased in the age group above 18 years and in the child group 0–14 years, while a reduction in the incidence rate was recorded in the 15–17-year-old group. A decline in the incidence was recorded across the country from 2019 to 2020 at the beginning of the COVID-19 pandemic.

Data from other Central Asian countries were obtained to compare with local statistics. According to the Statistical Collection titled—"Health of the Population of the Republic of Tajikistan. 30 Years of State Independence", Tajikistan, like Kazakhstan, has seen an increase in morbidity. While in 2011, the morbidity rate was 3729

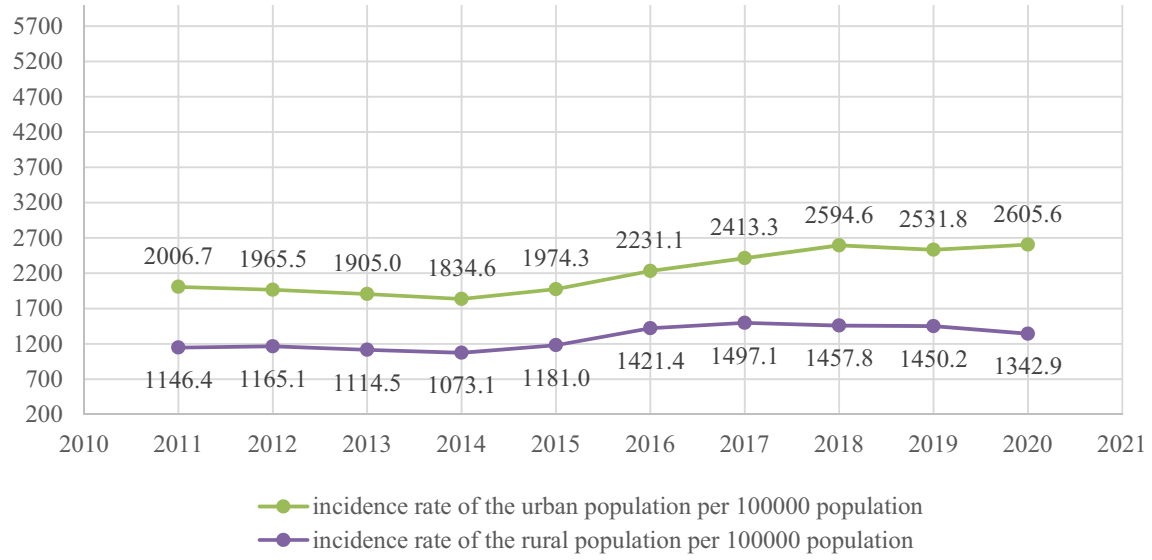

Fig. 2 Dynamics of incidence of musculoskeletal disorders among rural and urban populations in Kazakhstan (per 100 000 inhabitants) *Statistical data on diseases of the musculoskeletal system according to statistical yearbooks of the Ministry of Health of Kazakhstan titled—"Population health of the Republic of Kazakhstan and activity of public health organizations" (2011–2020 years). *The graphs were made using Excel

cases, by 2020, it had reached 52,483. In 2019, the incidence rate was higher at 64,417 [17]. A notable morbidity dynamic was observed in Kyrgyzstan. According to the National Statistical Committee of the Kyrgyz Republic, the primary incidence of diseases of the musculoskeletal system and connective tissue decreased from 40,276 to 37,751 cases from 2011 to 2020 [18]. However, 55,000 cases were reported in 2019 [18]. The COVID-19 pandemic and related quarantine are the most likely reasons for a sharp decline in the incidence from 2019 to 2020. Apparently, referrals to doctors had declined in the pandemic.

A decrease in domestic and crime-related injuries, which also account for a proportion of musculoskeletal disorders, can also be a big issue. A reverse increase in the incidence of musculoskeletal diseases from 2019 to 2020 could mean an improvement in the diagnostic capacity of health facilities. The consequence of this increase in musculoskeletal diseases is a steady increase in the rate of temporary and permanent disability among the patients [19]. Premature disability, in addition to physical and psychological damage, causes economic damage, primarily to the patients, their families, and ultimately to the whole health-care system and the state.

The limitations of this study are that the incidence rates for 2021, 2022 and 2023 are not reflected in the study. The authors plan to make a new information and analysis study as soon as the new statistical yearbooks are available.

Conclusion

As this informational-analytical study demonstrates, morbidity incidence throughout the country has been steadily increasing over the study period. Musculoskeletal diseases is a priority issue due to the poorly understood etiopathogenesis and progressive course. The issue of timely diagnosis and complexity of therapeutic tactic confound an increasing level of disabilities in the population. This study results draw the attention to this big issue and encourage the scientific community to act jointly to prevent further increases in the incidence of musculoskeletal diseases.

Author contribution All authors substantively contributed to the data processing and writing. They agreed to be fully accountable for the integrity of all aspects of the work.

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Data availability All data processed for this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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Structure, demography, and medico-social characteristics of articular syndrome in rheumatic diseases: a retrospective monocentric analysis of 2019–2021 data

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Abstract

Rheumatic diseases encompass a wide range of conditions characterised by joint inflammation and pain, significantly impacting individuals' quality of life. Articular syndrome, manifested through joint-related symptoms such as pain, swelling, and reduced mobility, is a common feature of rheumatic diseases. This study aimed to analyze articular syndrome's structure, demography, and medico-social characteristics in rheumatic diseases. We retrieved case notes of 370 patients examined in 2019–2021 at the Rheumatology Department of the Regional Clinical Hospital, Shymkent, Kazakhstan. We processed data on gender, age, place of residence, social status, clinical diagnosis, comorbid conditions, complications, and delays. The material was counted by frequency analysis. Statistical and mathematical data processing was performed using the SPSS application software package version 26.0 (IBM). The identified rheumatic diseases among the patients included rheumatoid arthritis (183), systemic lupus erythematosus (47), osteoarthritis (42), ankylosing spondylitis (31), systemic scleroderma (30), reactive arthritis (18), gouty arthritis (14), psoriatic arthritis (3), and dermatomyositis (2). The distribution of patients with articular syndrome varied across the study years, with 102 patients in 2019, 216 patients in 2020, and 52 patients in 2021. The study revealed the age distribution of patients, with an average age of 46 at the time of examination and an average age of disease onset at 39. The study further investigated the distribution of rheumatic diseases categorized by gender, place of residence (urban or rural), and disease duration. Additionally, the study examined the prevalence of comorbid conditions and complications related to the underlying rheumatic disease. By examining the structure, demography, and medico-social characteristics of the articular syndrome in patients with rheumatic diseases, this retrospective analysis provides valuable insights into the epidemiological aspects of these conditions. The findings may contribute to a better understanding of the burden of rheumatic diseases on individuals and society. Such knowledge can aid in developing targeted interventions, improving healthcare delivery, and enhancing patients' overall well-being.

Keywords Articular syndrome · Joint diseases · Arthritis · Rheumatic diseases · Retrospective studies · Kazakhstan

Introduction

The articular syndrome is a constellation of symptoms arising from various joint disorders. According to the Medical Subject Headings Dictionary (MESH), articular disorders encompass pathological processes affecting the joints [1]. Pain, or "arthralgia," is one of the primary manifestations of articular syndrome. However, isolated arthralgia lacks other features of the inflammatory syndrome, such as swelling, joint dysfunction, local increase in temperature, and hyperemia. Arthralgia can either occur as an independent manifestation of a disease or, when accompanied by the features above, indicate the presence of arthritis. MESH defines *arthritis* as acute or chronic inflammation of a joint. Arthritis can manifest as a primary condition or a concomitant clinical presentation of various pathological conditions, including infectious diseases, blood disorders, trauma, cancer, metabolic disorders, and autoimmune diseases. A study by Briggs et al. estimated that approximately 300 million individuals worldwide have arthritis [2]. Rheumatic

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diseases, characterized by inflammation, degeneration, or metabolic destruction in the joints and associated structures, are among the most complex causes of articular syndrome (according to the MESH). These diseases can be classified into inflammatory and non-inflammatory categories, with non-inflammatory rheumatic diseases being more common and generally having a better prognosis [3]. Some of the rheumatic diseases commonly associated with the articular syndrome include osteoarthritis (OA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), dermatomyositis (DM), psoriatic arthritis (PsA), systemic scleroderma (SSD), gouty arthritis (GA), rheumatoid arthritis (RA), and reactive arthritis (ReA) [4–6]. Complex pathogenetic mechanisms characterize these diseases and often exhibit a chronic course. Chronic arthritis can be viewed as a pathological process resulting from an imbalance between pro-inflammatory and anti-inflammatory cytokines [7]. In developing joint damage in osteoarthritis, traumatic factors accompanied by the systematic overuse of joints play a significant role. Tissue damage leads to the formation of damage-related molecular patterns, including products of cartilage extracellular matrix breakdown. These molecular patterns transmit signals through pattern recognition receptors on synovial macrophages and fibroblast-like chondrocytes, triggering the local synthesis of inflammatory mediators. Inflammation-induced increased vascular permeability results in the migration of plasma proteins, which can also serve as damage-related molecular patterns [8]. The production of inflammatory mediators and their actions inducing proteolytic enzymes contribute to further cartilage degradation [8]. Systemic scleroderma, a chronic autoimmune disease characterized by skin fibrosis, internal organ involvement, and vasculopathy, can also affect the joints [9]. The disease mechanism involves a genetically mediated immune system dysregulation, leading to the release of multiple cytokines, chemokines, and autoantibodies, which promote fibroblast activation, myofibroblast formation, and deposition of connective tissue [9]. In SSD, articular involvement is characterized by arthralgia, although some patients may develop erosive arthritis [10]. Systemic lupus erythematosus, another disease with joint involvement, often presents with multiple organ and system damage manifestations (e.g., kidneys, hematopoiesis). Research has revealed that B-lymphocytes in SLE produce numerous autoantibodies against soluble and cellular components, particularly intranuclear antigens (ANA), which subsequently lead to tissue and organ destruction. Several factors contribute to this phenomenon, including molecular abnormalities of immune cells, hormonal and sex chromosome effects, and genetic and environmental factors [11]. Recent large-scale studies have identified risk loci such as TNIP1, PRDM1, JAZF1, UHRF1BP1, and IL10 in developing systemic lupus erythematosus [12]. T cells have also been found to overexpress B cells and exacerbate inflammatory responses by producing insufficient interleukin-2 in SLE development [13]. Ankylosing spondylitis, characterized by inflammation of the entheses, bone erosions, and syndesmophyte formation, is associated with a genetic factor, particularly the presence of the HLA-B27 antigen. Chronic inflammation in AS can lead to ankylosis and impaired spinal mobility over time [14]. Dermatomyositis, an autoimmune myopathy, manifests as proximal muscle weakness, muscle inflammation, extra muscular manifestations, and autoantibodies [15]. Psoriasis, a common dermatosis characterized by scaly, thickened plaques, can cause arthritis. Psoriatic arthritis occurs in 10–40% of patients with psoriasis, often developing after ten years or more of psoriasis. In psoriatic arthritis, autoimmune damage occurs in the synovium and entheses, with initial infiltration of T cells, followed by a synovial and endothelial response to the inflammatory infiltrate products [16, 17]. Gout and gouty arthritis present a notable articular syndrome. Arthritis in gout is primarily caused by elevated serum urate levels, which subsequently form urate crystals in the joints [18]. The entry of these crystals into the joint cavity triggers an inflammatory cascade, resulting in acute painful arthritis [18]. However, the current understanding of gout is evolving from viewing it purely as a metabolic disease to recognizing its broader autoinflammatory nature [19]. Psoriatic arthritis most commonly affects the first metatarsophalangeal joint but can also involve larger joints such as the knee, wrist, or ankle [19]. Rheumatoid arthritis, a chronic systemic autoimmune disease, predominantly affects the hands and feet [20]. The disease's progression involves immune cell infiltration, synovial membrane hyperplasia, pannus formation, and articular cartilage and bone destruction. As the disease advances, focal necrosis may appear on articular surfaces, leading to joint deformities and, eventually, ankylosis [21]. Genetic factors leading to the formation of autoreactive T and B cells play a crucial role in the development of rheumatoid arthritis, along with triggers such as infections or traumatic tissue damage that activate previously generated autoreactive lymphocytes, leading to impaired immune tolerance and subsequent tissue destruction [22]. Reactive arthritis, also known as post-infectious arthritis, occurs several days or weeks after infections of the urogenital or gastrointestinal systems [23]. Despite being an often underestimated condition, reactive arthritis has gained attention during the COVID-19 pandemic [24–26].

Rheumatic diseases encompass a broad range of conditions characterized by inflammation and pain in the joints and connective tissues. These conditions affect millions of individuals worldwide and significantly impact their quality of life [27]. Articular syndrome, a common manifestation of rheumatic diseases, refers to joint-related symptoms such as pain, swelling, stiffness, and reduced mobility. This study examines the gender, age, and medico-social structure of

articular syndrome in rheumatic diseases in the Turkestan region of the Republic of Kazakhstan. This study aims to provide a comprehensive analysis of articular syndrome in rheumatic diseases using data collected from 2019 to 2021. Understanding the structure, demography, and medico-social characteristics of articular syndrome in rheumatic diseases is crucial for effective management and care. By examining retrospective data from a single center over a specific period, valuable insights can be gained regarding the prevalence, distribution, and clinical features of articular syndrome among individuals with rheumatic diseases.

Methods

A retrospective monocentric study was conducted, utilizing patient case notes as the primary data source. The study was conducted at the Regional Clinical Hospital of the Regional Health Care Department in the Turkestan region. The research focused on patients with articular syndrome of rheumatic origin.

Inclusion and exclusion criteria were established to determine the patients eligible for the study.

The inclusion criteria consisted of the following:

- Patients aged 18 years and over with rheumatic diseases accompanied by articular syndrome. The following exclusion criteria were applied:
- Patients with articular syndrome are attributed to causes other than rheumatic conditions (e.g., an articular syndrome in cancer, haematological or endocrine pathologies).
- Patients under the age of 18.
- Patients residing outside the Turkestan region. The place of residence is indicated on the title page of the case note. The study did not include patients with residence registration in other regions of Kazakhstan.

The final sample consisted of 370 individuals with articular syndrome of rheumatic origin and reactive arthritis residing in the Turkestan region of the Republic of Kazakhstan. Gender distribution was considered irrespective of gender identity, while the age criteria set the minimum age at 18. The study did not consider racial or ethnic distribution; instead, participants were selected from residents of the country's Turkestan region regardless of race or ethnicity. Data for the study were collected from patients with articular syndrome of rheumatic origin and reactive arthritis between 2019 and 2021.

Data collection was conducted through the completion of summary cards. Each patient had an individual summary card, ensuring anonymization by excluding personal identifying information such as names, document numbers, phone numbers, or specific addresses.

The summary card included the following patient details:

- Case note's No
- Gender/age
- Place of residence (city/village)
- Employment status (working/student/unemployed/pensioner/disabled)
- Dates of hospitalization/discharge
- Main diagnosis
- Comorbid conditions
- Complications related to the primary diagnosis
- Date of diagnosis
- Delayed diagnosis

The data collection was conducted only at the tertiary level of care.

Statistical analysis involved frequency analysis of the collected data; for the processing of variables, such statistical methods as grouping by gender and age, the formation of graphs and tables were used. The SPSS software package version 26.0 (IBM) was used for statistical and mathematical data processing.

Results

This retrospective monocentric study analyzed the case notes of 370 patients with articular syndrome associated with rheumatic diseases who received treatment at the Regional Clinical Hospital from 2019 to 2021. The study population comprised a nearly equal distribution of male and female patients. Among the 370 patients, the following rheumatic diseases were identified: rheumatoid arthritis (183), systemic lupus erythematosus (47), osteoarthritis (42), ankylosing spondylitis (31), systemic scleroderma (30), reactive arthritis (18), gouty arthritis (14), psoriatic arthritis (3), and dermatomyositis (2). Figure 1 illustrates the statistical

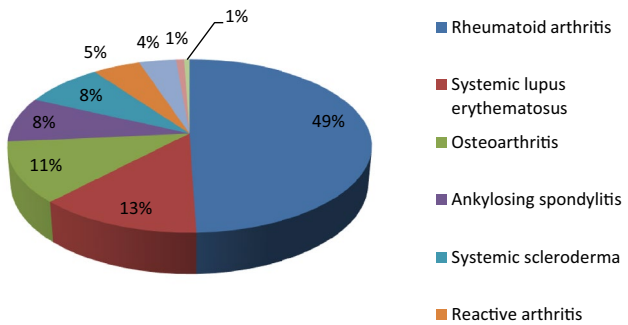

Fig. 1 Percentage structure of rheumatic diseases with articular syndrome for the period 2019–2021 ($n = 370$)

distribution of rheumatic diseases accompanied by articular syndrome as a percentage.

The distribution of patients with articular syndrome across the study years was as follows: 102 patients in 2019, 216 patients in 2020, and 52 patients in 2021. In 2019, out of the 102 patients with the articular syndrome, 49 had rheumatoid arthritis, 16 had osteoarthritis, 13 had reactive arthritis, 11 had systemic lupus erythematosus, 7 had ankylosing spondylitis, 4 had systemic scleroderma, and 2 had gouty arthritis. In 2020, among the 216 individuals with articular syndrome, the distribution was as follows: 114 cases of rheumatoid arthritis, 29 cases of systemic lupus erythematosus, 25 cases of osteoarthritis, 20 cases of systemic scleroderma, 15 cases of ankylosing spondylitis, 4 cases of reactive arthritis, 7 cases of gouty arthritis, 1 case of psoriatic arthritis, and 1 case of dermatomyositis. In the partial data available for 2021, out of the total 52 patients with articular syndrome, the distribution was as follows: 20 cases of rheumatoid arthritis, 9 cases of ankylosing spondylitis, 7 cases of systemic lupus erythematosus, 6 cases of systemic scleroderma, 5 cases of gouty arthritis, 2 cases of psoriatic arthritis, and 1 case each of reactive arthritis, osteoarthritis, and dermatomyositis.

The percentage distribution of diseases in different age groups is presented in Table 1.

The study revealed that among the 370 patients, the average age at the time of examination was 46 years, with a minimum age of 18 and a maximum age of 78. For the onset of the underlying rheumatic disease, the average age was 39, with a minimum age of 11 and a maximum age of 69.

Among males, rheumatoid arthritis (40.91%), ankylosing spondylitis (25.45%), and gouty arthritis (12.73%) were found to be the leading rheumatic diseases. On the other hand, among the female population, rheumatoid arthritis (53.08%), systemic lupus erythematosus (17.31%), and osteoarthritis (11.92%) were the predominant conditions. Figure 2 visually represents the structure of rheumatic diseases categorized by gender.

The distribution of rheumatic diseases accompanied by articular syndrome among urban residents is as follows: rheumatoid arthritis (38.30%), systemic lupus erythematosus (15.96%), and osteoarthritis (15.96%). Figure 3 visually illustrates the distribution of rheumatic diseases with articular syndrome among urban residents.

Among rural residents, the distribution of rheumatic diseases accompanied by articular syndrome was as follows:

Table 1 Percentage distribution of rheumatic diseases presenting with articular syndrome in different age groups for the period 2019–2021 ($n=370$)

Disease	18–44 years	45–59 years	60 years and over
Rheumatoid arthritis, $n=183$ (49.4%)	42.6%	57.6%	47.4%
Systemic lupus erythematosus, $n=47$ (12.7%)	22.8%	6.0%	1.75%
Osteoarthritis, $n=42$ (11.4%)	1.8%	14.6%	29.8%
Ankylosing spondylitis, $n=31$ (8.4%)	14.2%	4.6%	1.75%
Systemic scleroderma, $n=30$ (8.1%)	5.6%	11.9%	5.3%
Reactive arthritis, $n=18$ (4.9%)	9.3%	2.0%	–
Gouty arthritis, $n=14$ (3.8%)	2.5%	1.3%	14.0%
Psoriatic arthritis, $n=3$ (0.8%)	0.6%	1.3%	–
Dermatomyositis, $n=2$ (0.5%)	0.6%	0.7%	–

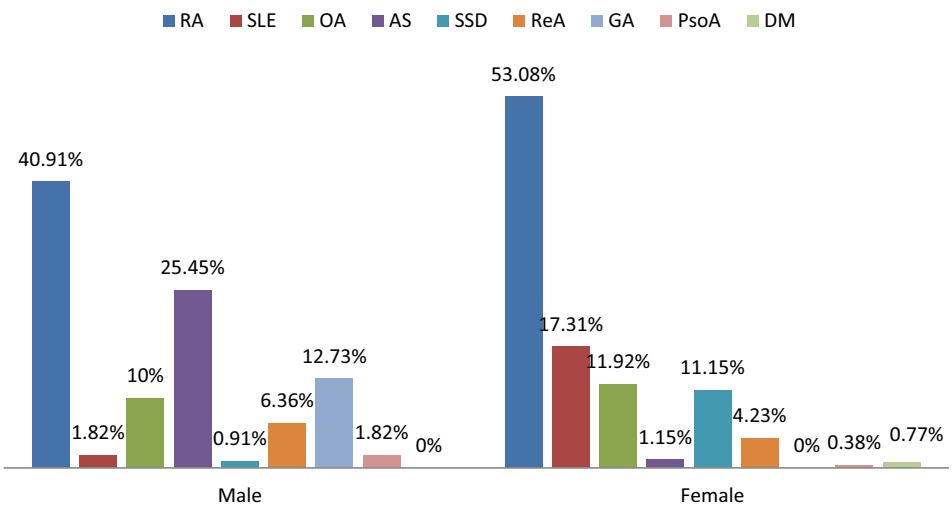

Fig. 2 Structure of rheumatic diseases by gender for the period 2019–2021 ($n=370$)

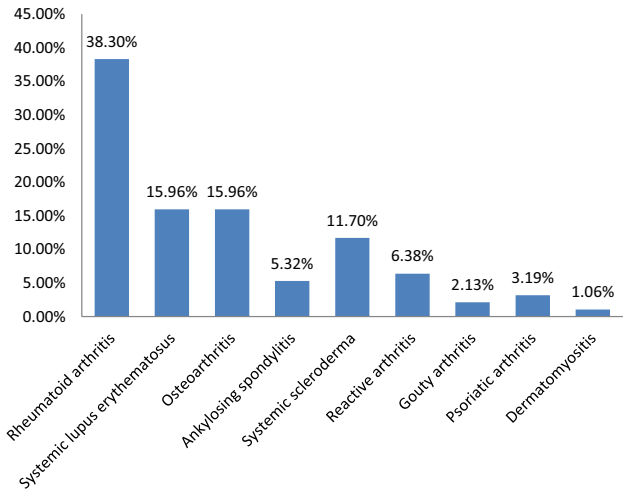

Fig. 3 Distribution of rheumatic diseases accompanied by articular syndrome among urban residents for the period 2019–2021 ($n=370$)

53.26% had rheumatoid arthritis (RA), 11.59% had systemic lupus erythematosus (SLE), and 9.78% had osteoarthritis (OA). Figure 4 visually presents the distribution of rheumatic diseases accompanied by articular syndrome among rural residents.

In rheumatoid arthritis, the distribution of patients based on the duration of the disease is as follows: 0–1 year (26.32%), 2–5 years (47.15%), 6–9 years (54.72%), and ten years or more (55.34%). For systemic lupus erythematosus, the distribution is 0–1 year (26.32%), 2–5 years (15.45%), 6–9 years (9.43%), and ten years or more (7.77%). In osteoarthritis, the distribution is 0–1 year (15.79%), 2–5 years (11.38%), 6–9 years (14.15%), and ten years or more (6.80%). Ankylosing spondyloarthritis follows with 0–1 year (2.63%), 2–5 years (7.32%), 6–9 years (2.83%), and ten years or more (17.48%). Systemic scleroderma has the following distribution: 0–1 year (0%), 2–5 years (6.50%), 6–9 years (9.43%), and ten years or more (11.65%). Reactive arthritis distribution is 0–1 year (15.79%), 2–5 years (8.13%), 6–9 years (1.89%), and ten years or more (0%). For gouty arthritis, the distribution is 0–1 year (7.89%), 2–5 years (4.07%), 6–9 years (4.72%), and ten years or more (0.97%). Psoriatic arthritis has a distribution of 0–1 year (0%), 2–5 years (0%), 6–9 years (2.83%), and ten years or more (0%). Dermatomyositis distribution is 0–1 year (5.26%), 2–5 years (0%), 6–9 years (0%), and ten years or more (0%).

Among the 370 patients, 53.78% were found to have comorbid conditions, while 54.05% experienced complications related to their underlying rheumatic disease. Comorbid conditions were present in 32.10% of patients aged 18 to 44 years, 70.20% in patients aged 45 to 59 years, and 71.93% in elderly patients over 60 years. Comorbid conditions were 55.45% in males and 53.08% in females. Concerning urban and rural populations, comorbid conditions were found in 51.06% of urban residents and 54.71% of rural residents.

Regarding complications, they occurred in 51.23% of patients aged 18–44, 60.93% of patients aged 45–59, and 43.86% of patients over 60. Complications were found in 49.09% of males and 56.15% of females. In the urban population, complications were observed in 52.13% of individuals, while in the rural population, the rate was 54.71%. Figure 5 illustrates the percentage of complications in different duration groups of the underlying rheumatic disease.

The duration of delayed diagnosis (in months) in patients with rheumatic diseases for 2019–2021 ($n=370$) had a mean value of 31.4 months, with a minimum value of 0 months and a maximum value of 218 months.

Discussion

Osteoarthritis affects a significant proportion of the population globally, with varying prevalence rates across different countries. In Canada, approximately 10% of the population is affected, with a higher prevalence observed in females.

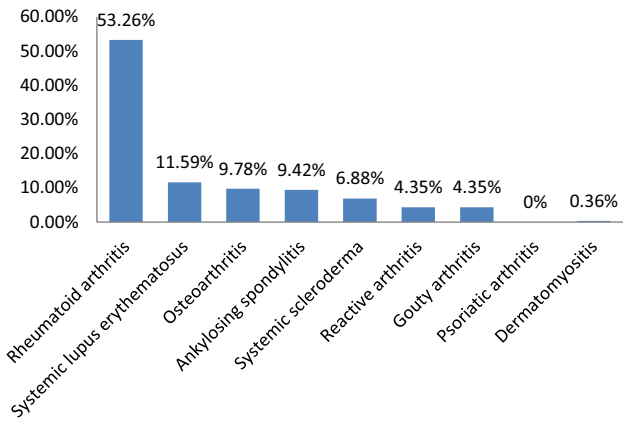

Fig. 4 Distribution of rheumatic diseases accompanied by articular syndrome among rural residents for the period 2019–2021 ($n=370$)

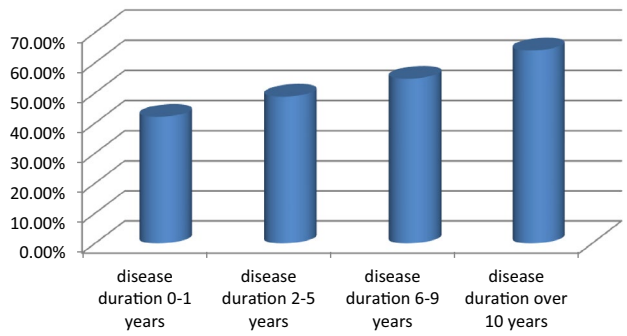

Fig. 5 Percentage of complications in groups according to the duration of underlying disease for the period 2019–2021 ($n=370$)

The United States reports a prevalence rate of up to 16.4%. In countries such as the United Kingdom, Australia, New Zealand, Belgium, and the Netherlands, the prevalence ranges from 8.0 to 13.0%. In contrast, lower-income countries tend to have lower incidence rates, ranging from 2.3 to 11.3% [28]. Rheumatoid arthritis has a prevalence of less than 1% globally, although prevalence rates of up to 4% have been reported in Australia, New Zealand, and the Netherlands. Ankylosing spondylitis's prevalence ranges from 0.1 to 0.5% worldwide, with a higher occurrence in males [28]. The prevalence of psoriatic arthritis ranges from 0.4% in the US and various European countries. Systemic lupus erythematosus and systemic scleroderma have a prevalence of 0.1% to 0.5% worldwide [28]. According to Mohammadhassan Jokar et al., rheumatoid arthritis (47.30%) is the most frequent pathology among rheumatic diseases, followed by spondyloarthropathies (17.23%), systemic lupus erythematosus (8.10%), and gout (7.84%) [29].

In the current retrospective monocentric study, the predominance of rheumatoid arthritis (RA) was observed in the structure of rheumatic diseases accompanied by articular syndrome in the Turkestan region of the Republic of Kazakhstan. This was followed by systemic lupus erythematosus (SLE), osteoarthritis (OA), ankylosing spondylitis (AS), systemic scleroderma (SSD), reactive arthritis, gouty arthritis, psoriatic arthritis, and dermatomyositis. Rheumatoid arthritis was the predominant disease across all age groups, while systemic lupus erythematosus was more prevalent in the 18 to 44 age group. Osteoarthritis was more common in the 45 to 59 and 60 and over age groups. Females were more frequently affected by rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, systemic scleroderma, and dermatomyositis. Males had a higher incidence of ankylosing spondylitis, reactive arthritis, gouty arthritis, and psoriatic arthritis. Differences in disease incidence were observed between urban and rural populations. Rheumatoid arthritis, ankylosing spondylitis, and gouty arthritis were more common in rural areas.

In contrast, systemic lupus erythematosus, osteoarthritis, systemic scleroderma, reactive arthritis, psoriatic arthritis, and dermatomyositis were more prevalent among urban residents. Rheumatoid arthritis, ankylosing spondylitis, and systemic scleroderma had a more significant number of patients with disease duration over ten years. Conversely, systemic lupus erythematosus, osteoarthritis, reactive arthritis, gouty arthritis, and dermatomyositis had shorter durations of 0–1 year. Nearly half of all patients had comorbid conditions and complications related to their underlying rheumatic disease. Comorbid conditions were most common in the age group over 60 years, and complications occurred more frequently in the 45–59 age group. Males had a higher rate of complications compared to females. The incidence of comorbid conditions and complications was similar between rural and urban residents. There was a correlation between the duration of the disease and the percentage of complications, with longer durations associated with a higher percentage of complications. Delayed diagnosis of rheumatic diseases was identified as a significant problem due to their complex pathogenesis and varied clinical presentations, leading to delayed treatment, complications, and a worsened prognosis.

The study also highlighted the trend of delayed diagnosis in several rheumatic diseases, including reactive arthritis. In 2019, most patients were diagnosed within two months of the onset of symptoms. However, in 2020, there was an increase in delayed diagnosis, with most patients being diagnosed between 3 to 6 months. In 2021, the trend reversed, and nearly all patients were diagnosed within less than two months. For rheumatoid arthritis, the delayed diagnosis was highest in 2019, with a significant proportion of patients being diagnosed between 13 and 24 months. In 2020, the delayed diagnosis increased for most patients, with diagnoses occurring after 25 months or more. In 2021, a similar pattern to 2019 was observed, with the majority of patients being diagnosed between 13 and 24 months. Systemic lupus erythematosus showed a delayed diagnosis of 3–6 months for most patients in 2019 and 2020. However, in 2021, most patients' delayed diagnosis was reduced to 2 months. Systemic scleroderma consistently exhibited delayed diagnosis of 25 months or more across all three years, with an increasing percentage of patients diagnosed later each year. Osteoarthritis also showed delayed diagnosis of 25 months or more in 2019, 2020, and 2021. Ankylosing spondylitis, gouty arthritis, and psoriatic arthritis shared a similar pattern of delayed diagnosis, with most patients being diagnosed after 25 months or more across all three years. Overall, most patients across all rheumatic diseases experienced delayed diagnosis of 25 months or more.

Limitations

This study has certain limitations as it was a monocentric retrospective study. Another limitation of the study is that the data collection was conducted only at the tertiary level of care. Therefore, further investigation and research are needed to generalize the results to a broader population.

Conclusion

By examining the structure, demography, and medico-social characteristics of the articular syndrome in patients with rheumatic diseases, this retrospective analysis provides valuable insights into the epidemiological aspects of these conditions. The findings may contribute to a better understanding

of the burden of rheumatic diseases on individuals and society. Such knowledge can aid in developing targeted interventions, improving healthcare delivery, and enhancing patients' overall well-being.

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Data availability The data that support the finding of this study are available on a reasonable request from the corresponding author.

Declarations

Conflict of interest The authors have stated that there are no conflicts of interest in connection with this article.

Ethical approval This study was approved by the Local Ethics Committee at South Kazakhstan Medical Academy, protocol N 044-65/08-47, 2021.

Informed consent The requirement for additional written informed consent was waived because of the retrospective design of this study and the use of anonymous patient data.

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REVIEW

Revisiting articular syndrome in the peri-pandemic COVID-19 era

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Abstract
Articular syndrome is often the presentation of a person's various rheumatic or related diseases. It includes both arthralgia and arthritis, with objective signs of joint inflammation defining the latter. This syndromic approach to joint pain enables a scientific method for early diagnosis of common rheumatic conditions without compromising the recognition of uncommon conditions. This review explores common rheumatic conditions associated with articular syndrome, including osteoarthritis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE). It supports the early differentiation of uncommon but emerging entities such as reactive arthritis (ReA). The aim of the review is to comprehensively overview various forms of articular syndrome to update rheumatologists' and allied health specialists' knowledge. Epidemiology, clinical presentations, diagnostic approaches, and therapeutic strategies are discussed in the context of articular syndrome. The challenges emerging in the peri-pandemic COVID-19 era are highlighted. The improved understanding of the spectrum of clinical conditions and disease states presenting with articular syndrome may facilitate early diagnosis, optimal management, and enhanced patient outcomes within the realm of rheumatology.

Keywords Articular syndrome · Joint diseases · Arthritis · Rheumatic diseases

Introduction

Arthralgia and arthritis constitute two ends of the articular syndrome. Arthritis presents with objective signs of joint inflammation while arthralgia accompanies various inflammatory and non-inflammatory conditions, frequently heralding (auto)immune and inflammatory processes in the joint [1]. The most common conditions and disease states presenting with arthralgia include osteoarthritis (OA), fibromyalgia, systemic viral infections such as chikungunya and dengue fever, osteonecrosis, pregnancy, menopause, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren's syndrome. Symmetric polyarthralgia often marks the debut of RA and prompts comprehensive serological and radiographic exams [1–4]. Joint pain without clinically evident inflammation (arthralgia) and arthritis are briefly analyzed in Table 1.

For rheumatologists and allied specialists, the forgotten term "articular syndrome" may be helpful to better understand a variety of conditions presenting with periarticular pain, arthralgia, and arthritis. This review aims to comprehensively overview articular syndrome in the context of rheumatic diseases to update general practitioners' and rheumatologists' knowledge in the field. The review covers epidemiology, clinical presentations, diagnostic approaches, and treatment options for articular syndrome. The challenges emerging in the peri-pandemic COVID-19 era are discussed. This overview may help to improve understanding of articular syndrome, facilitating early diagnosis, optimal management, and enhanced patient outcomes.

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Table 1 Brief overview of arthralgia and arthritis

Features	Arthralgia	Arthritis
Definition	Specific or non-specific pain localized to a joint	Inflammatory change in a joint
Symptoms	Pain	Pain Swelling Redness of overlying skin Limited movements
Origins	Inflammatory and non-inflammatory (degenerative) conditions	Inflammatory disease states
Specificity	May not be due to joint disease	True joint disease

Search strategy

For the purpose of the review, comprehensive searches were conducted on Medline/PubMed, Scopus, and Web of Science with terms related to arthritis, arthralgia, and articular syndrome. English articles on diagnosis and differential diagnosis of various forms of arthritis and arthralgia were preferentially retrieved and analyzed in line with the widely publicized recommendations on writing narrative reviews [5].

Epidemiology of articular syndrome

The available data on articular syndrome in RA and spondyloarthritis (SpA) mostly stem from global studies of the prevalence of disease states rather than symptom complexes. The prevalence of RA ranges from 0.1% in Southeast Asia to nearly 1% in Europe and some ethnicities of Latin America [6]. Although there is an abundance of epidemiological data from different countries, continents, and ethnicities, related studies are heterogeneous. The Global Burden of Disease 2017 study reported an incidence of RA to be around 1,204,599 per year (95% CI 1071.1–1331.7) and a prevalence of 19,965,115 (17,990.5 to 21,955.7) [7]. Developed countries reported most cases of RA, closely followed by India and Sub-Saharan Africa [7].

RA is a female-predominant disease. Although the exact sex ratio varies globally, the average female-to-male sex ratio is 2:1 [8]. With the global life expectancy increasing, the prevalence of RA is rising and with robust medical aid, early diagnosis and treatment are translating to reduced cardiovascular (CV) mortality in these patients, as these individuals develop a 50% higher risk than the general population for a CV event [9]. In recent years, the crude disability-adjusted life years (DALY) have also shown an improvement with better access to healthcare and advancements in treatment. However, this data may not be uniform from the rural population, where disease management may be limited by access to healthcare, financial restrictions, and poor awareness. These patients may potentially have a higher propensity to develop higher damage as their time to initiation of DMARDs may be late and the optimization of therapy may be poor. Telemedicine practices can aid greatly in bridging this gap and can bring the rheumatologist closer to the patient to ensure good disease control and achieve a good quality of life [10].

Based on population studies, prevalence estimates of spondyloarthritis vary among different types of SpA such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), and reactive arthritis (ReA). The highest prevalence of AS is reported in population-based reports from North America (6–10%) with a 50% association with HLA-B27 [11, 12]. Asian evidence stems from Chinese reports, which state a prevalence of SpA in 0.2–0.3% of the general population [13]. While AS predominates in males, non-radiographic axial SpA (nr-ax-SpA) is more prevalent in females [14]. Overall, ReA is uncommon, but pockets of relatively higher incidence seem to exist [15]. As ReA is self-limiting, in countries where a referral system is in place, the joint inflammation may resolve on non-steroidal anti-inflammatory therapies by the time the patient reaches a rheumatologist.

Differential approach to articular syndrome

Once a patient presents with pain, the first step is to determine whether the pain is actually from within or around the joint. Pathologies arising from around the joints are usually referred to as "periarthritis" [16]. The characteristic feature is that pain occurs predominantly with active movements rather than with passive movements of the joint. In inflammatory arthritis, pain occurs during both active and passive movements of the joints.

Periarthritis

The term periarthritis refers to the inflammatory affliction of tissues surrounding a joint rather than inflammation of the joint itself. Most commonly affecting the shoulder joint, it is characterized by inflammation of tissues and excessive scar formation and adhesion of tissues, eventually leading to pain, restriction of movements, and loss of shoulder function [17]. This clinical entity was described by Codman in 1934,

and has been labeled frozen shoulder (FS) due to debilitating loss of function of the shoulder joint or adhesive capsulitis (AC) due to extensive adhesions following inflammatory changes in the bursa or capsule tissue (typically in middle-aged to the elderly population) [18, 19]. Adhesive capsulitis can be classified as primary and secondary. Primary, or idiopathic periarthritis, occurs without inciting causes or trauma, although various risk factors such as diabetes mellitus, thyroid disorders, cerebrovascular disease, coronary artery disease, Parkinson's disease, Dupuytren's disease, and autoimmune disorders can be associated [20]. Secondary periarthritis usually occurs after severe articular trauma such as fractures and dislocations of the glenohumeral joint and open or arthroscopic surgeries of the shoulder [21, 22]. Recently, there have been reports of an increase in the incidence of periarthritis after COVID-19 [23]. Management of AC consists of non-operative therapy with non-steroidal anti-inflammatory drugs (NSAIDs), oral or locally injectable corticosteroids, physiotherapy, extracorporeal shock wave therapy, hydrodilatation, nerve blocks, and operative treatments such as manipulation under general anesthesia, and arthroscopic capsular release; however the UK FROST trial found no superiority of any one technique over another [24, 25].

Non-inflammatory arthritis

Osteoarthritis and Charcot disease will fall under the category of non-inflammatory arthritis. Once pain has been established to arise from within the joint, it is vital to delineate inflammatory and non-inflammatory origins (Table 2). Inflammatory arthritis usually presents with cardinal signs of inflammation such as dolor (pain), rubor (redness/erythema), calor (warmth), tumor (swelling), and function laesa (loss of function) and is associated with early morning stiffness lasting for more than 30 min, with the pain aggravating on rest and relieving with activity [26]. Non-inflammatory arthritis is typically due to osteoarthritis (OA), a degenerative change in the joints of mostly the geriatric population, though early OA in subjects under 45 years is also reported (due to metabolic syndrome and deformities of the articular surfaces). The symptoms of pain worsen with activity and relieve with rest, and stiffness lasts less than 30 min [27]. Inflammatory arthritis may involve a single (monoarthritis) or multiple joints (polyarthritis) of both upper and lower limbs while degenerative arthritis mostly affects weight-bearing large joints.

Evidence-based approach to the articular syndrome

Spondyloarthritides (SpA) constitute inflammatory arthritides that are defined as seronegative due to the absence of antibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA). The commonality among these arthritides is the association with HLA-B27, the main genetic risk factor for these diseases. The prevalence of HLA-B27 varies across the spectrum of SpA. Axial SpA (ax-SpA), peripheral spondyloarthritis (pSpA), and non-radiographc-ax-SpA. Currently, according to the Assessment in Ankylosing Spondylitis (ASAS) study group, SpA is defined as a spectrum that includes ax-SpA, pSpA, AS, PsA, ReA, and inflammatory bowel disease (IBD)-associated arthritis [28]. The term ax-SpA was proposed to include pre-clinical and subclinical disease states in which the patients are asymptomatic or mildly symptomatic, acute-phase reactants are elevated, however, there is no evidence of radiographic sacroiliitis, and the patient does not meet the AS criteria. This is a progressive disease process. The concept of ax-SpA is

Table 2 Brief overview of inflammatory and non-inflammatory arthritides

Feature	Inflammatory	Non-inflammatory
Temporary characteristics of pain	Morning pain, reduces during a day	Evening pain, reduces with rest
Morning stiffness	More than an hour	Less than 30 min
Onset	Sudden, relapsing, and remitting	Slow, progressive
Swelling	Present	Usually absent
Redness	Present	Absent
Warmth	Present	Present sometimes
Fever, night sweats, unintentional weight loss	Present sometimes	Absent
Serum inflammatory markers	Elevated	Usually normal
Synovial fluid white blood cells	More than 2000 cells/mm^3	Less than 2000/mm^3
Knee radiography	Periarticular osteopenia, panarticular involvement	Periarticular sclerosis, usually involves the medial compartment
Examples of related diseases	Rheumatoid Arthritis, Spondyloarthritis, Psoriatic Arthritis, Reactive Arthritis, Crystal induced arthritis	Osteoarthritis, osteonecrosis, Charcot joint

proposed to include the whole spectrum, from the onset of nr-ax-SpA and to its progression to radiographic ax-SpA or AS [29].

This spectrum of arthritis presents with an inflammatory back pain (IBP) that is classically described as low back pain or alternating buttock pain in an individual who is under 40 years at the start of symptoms. It is an insidious process in onset, persists for at least 3 months, associated with morning stiffness of around an hour, worse in the second half of the night, and improves with activity. The Calin criteria described IBP with a sensitivity of 95% and specificity of 76%, and it is also adopted to define IBP in the New York classification criteria for AS [30, 31]. However, Calin criteria have little clinical utility[32]. Other criteria for low back pain include the Berlin and European Spondyloarthritis Study Group (ESSG) criteria [33, 34].

Enthesitis is a predominant and specific symptom of SpA. Enthesis is the site where a tendon or a ligament inserts into the bone. Enthesitis is not merely the inflammation of these soft tissues at their insertion, but also the damage to the bone, leading to enthesophytes formation. With this understanding, came the concept of an "entheseal organ" that involved the bone, fat pad, bursa, fascial planes, and enthesis [35]. Clinical entheseal scoring systems are adopted to assess the extent of entheseal inflammation in SpA, and they include Leeds enthesitis index (LEI) used in PsA, Maastricht ankylosing spondylitis enthesitis index (MASES) used in AS and Spondyloarthritis research consortium of Canada (SPARCC) [36–38]. Musculoskeletal ultrasonography and magnetic resonance imaging (MRI) have been widely used for the assessment of enthesitis [39]. Assessment of enthesitis is of value in SpA as it is potentially refractory to therapy and may result in persistent high disease activity and ambulatory difficulties despite the absence of active arthritis.

Psoriatic arthritis

Axial disease in other types of SpA may not be symmetric and gradually ascending as it is in AS. In PsA, the prevalence of axial disease varies widely from 25% to 70%, however, only less than 5% have an exclusive sacroiliac involvement [40–42]. In a large follow-up cohort study of Canadian patients with PsA who had unilateral radiographic Grade II sacroiliitis at baseline, more than 50% of patients progressed to bilateral Grade II or higher and/or unilateral Grade III or higher, fulfilling the modified New York criteria for AS over a period of 5.5 years [41]. Some of the risk factors that have been attributed to axial involvement in PsA are male gender, smoking, more extensive nail involvement, and responsiveness to anti-TNF agents [43].

IBD-associated arthritis

Arthritis is the most common extra-intestinal manifestation in IBD, affecting around 30% of patients; however, the prevalence of sacroiliitis is not as common as in PsA [44, 45]. In a population-based cohort study from Italy and Netherlands, 12.5% of patients reported buttock pain and 8.8% reported inflammatory low back pain; however, radiographic sacroiliitis was demonstrable in only 3.6% of cases [44]. A Brazilian cohort study reported inflammatory low back pain in 10%, but radiographic sacroiliitis was present in only 6% [45]. IBD-associated arthritis more commonly presents as peripheral oligoarthritis that can be transient and resolve with low-dose steroids or in some cases persist, warranting the administration of DMARDs or anti-TNF agents.

Reactive arthritis

ReA is primarily classified as pSpA and is classically described as a lower-limb oligoarthritis that occurs following a distant infection in the gut or the genitourinary (GU) tract. Axial involvement is sparsely described in the literature, though there are no large-scale population-based studies assessing the same [46]. Clinical experience suggests that less than 10% of patients with ReA have axial involvement at the onset, and the traditional description is a self-limiting arthritis that resolves within 6 months on NSAID therapies. Although the treatment of pSpA and ax-SpA have been extrapolated to ReA, a robust diagnostic and treatment guide is still lacking.

HLA-B27-negative SpA

While HLA-B27 is known as a risk factor for the development of chronic and aggressive phenotype of SpA, its absence does not translate into the absence of disease. There is a potential risk of delay in the diagnosis ranging from 3 to 7 years, which is partly due to milder disease or misdiagnosis [47, 48]. The prevalence is reported to be lesser in women (around 40%) and is more commonly associated with nr-ax-SpA [49]. A HLA-B27-negative disease may have a milder course with lesser damage accrued over the years; however, the response to therapy in these patients is also suboptimal. Studies have demonstrated that as compared to HLA-B27-positive patients, these patients had a poorer response to both anti-TNF and anti-IL-17 agents [50–52]. Physicians have to be alerted to recognize cases of HLA-B27-negative SpA and avoid diagnostic delays that may result in delayed administration of therapy and higher damage accrual.

Laboratory evaluation is mostly to detect systemic inflammation in the form of raised acute-phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein

(CRP). A strong HLA-B27 association has been reported in these diseases with the highest prevalence in AS and nr-ax-SpA (75–90%) [14, 53], followed by PsA (35%) [54, 55], ReA and IBD-associated arthritis [56]. Additionally, patients positive for HLA-B27 tend to be males who are younger at the onset of symptoms, have an aggressive course of the disease, with strong familial aggregation [57]. They also have a higher frequency of uveitis and respond well to anti-TNF agents [58]. Radiographically, the ASAS and modified New York criteria have been described for MRI and plain radiographic definition of sacroiliitis [28, 31, 59].

NSAIDs and physical therapy are initially prescribed for the treatment of ax-SpA [60]. The other drugs include Janus kinase inhibitors (JAKi) such as tofacitinib, anti-TNF agents, anti-IL-17 agents such as secukinumab and anti-IL-12/23 agents such as ustekinumab, the administration guidelines for which have been proposed by ACR/EULAR [61]. Conventional synthetic DMARDs (csDMARDs) such as methotrexate, sulfasalazine, and leflunomide are initially prescribed to treat PsA; biologic DMARDs such as JAKi, anti-TNF, anti-IL-17, and anti-IL12/23 agents are indicated when csDMARDs fail to suppress arthritis [62]. The treatment of ReA is not guided by quality evidence or recommendations and is mostly based on empirical experience, evidence from observational studies, and case reports, while extrapolating the therapeutic armamentarium of pSpA, mostly PsA [63].

Future areas for research

ReA comes under the spectrum of pSpA occurring after an infective trigger. The other entity described like ReA is undifferentiated pSpA (UpSpA), where the phenotype of arthritis is similar, however, it lacks a preceding gastrointestinal (GI) or GU infection. Aggarwal et al. suggest that this entity is a "*forme furste* of ReA" [64], where the infection is subclinical, as the two entities share clinical characteristics, HLA-B27 prevalence, cytokine profiles, synovial fluid metabolomics, and proteomic profiles [56, 65–67]. A metagenomics study in ReA has revealed that patients with ReA have higher alpha and beta diversity of gut microbiota as compared to controls. Furthermore, this study showed strong associations of ReA with known pathobionts such as *Staphylococcus aureus, Escherichia coli,* and *Klebsiella pneumoniae* as well as several new microbiota such as *Empedobacter brevis*, *Roseburia hominis, Bacillus velezensis*, and *Crassaminicella* [68].

As gut infection is deemed central to the pathogenesis of ReA, a related attempt to prevent ReA is an interesting and plausible arena for further research. Risk factors for chronicity in ReA can be modifiable (gut infection) and non-modifiable (HLA-B27). The role of probiotics in the inflammatory process has been studied mainly in the context of inflammatory arthritis such as RA, PsA, juvenile idiopathic arthritis (JIA), and IBD-associated arthritis; however, evidence in this field is lacking. The adjunctive use of probiotics in RA has shown anti-inflammatory benefits, however, in the context of PsA, which shares the pSpA phenotype with ReA, there was no significant benefit [69].

Research in ReA is limited, and thus it presents a unique opportunity to understand how a mucosal infection leads to a sterile inflammation far away in the synovium without direct invasion.

Articular syndrome in other inflammatory rheumatic diseases

Autoimmune rheumatic diseases (AIRDs) such as RA, SLE, Sjögren syndrome, anti-synthetase syndrome (ASS), systemic sclerosis (SSc), relapsing polychondritis (RP), IgG4-related disease (IgG-RD) are among the common inflammatory conditions which may present with arthritis. In this review, we focus mainly on RA and SLE.

The arthritis of RA and SLE presents as symmetric, additive, inflammatory polyarthritis, however, the former causes deforming arthritis while the latter does not; though it may be associated with correctable deformities occurring secondary to ligamental laxity, termed Jaccoud's arthropathy [70]. The clinical distinction is based on the presence of deformities, prolonged early morning stiffness lasting more than one hour in RA, and the absence of other associated features such as photosensitive rash, oral ulcers, facial puffiness, hair loss, and muscle weakness, which would favor SLE.

The timeline of development of established RA evolves over the phases of pre-clinical disease, clinically suspicious arthralgia at risk of development of RA, and established RA. EULAR experts have described these phases as "(i) presence of genetic and environmental risk factors for RA, (ii) systemic autoimmunity associated with RA, (iii) symptoms without clinical arthritis, (iv) unclassified arthritis, (v) RA" [71]. The therapeutic window of opportunity would be during the third phase, when the patient is symptomatic, which is now termed "clinically suspect arthralgia (CSA)" and around 20% of these patients develope arthritis in due course [72]. CSA is defined by EULAR as an arthralgia without frank arthritis in a patient with no other explanation for the arthralgia and with symptoms being present for ≤ 1 year, involving the metacarpophalangeal (MCP) joints, early morning stiffness lasting ≥ 1 h, presence of a first-degree relative with RA, and having a difficulty in making a fist with a positive MCP squeeze test [73]. Early intervention at this stage with DMARDs has been shown to reduce the disease progression and damage. However, the practicality of this approach is limited as most of these patients may not be referred to rheumatologists, and general practitioners are not adequately alerted to suspect RA at this stage.

Diagnostic delays with the initiation of DMARD therapies are associated with poorer outcomes with a higher incidence of joint damage, extra-articular involvement, and accelerated atherosclerosis, with the latter of vital importance since atherosclerotic coronary vascular disease (ASCVD) is the most common cause of death in patients with RA.

On the other hand, lupus arthritis is not severe and the diagnosis may be potentially missed unless the patient has an obvious photosensitive malar rash or other specific symptoms. Many lupus patients may complain of only arthralgia at the onset, which may persist throughout the disease course, without progression to active arthritis. Even in the presence of active arthritis, the phenotype in SLE is usually non-deforming. While RA grants a longer time for the physician to institute treatment until damage occurs, the therapeutic window of opportunity in SLE is narrower since arthritis can be the initial presentation in up to 50% and almost 95% of them develop their symptoms during the disease course [74, 75]. While arthritis is not a life-threatening manifestation, nephritis is. Diagnostic delays in SLE may prove detrimental if the disease progresses to involve major organs such as the kidneys, heart, and brain.

Articular syndrome in the elderly

Articular syndrome in the elderly is often due to degenerative rather than inflammatory processes. Osteoarthritis is the main cause of articular syndrome in the elderly. Infrequent inflammatory causes include polymyalgia rheumatica (PMR) and crystal arthropathies such as gouty arthritis and calcium pyrophosphate deposition disease (CPPD).

There are some diseases that pose a diagnostic challenge. These include late-onset rheumatoid arthritis (LORA), paraneoplastic arthritis, multiple myeloma, osteoporosis with compression fractures [76]. LORA can present like the classical RA with RF and ACPA positivity and symmetric, erosive polyarthritis, or it can also present like PMR with predominant shoulder girdle pain and an asymmetric non-erosive phenotype with a better prognosis [77]. Rarely, LORA can present with diffuse swelling of extremities mimicking a remitting seronegative symmetrical synovitis with pitting edema (RS3PE). Owing to varied presentation, LORA may potentially pose a diagnostic challenge since the prevalence of RF and anti-CCP is lower than in young-onset RA [78]. However, it has an excellent response to MTX with no increased safety concerns [78].

Paraneoplastic arthritis should be included in the differential diagnosis of elderly subjects with articular syndrome. It usually starts with acute or subacute polyarthritis mainly involving large joints. It largely mimics RA and is commonly mistaken for it clinically. It differs from RA in terms of an older age of onset (median age 54 years), male predominance, asymmetry, predominantly large joint involvement, severe pain that may be out of proportion to the joint swelling and radiographic absence of erosions [79]. Adenocarcinoma of the lung is most commonly associated, closely followed by hematological malignancies and other solid organ malignancies such as breast cancer [79]. The other phenotypes include RS3PE, palmar fasciitis with polyarthritis that is commonly associated with ovarian and genitourinary malignancies [80, 81], and hypertrophic osteoarthropathy commonly presented with lung cancer [82]. This entity has minimal response to steroids and improves with the treatment of underlying malignancy.

Although the conditions discussed above must be considered, the most common conditions for an elderly subject presenting with articular syndrome would be a degenerative joint or an osteoporotic joint. Degenerative joint disease is most often seen in large, weight-bearing joints. With an advanced articular syndrome, diffuse idiopathic skeletal hyperostosis (DISH) or Forestier's disease can also develop and mimic AS [83]. The exact pathogenesis of DISH is not established. While degenerative processes are known to contribute, the main player is a probable genetic risk that causes higher concentrations of growth factors such as transforming growth factor β (TGF-β) and insulin-like growth factor that induce the transformation of mesenchymal cells into fibroblasts and osteoblasts, resulting in new bone formation [84]. Long-standing uncontrolled diabetes mellitus is a powerful risk factor for the causation of DISH [85]. While there is no definite treatment once the new bone formed, some patients may benefit from NSAID and physical therapies [86].

To sum up, in the elderly, degenerative processes predominate, and articular syndrome is mostly mechanical. Physical therapy with lifestyle modifications constitutes the mainstay of treatment. However, in the presence of red flags or the typical inflammatory nature of the articular syndrome, one has to exercise clinical suspicion to recognize the disease and initiate specific treatment.

Articular syndrome in the peri-pandemic COVID-19 era

The emergence of post-COVID ReA brought to question the current working definitions of ReA [87]. In addition, SARS-CoV-2 influenced both the presentation of rheumatic diseases [88] and the propensity to develop new rheumatic diseases [89]. An international online survey exploring the diagnosis and management of ReA showed there are wide variations of approaches to ReA at the current stage [63]. The concept of long COVID has been formulated to include a wide variety of lasting pulmonary, cardiovascular, musculoskeletal, and other symptoms [90]. These musculoskeletal symptoms can be classified as post-COVID ReA or they can be considered as a part of long COVID itself [91, 92].

Thus, there is an unmet need to recognize the wide variety of causes of articular syndrome that are being encountered in the peri-pandemic COVID-19 period, ranging from virus-mediated arthritis secondary to SARS-CoV-2 to ReA, osteonecrosis, and inflammatory arthritis in long COVID.

Conclusion

The importance of understanding articular syndrome is that it enables rheumatologists and allied health specialists to easily diagnose and manage arthralgia and arthritis across rheumatic diseases. Such an approach will help reduce delays in care pathways. In addition, it will help to draft definitions and classification criteria for enrolling patients in surveys, cohort studies, and clinical trials.

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CASE BASED REVIEW

Reactive arthritis following COVID-19: clinical case presentation and literature review

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Abstract

Reactive arthritis (ReA) is a clinical condition typically triggered by extra-articular bacterial infections and often associated with the presence of HLA-B27. While ReA has traditionally been associated with gastrointestinal and genitourinary infections, its pathogenesis involves immune and inflammatory responses that lead to joint affections. The emergence of COVID-19, caused by SARS-CoV-2, has prompted studies of plausible associations of the virus with ReA. We present a case of ReA in a patient who survived COVID-19 and presented with joint affections. The patient, a 31-year-old man, presented with lower limb joints pain. SARS-CoV-2 was confirmed by PCR testing during COVID-19-associated pneumonia. Following a thorough examination and exclusion of all ReA-associated infections, a diagnosis of ReA after COVID-19 was confirmed. In addition, this article encompasses a study of similar clinical cases of ReA following COVID-19 reported worldwide.

Keywords Case reports · COVID-19 · Reactive arthritis · SARS-CoV-2

Introduction

The term reactive arthritis (ReA) describes acute arthritis triggered by an extra-articular bacterial infection without detection of the bacterial agent in the synovial specimens [1]. According to The Medical Subject Headings (MeSH) definition introduced in 1992, ReA is "an aseptic, inflammatory arthritis developing secondary to a primary extra-articular infection, most typically of the GASTROINTESTINAL TRACT or UROGENITAL SYSTEM. The initiating trigger pathogens are usually SHIGELLA; SALMONELLA; YERSINIA; CAMPYLOBACTER; or CHLAMYDIA TRACHOMATIS. Reactive arthritis is strongly associated with HLA-B27 ANTIGEN" [2]. The presence of HLA-B27 is indicative of severe and protracted course of ReA [3]. CD4+ and CD8+ T-cell responses to invading microorganisms trigger joint inflammation [4]. These complex immune reactions lead to an imbalanced production of Th2 cytokines [5]. While the development of ReA is traditionally associated with a triad of symptoms, including conjunctivitis, arthritis, and urethritis, it may variably manifest with diverse clinical features [6]. Arthritis in ReA typically manifests as asymmetric oligoarthritis of the lower limb joints [7], and patients may also develop sacroiliitis, enthesitis, and dactylitis [8].

Although the incidence of ReA is believed to be decreasing worldwide, it remains prevalent in developing countries [9]. The annual incidence of ReA ranges from 0.6 to 27 cases per 100,000 population [10]. The prevalence of ReA differs in association with triggering infections [11, 12], with Campylobacter and Salmonella infections being the most commonly identified triggers [10]. ReA may develop after certain viral infections [13]. HIV, parvovirus, hepatitis B, hepatitis C, and Epstein–Barr viruses are viewed as possible triggers of ReA [14, 15]. The emergence of SARS-CoV-2 and the COVID-19 pandemic have had a significant impact on the global population, with frequent reports of associated new-onset rheumatic diseases [16], including ReA [17–19]. SARS-CoV-2 activates interleukin-6 signaling pathways, leading to cytokine storms and macrophage activation syndrome [20]. The same pathways may also lead to the symptom complex of ReA. In fact, the growing number of post-COVID-19 ReA reports, analyzed in this study, points to the triggering role of SARS-CoV-2 [21, 22].

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Herein, we present our own case of ReA and analyze examples of reported similar cases. We believe that SARS-CoV-2 can be considered as a trigger of ReA in all presented cases.

Case report

A 31-year-old male residing in a rural area was admitted to the hospital with multiple complaints, including malaise, sore throat, cough, high-grade fever, and weakness. In the past 7 days, his condition deteriorated, leading to the hospitalization due to respiratory failure and lasting high-grade fever. Polysegmental pneumonia associated with PCR-confirmed SARS-CoV-2 infection was diagnosed. The progression of respiratory distress coincided with the development of articular syndrome (pain in the right knee, right hip, and left elbow joints) Thus, the joint syndrome occurred in the patient on day 8 after the first signs of coronavirus infection. The patient was referred to an infectious diseases hospital, where he received treatment for 17 days. He was then discharged with noticeable improvement related to his respiratory symptoms and fever. Nonetheless, the patients continued to experience joint pain and referred to the rheumatology department.

The patient's past medical history was unremarkable, with no history of tuberculosis and hepatitis. Sexually transmitted infections and intestinal infections were excluded. Upon examination, no pathological changes were observed in the skin and mucous membranes. The cardiovascular, gastrointestinal, and urinary systems appeared normal. The musculoskeletal examination revealed tenderness in the right knee, right hip, and left elbow joints. There were no swollen joints, but the patient complained of pain in the three joints. He experienced morning stiffness lasting up to 10 min. Per the Visual Analog Scale (VAS), his pain level was initially recorded at 60 mm upon admission to the hospital and decreased to 30 mm at discharge.

Laboratory tests yielded the following results: blood group and Rh factor were A+; elevated erythrocyte sedimentation rate (14 mm/hour), leukopenia (3.6×10^9/L), thrombocytopenia (157×10^9/L), elevated C-reactive protein (6.5 mg/L). Uric acid levels were within their normal range. Rheumatoid factor test was negative. Immunoassays for Treponema pallidum (with cardiolipin antigen) were negative. The repeated PCR test for SARS CoV-2 RNA turned negative by the time of the admission to the rheumatology department.

On ultrasound exam, minimal bursitis around the right knee, signs of coxitis (narrowing of the articular space on the right and expansion of the neck-capsular space on the right up to 14 mm (7 mm is normal), indicating exudate in the joint cavity), and enthesitis around the right hip were detected. Pelvic girdle radiography indicated thickening of the contours of the acetabular roof, pelvic tilt to the right. No signs of sacroiliitis were described.

The patient was diagnosed with ReA, oligoarthritis (involvement of the right knee, right hip, and left elbow joints). He was treated with non-steroidal anti-inflammatory drugs (diclofenac and meloxicam), intravenous dexamethasone 8 mg/daily for 3 days, intramuscular methotrexate 15 mg/daily for 2 days, and pantoprazole. At the time of the discharge from rheumatology department, the patient's condition had notably improved, with a reduction of joint pain intensity (VAS score of 30 mm). Recommendations upon discharge included a 6-month course of sulfasalazine, 1 month of nimesulide, local treatment with dimethoxide applications, non-steroidal anti-inflammatory drug gels, and calcium supplementation for 2–3 months. On follow-up evaluations, no complaints of joint pain were recorded.

Search strategy

We searched for COVID-19-associated ReA case reports through Medline/PubMed, Scopus, and Web of Science in line with previously published recommendations for comprehensive and systematic searches [23]. We employed the following keywords: “COVID-19” OR “SARS-CoV-2” AND “Reactive Arthritis” AND “Case Report.” Our inclusion criteria encompassed cases of ReA that developed after laboratory-confirmed COVID-19. We excluded articles that documented ReA cases following COVID-19 vaccination. In addition, we excluded pediatric ReA cases.

Results

Ten case reports of ReA following COVID-19 have been analyzed. The results are presented in Table 1. Seven ReA patients were males and three were females. The patients age ranged from 27 to 73 years (mean 49.2 years). Six patients presented with comorbidities. Diarrhoea and urogenital infections were excluded in five cases. Laboratory-verified coronavirus infection was recorded in all cases (viral RNA–PCR test in nine cases). The time interval between the onset of coronavirus infection and the onset of articular syndrome ranged from 10 to 48 days. Eight patients received non-steroidal anti-inflammatory drug therapies.

Discussion

ReA is basically diagnosed through comprehensive evaluation of medical history and physical examination [34]. Long-term follow-up studies have highlighted several factors

Table 1 Examples of case reports of reactive arthritis after COVID-19

References	Age/gender	Confirmation of trigger infection	Time lapse	Clinical features	Therapies	Outcomes
Cincinelli et al., 2021 [24]	27/M	PCR	2 weeks	Swelling and pain of the first metacarpophalangeal joint of the right hand	Oral prednisone 10 mg/day with rapid tapering	Absence of pain or motion range limitations and minimal residual swelling of the affected joint
Saricaoglu EM, et al., 2021 [25]	73/M	PCR	2 weeks	Swelling, redness, pain, and tenderness in the left first metatarsophalangeal and proximal and distal interphalangeal joints	Nonsteroidal anti-inflammatory drugs	Articular syndrome completely resolved
Gasparotto M, et al., 2021 [26]	60/M	PCR	13 days	Right ankle inflammation and right knee arthritis	NSAID therapy with ibuprofen 600 mg/day	Articular syndrome completely resolved
Basheikh M, 2022 [27]	43/M	PCR	15 days	Bilateral conjunctivitis, circinate balanitis, focal tenderness in the sacroiliac area	Ibuprofen 600 mg three times daily and prednisolone 25 mg/daily for five days	No signs of arthritis at 2-month follow-up
Shokraee K, et al., 2021 [28]	58/F	PCR	10 days	Radiating pain in the right hip	Indomethacin 100 mg twice a day and 80 mg intramuscular depot injection of prednisolone	Remission of arthritis within 14 days
Ouedraogo F, et al., 2021 [29]	45/M	PCR	48 days	Pain in shoulders, left elbow, and left knee, fever	Oral corticosteroids with dose tapering	Significant reduction in pain intensity and resolution of fever
Coath FL, et al., 2021 [30]	53/M	Positive SARS-CoV-2 antibody test	N/A	Lumbar, thoracic, and cervical pain associated with chest pain	Intramuscular methylprednisolone 120 mg and diclofenac 75 mg once daily	No signs of arthritis at 6-week follow-up
Hønge BL, et al., 2021 [31]	53/M	PCR	16 days	Pain in the right knee, both ankles, and the lateral side of the left foot	Ibuprofen 400 mg three times a day and prednisolone 25 mg orally once daily	Complete recovery within 4 months
Kocyigit BF, et al., 2021 [32]	53/F	PCR	29 days	Pain and swelling in the left knee, morning stiffness, and limitation of joint movement	Diclofenac 150 mg/day	Arthritis was not observed in the follow-up examinations
Sureja NP, et al., 2021 [33]	27/F	PCR	2 weeks	Severe arthritis of lower extremities joints and mild arthritis of the right hand joints	NSAID and oral opioid analgesic	Significant improvement at 4-week follow-up

confounding the disease course and prognosis: the origin of triggering infection, presence of HLA-B27, gender, and recurrence of arthritis [35]. ReA typically manifests with joint involvement in the lower extremities [36], frequently presenting as mono- or asymmetric oligoarthritis, consistent with the same features in our patient. The frequent development of dactylitis and enthesitis supports the diagnosis of ReA [37].

When diagnosing ReA, the attention is typically drawn to the history of triggering urogenital or gastrointestinal infection. No such infectious diseases were reported in our patient. It is crucial that the 7-day interval between the initial signs of coronavirus infection and the onset of articular syndrome, while not fitting the classical concept of ReA, may hold significance depending on the pathogen involved [38]. Notably, latest reports document associations of ReA with various viral infections, including COVID-19 [39–41].

The description of own case of ReA after COVID-19 is accompanied with analysis of individual reports published elsewhere. With seven males and three females included in our analysis, gender distribution is in line with the literature on ReA. Clinical features of analysed reports display considerable heterogeneity, ranging from joint pain and swelling to more complex symptoms such as conjunctivitis and circinate balanitis. Treatment strategies also vary, with some patients receiving non-steroidal anti-inflammatory therapies while others switching to corticosteroid therapies. The therapeutic variations may be confounded by the trigger origin and severity articular syndrome.

Conclusion

In this study, we presented our own case and analyzed published reports of ReA after SARS-CoV-2 infection. The onset of joint symptoms post-COVID-19 points to the changing spectrum of ReA in the time of the COVID-19 pandemic. The trend of frequent use of corticosteroids in the treatment of ReA merits further evaluation in view of the risk of related complications such as osteonecrosis [42, 43]. Our study reinforces the need for further research and improved awareness of ReA in the peri-pandemic COVID-19 era.

Author contributions All co-authors have contributed substantially to the concept, case description, searches of relevant articles, and revisions. They approved the final version of the manuscript and take full responsibility for all aspects of the work.

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Declarations

Conflicts of interest The authors have no conflict of interest to declare.

Informed consent Written informed consent was obtained from the patient for publication of this report.

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