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REVIEWS

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REVIEW

Ongoing projects of Turkish Vasculitis Study Group (TRVaS): an update

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ABSTRACT

The Hacettepe University Vasculitis Research Centre (HUVAC) initiated prospective patient registration in 2014 to advance clinical and translational research in vasculitis. The transition to a web-based platform enabled the establishment of the Turkey Vasculitis Study Group (TRVaS), which was formally launched in 2021. By 2025, TRVaS had expanded from its initial six centers to a nationwide network comprising 46 centers—14 pediatric and 32 adult rheumatology clinics. Since its inception, TRVaS has developed structured, disease-specific registries and initiated multiple multicenter projects at both national and international levels. TRVaS continues to strengthen Türkiye's vasculitis research capacity by fostering data collection, promoting large-scale collaboration, and enabling high-quality clinical and translational studies that contribute to global scientific efforts.

Keywords: collaborative networks, national registry, prospective data, vasculitis.

INTRODUCTION

The Hacettepe University Vasculitis Research Centre (HUVAC) was established in May 2014 with the initiation of prospective patient registration to advance clinical and translational research in vasculitis. In 2020, the registry transitioned to a web-based platform, facilitating the development of the Turkey Vasculitis Study Group (TRVaS), which was formally launched in 2021 with an inventory encompassing all vasculitis subtypes and initially involving six centers. By 2025, TRVaS had expanded to include 46 centers — 14 pediatric and 32 adult rheumatology clinics — thereby fostering broader national collaboration (Figure 1). This chapter provides an updated overview of the ongoing projects and key developments within TRVaS.

1. Projects on ANCA-associated vasculitis

1.1. Disease-specific form

A disease-specific form for ANCA-associated vasculitis (AAV) has been developed within the TRVaS database to systematically capture baseline characteristics and clinical information of patients diagnosed with AAV. The form remains active and open for data entry. The data collected will allow a comprehensive evaluation of disease features, treatment protocols, and therapeutic responses in this patient population.

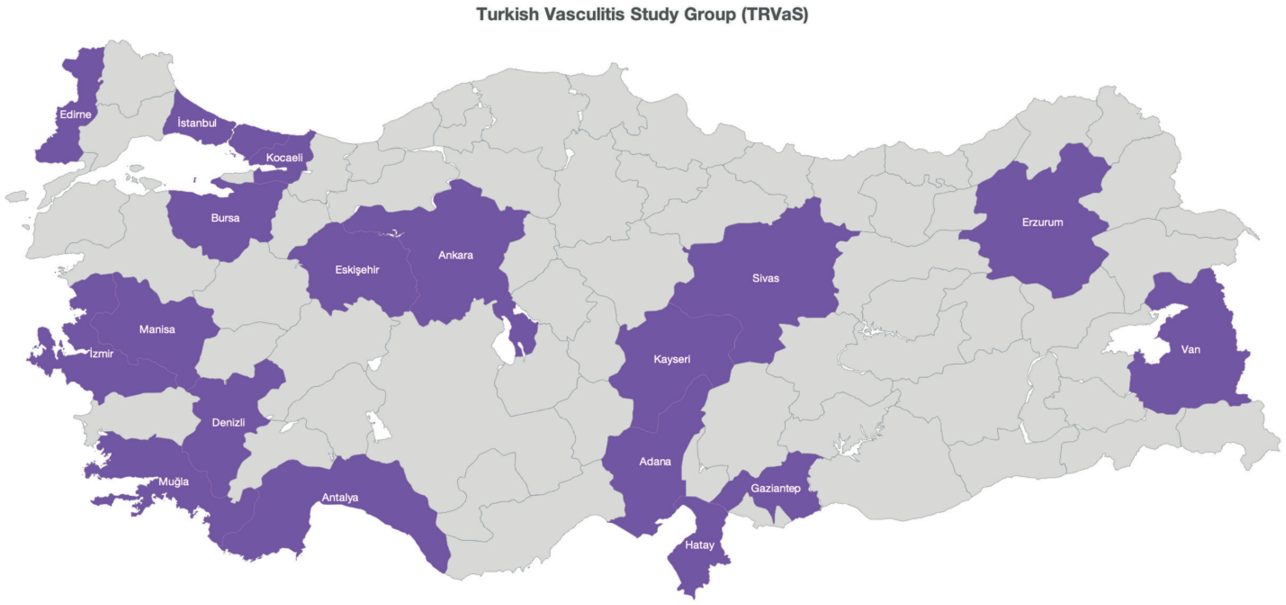

Figure 1. Distribution of TRVaS centers in Turkey. Provinces shown in purple indicate regions with adult and/or pediatric rheumatology centers.

1.2. AAV-Metabolic syndrome

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors, including insulin resistance, obesity, hyperglycemia, hypertension, hypertriglyceridemia, and low levels of high-density lipoprotein (HDL) cholesterol. The presence of MetS is associated with an increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).

Recent studies have suggested that the elevated cardiovascular risk observed in patients with AAV may be partly explained by the high prevalence of MetS in this population [1,2]. MetS provides a simple, reliable, and cost-effective indicator of increased risk for both CVD and T2DM. However, data regarding the prevalence of MetS and its associated risk factors in patients with AAV remain limited [3].

To date, a single-center study, which included 37 patients with AAV, has demonstrated an increased frequency of MetS in this patient group [4]. Building on these findings, we have launched the "Multicenter Study on the Prevalence of Metabolic Syndrome in Patients with ANCA-Associated Vasculitis (AAA-METS)" under the umbrella of the Turkey Vasculitis Database (TRVaS), bringing together vasculitis referral centers across Türkiye. This extensive, multicenter study aims to: a. Determine the prevalence of MetS in a broader AAV patient cohort, b. Investigate the association between MetS and clinical/laboratory parameters of AAV, c. Clarify the potential role of MetS in the pathogenesis and cardiovascular comorbidity burden of AAV. The project is still ongoing.

1.3. Understanding Central Nervous System Disease in AAV

Central nervous system (CNS) involvement in AAV is clinically essential but often under-recognized. Reported in about 7–11% of patients overall, CNS disease may manifest as ischemic stroke, intracranial hemorrhage, posterior reversible encephalopathy syndrome (PRES), hypertrophic pachymeningitis, pituitary lesions, spinal cord involvement, seizures, cognitive impairment, and other neuropsychiatric features [5]. Although survival is generally comparable to other AAV phenotypes, persistent neurological sequelae are frequent, especially with pachymeningeal or vasculitic CNS lesions [6]. Evidence to date is mostly from small, single-center series.

To address this gap, the TRVaS has introduced a dedicated CNS involvement form within its national AAV registry. This form collects demographic data, the timing and type of CNS disease (diagnosis vs. relapse), neurological symptoms, modified Rankin Scale (mRS) scores, imaging and CSF findings, histopathology (when available), treatment regimens, and outcomes, including relapse and survival. The AAV-CNS Project aims to: a. Define the prevalence and spectrum of CNS

manifestations in a large multicenter Turkish AAV cohort. b. Characterize clinical, radiological, and immunological patterns, including granulomatous vs vasculitic phenotypes. c. Evaluate treatment strategies, relapse risk, and long-term neurological outcomes.

1.4. Severe infections in patients with AAV and Outcome

Rituximab (RTX) and cyclophosphamide (CYC) are the two most widely used immunosuppressive agents for induction therapy in AAV. While highly effective, both agents are associated with an increased risk of serious infections, which remain a significant cause of morbidity and can significantly affect treatment decisions and long-term outcomes. This project aims to determine the frequency and spectrum of serious infections (grade ≥3 according to Common Terminology Criteria for Adverse Events [CTCAE] v5.0) in patients with organ/life-threatening AAV treated with RTX or CYC. Explore the association between hypogammaglobulinemia and infection risk in these patients. Compare the incidence and characteristics of serious infections in patients with organ-/life-threatening AAV versus those without such severe involvements.

1.5. AAV Projects in Development

Several additional projects are currently underway. The planned introduction of a visit-based follow-up form will enable longitudinal data collection.

The AAV Pulmonary Involvement Project aims to characterize the clinical and radiological features of AAV-associated interstitial lung disease (ILD), evaluate treatment response and disease progression through serial high-resolution chest CT (HRCT) scans, and identify clinical and serological predictors of radiologic progression and outcomes in patients with AAV-ILD.

The AAV Renal Pathology and Prognosis Project seeks to assess the predictive value of renal histopathological scoring systems (applied to kidney biopsy specimens) for determining 6-month renal function and long-term renal survival in AAV. It also aims to correlate histopathological findings with clinical parameters, treatment strategies, and renal outcomes to improve prognostic stratification and guide therapeutic decision-making.

1.6. Submitted TRVaS_AAV Projects

Two recent TRVaS projects have been completed and are currently under peer review in international journals. The first study demonstrated the importance of screening for osteoporosis among patients with AAV. The second study highlighted that the risk of venous thromboembolism is particularly elevated in the early phases of AAV and may be influenced by a high body mass index and disease activity. These results are expected to raise awareness and contribute to the optimization of comorbidity screening in AAV management.

2. Projects on IgG4-Related Disease (IgG4-RD)

In 2022, a baseline registration form for patients with IgG4-RD was established within the TRVaS database to capture disease and treatment-related characteristics systematically. This form records the key variables required for classification according to IgG4-RD criteria, together with detailed clinical, radiological, serological, and histopathological features. The initial data collected through this registry have provided the first multicenter overview of IgG4-RD in Türkiye. They are expected to inform both clinical practice and future research on disease course and treatment outcomes [7].

To facilitate longitudinal follow-up, a yearly visit form was subsequently developed. This form records treatment exposure, disease activity using the IgG4-RD Responder Index, organ involvement over time, damage assessment, physician global disease activity scores, and key laboratory parameters during follow-up. Both forms remain active and open for ongoing data entry, supporting the continuous expansion and refinement of the national IgG4-RD cohort.

3. Projects on IgA vasculitis

A disease-specific form for IgA vasculitis (IgAV) in both children and adults was developed within the TRVaS database to systematically record key disease characteristics, including time of diagnosis, clinical course, laboratory findings, histopathology (when available), presence of comorbidities, and treatment

approaches. This registry was designed to enhance physicians' understanding of the epidemiological and clinical spectrum of IgAV across different age groups, identify prognostic factors, and inform evidence-based follow-up algorithms for patients affected by IgAV. The first analysis of this cohort was published this year, providing new multicenter insights into the presentation and outcomes of IgAV [8]. The form remains active and open for data entry, supporting ongoing and future research projects aimed at improving the management and long-term outcomes of IgAV.

4. Projects on Polyarteritis Nodosa

The rarity of polyarteritis nodosa (PAN) necessitates global collaboration better to define the characteristics and outcomes of this disease spectrum. The GLOBAL-PAN projects represent such an effort, bringing together the TRVaS and European Vasculitis Study Group (EUVAS), the Vasculitis Clinical Research Consortium (VCRC), and several national PAN cohorts. The first investigation from this initiative, GLOBAL PAN-I, published in 2024, reported on the clinical features, laboratory findings, and survival analysis of 358 patients with either cutaneous or systemic PAN [9].

In addition to recent progress, essential aspects of PAN remain unclear, including the geographic influences on clinical presentation, the natural disease course, relapse patterns, and the relationship between monogenic subtypes (FMF-PAN, DADA2-PAN, VEXAS-PAN) and classic PAN. The GLOBAL-PAN II study aims to address these questions by including a larger multinational cohort, which will enable a more precise characterization of disease phenotypes. The initiation of this project is expected in the near future.

As part of long-term objectives, the collaborative group has initiated GLOBAL PAN-III, a new multicenter project designed to investigate genetic susceptibility in PAN, conducted in continued partnership with the University of Pittsburgh, USA. Early results of this project will be presented at the 22nd International Vasculitis Workshop in 2026.

5. Projects on Giant Cell Arteritis

In patients with giant cell arteritis (GCA), both inflammation-induced accelerated atherosclerosis and advanced age contribute to concerns regarding an increased risk of cardiovascular disease. To address this issue, the TRVaS GCA Ankara longitudinal cohort was established this year to investigate the prevalence and characteristics of cardiovascular comorbidities in GCA. This project is currently ongoing, and patients enrolled will be prospectively followed to assess cardiovascular outcomes.

Future Directions

The incorporation of follow-up forms into the TRVaS database is planned. In addition to diagnostic and baseline characteristics, this will facilitate the systematic documentation of disease course, potential complications, relapses, and mortality. This approach will provide a more comprehensive framework for dynamic long-term monitoring of patients.

The FAIRVASC (Findable, Accessible, Interoperable, and Reusable data for Vasculitis) initiative is a Horizon 2020 project that enables rare-disease registries to be queried as a single virtual cohort while data remain at their home institutions. Using anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) as the demonstrator, FAIRVASC resolves three barriers to cross-border research—registry discovery, semantic harmonisation and governance—by combining a shared ontology curated with the Harmonisation Implementation Team (HIT), local "uplift" of relational tables to Resource Description Framework (RDF) via the RDB to RDF Mapping Language (R2RML) by the FAIRVASC Implementation Team (FIT) [10].

TRVaS (Turkey Vasculitis Study Group) has now started to onboarding process for FAIRVASC, and the onboarding process has begun. We are adapting our technical infrastructure to the FAIRVASC stack by mapping the TRVaS baseline and forthcoming visit-based elements to the FAIRVASC ontology, implementing R2RML mappings to generate RDF, setting up a secure local triple store with GDPR-compliant approvals, and integrating HIT/FIT/QIT cycles to validate semantics and federated queries.

This integration will increase statistical power for ultra-rare phenotypes relevant to our programme—such as central nervous system involvement, interstitial lung disease, and renal pathology strata—facilitate international benchmarking of comorbidity screening (e.g., osteoporosis and early venous thromboembolism risk), and accelerate the translation of TRVaS findings into evidence-informed clinical care.

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REVIEW

Switching of a country wide project to a global study 'IgG4-related disease, pediatric perspective'

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ABSTRACT

IgG4-related disease (IgG4-RD) is a multisystem fibroinflammatory disorder. It has the potential to affect almost any organ, resulting in highly varied clinical presentations.

Unlike adults, who often exhibit multiple organ involvement over time, pediatric patients tend to present with localized disease, frequently affecting the orbits. Diagnosing IgG4-RD can be challenging due to its non-specific clinical manifestations and varied organ involvement. Laboratory investigations, histopathological examinations, and radiological assessments provide important information for making the diagnosis. However, the differential is important ruling out conditions such as malignancies, infections, ANCA-associated vasculitis, and sarcoidosis. Laboratory tests, histopathological findings, and radiological evaluations can help to confirm the diagnosis. As for treatment, glucocorticoids (GCs) remain the mainstay of first-line treatment either alone or in combination with immunosuppressants. Nevertheless, recurrence or relapses represent a major problem in the follow-up. The development of multicenter collaborative projects could provide important insights into the diagnosis, treatment, and long-term outcomes of pediatric patients.

Keywords: IgG4-related disease, children, multicenter study.

INTRODUCTION

IgG4-related disease (IgG4-RD) is a fibroinflammatory disease that typically affects middle-aged adults and is uncommon in children. In 2019, its incidence and prevalence were 1.39/100 000 person-years and 5.3/100 000, respectively, in an adult population-based analysis in the United States [1]. However, we lack data on the epidemiology of disease in childhood. Its rarity in childhood, together with limited awareness, contributes to under-recognition of the disease.

The clinical presentation is highly variable and may involve either a single organ or present as a multisystem disorder. The organs that are most commonly affected include the pancreas, kidneys, orbita, lacrimal and salivary glands, lungs, pleura, and peritoneum [2-4]. A diagnosis may be difficult to establish because of the nonspecific nature of the symptoms. Laboratory tests, histopathological findings, and radiological evaluation can help to reach a diagnosis. The histopathological features include lymphoplasmacytic infiltration, predominantly composed of IgG4-positive plasma cells, accompanied by fibrosis displaying a characteristic storiform pattern. A ratio of IgG4-positive plasma cells to IgG-positive cells greater than 40% and more than 10 IgG4-positive plasma cells per high-power field also supports the histopathological diagnosis of IgG4-RD [5].

It is important to exclude clinical mimickers of IgG4-RD, including malignancies, infections, ANCA-associated vasculitis, and sarcoidosis. These challenges emphasize the importance of a multidisciplinary diagnostic approach. Early diagnosis and treatment are crucial to preventing fibrosis.

Clinical features

IgG4-RD can affect almost any organ, leading to a heterogeneous clinical presentation. Although the disease can involve multiple organs, a review of the literature indicates that certain organs are more frequently affected. The first literature review of 25 pediatric IgG4-RD patients in 2016 revealed that IgG4-related orbital disease is the most common presentation (44%), following by IgG4-related pancreatitis (12%), IgG4-related cholangitis (8%), and IgG4-related pulmonary disease (8%) [6]. In a literature review of pediatric IgG4-RD patients up to January 2024, a total of 117 cases were reported, and 105 were included in the final analysis. Also, orbital involvement was the most commonly reported organ involvement, observed in 40% of patients, while constitutional symptoms were present in 52% of cases. Moreover, 68% of the patients were reported to present with localized disease [2]. Another data from French group including patients aged 9 to 25 years revealed the involvement of the organs in decreasing frequency; lymph nodes (59%), orbita (49%), salivary glands (31%), kidneys (31%), lacrimal glands (27%), pancreas (22%), liver and biliary tract (13%), lungs (13%), uveitis (13%), and mastoid (13%).

In our data of 35 pediatric IgG4-RD patients, we observed that the most common organ involvement was the eye (60%), followed by lymph nodes (34.3%), musculoskeletal system (34.3%), and neurological system (25.7%). In childhood, orbita seems to be the most commonly affected organ, which tends to be unilateral and affects the extraocular muscles and orbital soft tissues [7,8].

Diagnosis

Since there is no specific diagnostic criteria for pediatric IgG4-RD, the diagnosis is based on the adult revised comprehensive diagnostic (RCD) criteria [5,9]. These criteria consist of three components: a) clinical and radiological findings of organ involvement showing diffuse or localized swelling, mass, or nodular lesions, b) elevated serum levels of IgG4, and c) histopathological findings consistent with IgG4-RD [5]. According to these criteria, the presence of all three components is required for a definitive diagnosis. A diagnosis is considered *possible* when criteria (a) and (b) are met, and *probable* when criteria (a) and (c) are fulfilled.

Elevated levels of serum IgG4 are reported in 37.5-70% of cases in childhood [10-12]. Increased concentrations of serum IgG4 can also be observed in conditions such as infections, malignancies, bronchiectasis, and gastrointestinal system disease, resulting in a low positive predictive value for diagnostic purposes [13,14]. Additional common findings especially in adult cases include elevated IgG and IgE levels, peripheral eosinophilia, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), positivity for antinuclear antibodies (ANAs) and rheumatoid factor (RF), and reduced complement levels [15]. However, there are no diagnostic laboratory findings specific to the disease.

Subsequently, the 2019 ACR/EULAR classification criteria were published, which include exclusion criteria of clinical, serologic, radiologic, and pathologic items [16]. Its sensitivity and specificity were assessed in two independent validation cohorts, with reported sensitivities of 85.5% and 82.0%, and specificities of 99.2% and 97.8%, respectively [16]. Moreover, the 2020 RCD criteria were found to be more sensitive for identifying patients with IgG4-RD, while the 2019 ACR/EULAR criteria offered greater specificity, according to a study by Kogami et al. that compared the performance of these two criteria sets [17]. Although there is limited data on the performance of the 2019 ACR/EULAR criteria in pediatric IgG4-RD, approximately 20% of patients fulfilled the ACR/EULAR classification criteria [8]; this is due to the tendency to localised involvement of the disease in childhood. Moreover, patients with normal serum IgG4 levels tended to be younger and were more likely to present with involvement of fewer than three organs than those with elevated serum IgG4 levels [18]. This also leads to difficulty in diagnosis in childhood.

Differences between pediatric and adult forms of IgG4-RD

Pediatric IgG4-RD shares features of adult IgG4-RD but also shows many different characteristics in terms of clinical manifestations, diagnosis, and outcome. Patients with childhood-onset IgG4-RD were more likely to have constitutional symptoms, while systemic constitutional symptoms are more frequently observed in children [6,12,19]. Compared with adult IgG4-RD patients, juvenile cases with IgG4-RD were more frequently female, more likely to present with fever at diagnosis, exhibited involvement of fewer organs, and required second-line treatments more often (all $p < 0.05$) [10]. The patterns of involvement of the same organ may also vary between the two groups. For example, orbital involvement characteristically presents bilaterally with eyelid swelling and exhibits extraorbital involvement in at least 70% of adult cases. On the other hand, it typically presents with unilateral orbital swelling, with bilateral disease reported in only 15% and extraorbital disease in 20% [20]. Age-group-specific disease characteristics were assessed in one of the largest prospective studies of 737 IgG4-RD patients. In the pediatric group, male predominance was noted, and the majority of patients (70%) presented with Mikulicz's disease differently from adults. Additionally, compared to adults, a significantly smaller percentage of pediatric patients (70% vs. 92.6%, $p=0.036$) had elevated serum IgG4 [11]. As for outcome, recurrence is a serious concern with reported rates ranging from 24% to 63% in the evaluation of the six largest adult cohorts and up to 57% in pediatric patients [6,21].

Treatments

Given that children may have a longer disease duration and that the effects of fibrosis can be more severe, early treatment is essential to prevent organ damage. Current treatment approaches mainly rely on immunosuppressive drugs for both induction and maintenance of remission. Nevertheless, in some selected cases, such as IgG4-related lymphadenopathy, which is commonly asymptomatic and has been documented to persist over several decades, a watchful waiting approach may represent a management option [22,23].

Glucocorticoids (GCs) are widely used as the first-line treatment alone or in combination with immunosuppressants [24]. In a systematic review, 92 percent of the cases were reported to be treated with glucocorticoids at a dose of 0.5–2 mg/kg/day [6]. Clinical improvement typically occurs rapidly, though the rate of response may vary depending on the organs involved and the extent of fibrosis [25]. However, relapses or recurrence are common, especially during the tapering or discontinuation of glucocorticoids. Also, there is a considerable risk of toxicity with prolonged glucocorticoid exposure. Second-line treatments such as mycophenolate mofetil, azathioprine, methotrexate, rituximab, and cyclophosphamide were used as glucocorticoid-sparing agents or remission-maintenance drugs in patients as therapeutic options [26-29]. However, there are no clinical trials on their efficacy.

Relapse is a significant and common challenge in the management of IgG4-RD. In our multicenter registry in Turkey, relapse occurred in 31.4% of patients and was more frequent among those with systemic involvement [30]. A review of pediatric cases with ocular IgG4-RD also showed that 72.8% of patients relapsed or did not respond to initial treatment, necessitating treatment modification [7].

Project process: A step-by-step overview

There is a lack of knowledge on childhood IgG4-RD disease, and most of the current understanding is extrapolated from adult cohorts and case reports of pediatric cases. In this context, to contribute to the literature, we first published our single-center experience with eight pediatric IgG4-RD patients in 2022 [12]. Patients with a definite, probable, or possible diagnosis of IgG4-RD were included in this retrospective study. We showed that the disease mainly presents with orbital manifestations in the pediatric population but has wide phenotypic clinical variability. Subsequently, we established a registry through Turkey, and data of IgG4-RD patients in 13 pediatric rheumatology centers were recorded to a web-based registration system. Patient demographics and clinical and laboratory findings related to the diseases were recorded in the TRVaS (Turkish Vasculitis Study Group Longitudinal Database) system, which is a database aimed to prospectively and multicenter record patients diagnosed with vasculitis across Turkey.

A total of 35 pediatric patients were recorded, and we reported the clinical manifestations of disease in childhood and evaluated the sensitivities of the

2019 ACR/EULAR classification criteria and the 2020 RCD criteria in this group. We presented our findings at the Pediatric Rheumatology European Society (PReS) Congress in 2024, where our presentation was selected as the second-best oral communication. The study was also published in the Rheumatology journal (doi: 10.1093/rheumatology/keae497) [30]. Subsequently, we aimed to evaluate the clinical features of pediatric Ig4-RD patients across different ethnicities and countries, and to describe the clinical course, laboratory features, and outcomes in a multicenter international cohort. It also enables us to address the full spectrum of clinical manifestations of pediatric IgG4-RD in different geographic areas. The project proposal was also presented at the Vasculitis Working Party during the PReS 2024 congress in order to reach more pediatric rheumatology centers. The project is currently ongoing.

CONCLUSION

While IgG4-RD in children most often presents with orbital manifestations, its clinical spectrum remains highly variable. Despite the rarity of the disease in childhood, knowledge and awareness of the disease are essential to facilitate diagnosis and avoid delays in treatment. Developing multicentre and large-scale projects is highly valuable for improving understanding and optimising disease management in children.

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acta medica

REVIEW

Central nervous system involvement in ANCA-associated vasculitis

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) are rare but heterogeneous disorders. Although central nervous system (CNS) involvement is relatively uncommon, it is associated with substantial morbidity. Neurological involvement in AAV spans a broad spectrum. Diagnosis relies on clinical findings together with imaging—magnetic resonance imaging (MRI) being the mainstay—with dural thickening and characteristic signal changes serving as distinguishing features. When indicated, cerebrospinal fluid (CSF) analysis and tissue biopsy increase diagnostic certainty. On clinicoradiologic grounds, two principal phenotypes can be recognized: a granulomatous phenotype (pachymeningitis, intracranial granuloma, hypophysitis) and a vasculitic phenotype (ischemic/hemorrhagic stroke). These phenotypes may differ in immunologic underpinnings, clinical manifestations, therapeutic response, and prognosis. Induction therapy typically consists of high-dose corticosteroids combined with cyclophosphamide or rituximab, followed by long-term maintenance immunosuppression. Recognizing relationships between clinicoradiologic CNS subtypes and accompanying clusters of extra-CNS organ involvement may provide important clues for diagnostic evaluation and management.

Keywords: Anti-neutrophil cytoplasmic antibody–associated vasculitides, central nervous system, neurological involvement.

INTRODUCTION

Central nervous system (CNS) vasculitis poses a significant diagnostic challenge for clinicians due to its rarity and the heterogeneity of its clinical presentation. CNS vasculitides may arise as disorders confined to the CNS—termed primary CNS vasculitis [1]—or occur as part of a systemic vasculitic process. Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) constitute a heterogeneous group of vasculitides with an annual incidence of approximately 20 per million population [2]. This category encompasses three diseases: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA).

Neurological involvement in AAV spans a broad spectrum, including mononeuritis multiplex, sensory neuropathy, cranial nerve abnormalities, intracranial mass lesions, external ophthalmoplegia, and sensorineural hearing loss [3,4]. Peripheral nervous system involvement is common, reported in 20–65% of patients [5]. By contrast, central nervous system (CNS) involvement is observed in <15% of AAV cases [6]. It frequently appears early in the disease course; in some series, CNS manifestations were among the initial presentations in 33–86% of affected patients [5]. In certain studies, the rates are inflated because cranial nerve palsies were counted as CNS involvement; when these are excluded, the actual frequency of CNS disease in GPA is approximately 7–11% [7]. Although relatively uncommon, CNS involvement is associated with substantial morbidity [6].

Neurological manifestations vary according to the underlying histopathological pattern and the

specific anatomical structures involved. Clinically, CNS involvement in AAV is most often categorized into three patterns: cerebrovascular involvement, pituitary involvement, and leptomeningeal/dural involvement [4,8,9]. From a histopathologic standpoint, three principal patterns are recognized: (i) vasculitis of small vessels within the brain and spinal cord; (ii) contiguous invasion by granulomas arising from extracranial sites; and (iii) isolated intracranial granulomatous lesions (parenchymal or meningeal) [7]. On clinicoradiologic grounds, a distinction is commonly made between a granulomatous phenotype (pachymeningitis, intracranial granuloma, hypophysitis) and a vasculitic phenotype (ischemic/hemorrhagic stroke) [7]. Putative immunologic differences have been reported between these phenotypes, with Th1 predominance associated with the granulomatous pattern and Th2 skewing linked to the vasculitic pattern [10]. This dichotomy may influence therapeutic response and guide the selection of immunosuppressive agents [11].

In AAV, extra-CNS organ manifestations often predominate, and the heterogeneity of CNS findings can delay both diagnosis and treatment. Accordingly, recognizing the relationships between clinicoradiologic CNS subtypes and accompanying clusters of extra-organ involvement may yield important clues for diagnostic evaluation and clinical management. This review summarizes the patterns of CNS involvement in AAV, outlines plausible pathogenetic mechanisms, and highlights contemporary therapeutic approaches.

Spectrum of Clinical and Imaging Findings in CNS Involvement of AAV

1) Leptomeningeal/Dural Axis and Hypertrophic Pachymeningitis (HP)

Among the clinical patterns of AAV-related CNS disease, leptomeningeal involvement is the most frequently reported [7]. Hypertrophic pachymeningitis (HP) is a rarer, chronic inflammatory condition characterized by localized or diffuse thickening of the dura mater with inflammation extending to adjacent CNS structures. The etiologic spectrum includes autoimmune disorders as well as neoplasms, trauma, and infections. On leptomeningeal histopathology, findings may comprise granulomatous inflammation, collagen fiber proliferation, vasculitic lesions, and areas of necrosis [12].

Epidemiology and Classification of ANCA-Related Hypertrophic Pachymeningitis (HP)

Much of the available evidence on ANCA-related HP derives from single-center, retrospective series reported from East Asia [12,13]. A methodological challenge is that a subset of cases do not fulfill formal AAV classification criteria: in the literature, 14–16% of HP cases linked to AAV could not be classified as "vasculitis" [12–14]. This observation suggests that, in some patients, HP may represent the first and/or sole manifestation of AAV. Indeed, in GPA-associated HP, HP was reported as the initial presentation in ~60% of cases [9]. Several reports propose that ANCA-positive isolated HP can be classified as CNS-limited AAV [6,13].

Autoantibody profiles are heterogeneous. While De Luna et al. [7] found proteinase- 3 ANCA (PR3-ANCA) to predominate among patients with craniospinal pachymeningitis, other series have reported myeloperoxidase ANCA (MPO-ANCA) predominance [13,15–19]. Imafuku et al. [19] estimated that the incidence of AAV-related HP is higher in GPA than in MPA (60.2 vs 3.3 per 1000 patient-years). In the multicenter cross-sectional J-CANVAS cohort, among patients with HP, the proportions of GPA and MPA were similar in both new-onset and relapsing AAV [20]. However, in the overall AAV cohort, GPA classification was more frequent among those with HP than among those without HP; furthermore, among newly diagnosed AAV patients, PR3-ANCA positivity was significantly higher in those with HP [20]. In J-CANVAS, HP was identified in 4.52% (30/663) of AAV patients overall—3.58% (20/558) at the time of new diagnosis and 9.52% (10/105) at relapse [20].

Yokoseki et al. [13] reported that MPO-ANCA-positive HP is more common in older patients and women; this subgroup tends to have lower modified Rankin Scale (mRS) scores, milder neurological injury, lower disease activity, and less frequent progression to generalized disease. Shimojima et al. [20] demonstrated that among newly diagnosed AAV patients, those with HP had a higher prevalence of PR3-ANCA positivity. In summary, MPO-ANCA–

positive HP cases tend to align with CNS-limited AAV, whereas PR3-ANCA–positive cases—though they may initially appear CNS-limited—are more prone to evolve into systemic disease [12,20].

Clinical manifestations in ANCA-associated HP

The presentation varies with the location and extent of inflammation; headache, seizures, cranial neuropathies, and motor dysfunction are common. In granulomatous forms, headache is often severe and refractory to analgesics, typically without meningismus [21]. Dural thickening around cranial nerves can cause compressive/ischemic injury, leading to vision loss, diplopia, or facial palsy. In ANCA-associated HP, cranial neuropathies of virtually all types may occur—except those involving the olfactory nerve (CN I). Additional manifestations include pituitary dysfunction, cerebellar ataxia, myelopathy, papilledema, optic neuropathy, visual field defects, and even blindness [13]. Spread of pachymeningeal inflammation to adjacent parenchyma may precipitate altered consciousness and seizures [6,13].

Imaging findings in ANCA-associated HP

Cranial pachymeningitis may involve the tentorium cerebelli, cranial fossae, cavernous sinus, falx cerebri, and the cerebral convexities without a consistent site predilection. MRI/CT are essential for detecting hypertrophic dural thickening, monitoring disease activity, and assessing damage to adjacent structures [6]. On MRI, diffuse dural thickening with contrast enhancement and central hypointensity may be seen; on coronal, contrast-enhanced T1-weighted images this appearance has been described as the "Eiffel-by-night" sign [22]. The involved dura typically exhibits marked hypointensity on T2-weighted sequences, supporting the presence of a fibrous component [23]. MRI also facilitates evaluation of sinonasal and orbital structures, which are commonly affected in AAV.

Histopathologic findings in ANCA-associated HP

Autopsy/biopsy of pachymeningitic dura mater demonstrates increased T cells, neutrophils, eosinophils, plasma cells, and monocytes/macrophages, suggesting Th1-predominant granulomatous lesions, akin to those described in GPA lung or kidney involvement [13]. In meningeal tissue obtained from GPA patients with leptomeningeal disease, Di Comite et al. [24] most commonly observed necrotizing granulomatous inflammation (61.5%), followed by concomitant granulomatosis with vasculitis (15.4%) and small-vessel vasculitis (7.7%); nonspecific lymphocytic inflammation was present in 11.5%.

In ANCA-associated HP, CSF analysis typically shows mild to moderate pleocytosis with elevated protein and an increased IgG index [12]. TGF-β1 levels are elevated in immune-mediated HP—including ANCA-related forms—and have been implicated in the fibrosis of the thickened dura mater [14]. Members of the TNF superfamily, BAFF and APRIL, are also increased in CSF, correlate positively with the IgG index, and support the possibility of intracranial B-cell activation within the CNS [14,25–30]. Their decline in parallel with clinical improvement suggests that CSF BAFF/APRIL may serve as candidate CSF biomarkers of disease activity in AAV-related CNS involvement [31].

Association Between Disease Activity and Extra-Organ Involvement in ANCA-Associated HP

Several single-center AAV series have reported lower Birmingham Vasculitis Activity Score (BVAS) in patients with HP compared with those without HP [32–34]. In contrast, the J-CANVAS study found no significant differences in disease activity scores between patients with and without HP, whether at the time of new onset or relapse [20]. Ear, nose, and throat (ENT) and mucosal/ocular involvement have been confirmed to be associated with the development of HP [20]. Approximately 30% of patients with otitis media–associated AAV (OMAAV) develop HP [35–37]. HP lesions most commonly involve the middle cranial fossa, followed by the internal acoustic canal, tentorium cerebelli, and posterior cranial fossa—regions that are frequently contiguous with primary middle-ear pathology [36]. Accordingly, HP in OMAAV may reflect locally contiguous CNS disease rather than a purely systemic manifestation [38]. Notably, conductive hearing loss related to otitis media and sudden vision loss were associated with HP development in a multicenter AAV cohort [20].

Conversely, the incidence of cutaneous and renal involvement is lower in patients with HP [20]. In AAV, granulomatous inflammation tends to be accentuated in the upper and lower airways and, plausibly, the meninges through contiguous spread, whereas necrotizing vasculitis targets small- to medium-sized vessels and is more closely linked to renal involvement and mononeuritis multiplex; therefore, a weak association between HP and these latter manifestations is anticipated [20,39,40].

Prognosis and Treatment of ANCA-Associated HP

CNS involvement in AAV—particularly in the presence of meningeal inflammation or retro-orbital disease—is regarded as organ-threatening [6]. For induction therapy in ANCA-associated HP, high-dose corticosteroids are recommended: 0.5–1.0 g/day intravenously for three consecutive days, followed by oral corticosteroids at 0.5–1 mg/kg/day with a structured taper [12]. Corticosteroid monotherapy is insufficient for sustaining remission [12]. In granulomatous GPA—for example, orbital masses, subglottic/tracheobronchial stenosis, and/or pachymeningitis—clinical responses to rituximab may be less consistent, less complete, and/or more delayed compared with cyclophosphamide [41–44]. Consistent with this, the French vasculitis guideline recommends cyclophosphamide as first-line therapy for manifestations that include pachymeningitis within the spectrum of orbital mass or tracheal stenosis [11].

For remission maintenance, combinations of a low-dose glucocorticoid with an immunosuppressive agent such as azathioprine, methotrexate, mycophenolate mofetil, or rituximab are used [45]. During maintenance immunosuppression, relapse of ANCA-associated HP has been observed in approximately 8–57% of patients [12]. De Luna et al. [7] found that the presence of spinal cord pachymeningitis was significantly associated with the need for a new induction regimen due to relapse or refractory disease. In contrast, cerebral pachymeningitis tended to require retreatment less frequently. Rituximab may be employed when relapse occurs or in a refractory course [11]. Its efficacy in refractory HP has also been reported [33,46,47], supporting rituximab as a reliable option, particularly in patients resistant to standard therapy [12]. In patients presenting with HP as an isolated manifestation of AAV, the use of methotrexate in combination with corticosteroids is suggested as a beneficial option [48,49]. Given the potential severity of neurological involvement and the risk of relapse/refractoriness, prolonged maintenance therapy (>36 months) should be implemented, as it has been associated with a 66% reduction in relapse risk [7,50].

In patients with ANCA-associated HP, adding an immunosuppressive agent to corticosteroids during remission induction is preferable [12]. This combination both reduces relapse risk and facilitates effective steroid tapering. The choice of immunosuppressant should be individualized based on the patient's clinical context, including coexisting organ involvement and overall disease severity.

2) Pituitary Involvement

Pituitary involvement is an uncommon manifestation, reported in 1.1–3.9% of patients with GPA [6,51–53]. Proposed mechanisms include contiguous granulomatous invasion from neighboring structures (e.g., the ENT region, orbit, and meninges), primary vasculitis of the pituitary gland, or in situ granulomatous formation within the gland itself [54]. Thickened dura surrounding the cavernous sinus and optic nerves may be associated with pituitary dysfunction, visual loss, and cranial neuropathy [12]. Constitutional symptoms such as fatigue, malaise, headache, weight loss, and anorexia are frequent. GPA-associated hypophysitis can result in partial or global hypopituitarism. Central diabetes insipidus and hypogonadotropic hypogonadism are prominent endocrine features. Enlargement of the pituitary may compress the pituitary stalk, leading to hyperprolactinemia, while visual impairment typically results from compression of the optic chiasm [6].

The differential diagnosis of pituitary involvement in GPA includes other infectious and inflammatory granulomatous disorders, such as tuberculosis, sarcoidosis, Crohn's disease, and giant cell arteritis, as well as primary hypophysitis, particularly the lymphocyte-predominant variant [4]. MRI abnormalities are present in up to 90% of cases [55], although a normal MRI does not exclude pituitary involvement in some patients [53]. A brain MRI typically demonstrates an enlarged pituitary

gland or a thickened pituitary stalk with peripheral enhancement on post-contrast sequences. Loss of the posterior pituitary bright spot on T1-weighted images is another characteristic finding [6]. HP frequently involves the falx cerebri and tentorium cerebelli; involvement around the cavernous sinus is less common, and when present on imaging, should raise suspicion for pituitary dysfunction [51]. If there is concurrent extra-organ involvement and the clinical–serologic profile strongly supports GPA, histologic confirmation may not be required [4].

Pituitary disease in GPA is treated with the standard induction regimens used for systemic vasculitides. Although clinical remission has been reported in up to 69% of patients receiving one of these immunosuppressive approaches, relapse rates are lower when cyclophosphamide is used as the initial agent compared with alternatives [4,53]. In pituitary disease where granulomatous inflammation predominates—and given that rituximab's efficacy is more pronounced against the vasculitic component—cyclophosphamide is generally preferred over rituximab [53]. Pituitary enlargement may regress following immunosuppressive therapy [51]; however, long-term hypopituitarism frequently persists despite clinical and radiologic remission, and lifelong hormone replacement may be necessary in some cases [4].

3) Brain Parenchymal Involvement

Cerebrovascular events

As in other systemic vasculitides, AAV can cause inflammation of the CNS vasculature [4,9]. Clinico-radiologically, this corresponds to a vasculitic phenotype, which differs markedly from the granulomatous type in terms of presentation and prognosis [7]. Ischemic infarctions and intracranial hemorrhages, although uncommon, may represent the initial clinical manifestation of AAV and are invariably associated with substantial morbidity [6].

Ischemic infarctions typically present as isolated or multiple white matter lesions, reflecting predominant involvement of distal penetrating vessels. They are the most common ischemic complications and may manifest as transient ischemic attack or stroke with motor deficits, ischemic myelopathy, encephalopathy, cognitive impairment and dementia, mood disorders, seizures, and cortical blindness [4]. These events are characteristically refractory to antiplatelet therapy and tend to recur in the absence of appropriate immunosuppression [6]. Compared with patients who have cerebral pachymeningitis or pituitary involvement, those with a vasculitic cerebrovascular phenotype are at higher risk of neurological sequelae and of hemorrhagic transformation following reperfusion therapy for ischemic stroke [7,56].

Patients with AAV—particularly early in the disease course—have an increased risk of stroke and venous thromboembolism [57]. Although stroke incidence is higher than in the general population, it can be challenging to determine whether these events reflect vasculitic involvement or atherosclerosis-related mechanisms [5]. In addition, many patients receive long-term, high-dose glucocorticoids, which may exacerbate the intrinsic vascular fragility of AAV and thereby increase the risk of vascular events [58]. Features supporting a vasculitic etiology include a younger age, the absence of traditional atherosclerotic risk factors, concurrent AAV activity in other organ systems, and cranial imaging that demonstrates subacute and hemorrhagic acute ischemic lesions of varying ages and vascular territories [5]. In the series by De Luna et al. [7], no patients adjudicated as having a vasculitic CNS phenotype were MPO-ANCA–positive, whereas all were PR3-ANCA–positive.

Hemorrhagic events are less common but most often involve the brain parenchyma, and occasionally the subarachnoid space [6]. In a pooled review of AAV-related intracranial hemorrhage cases by Achkar et al. [59], EGPA—despite being the least prevalent of the three major AAV subtypes—emerged as the most frequently represented subtype among AAV-associated intracranial hemorrhage. CNS involvement in EGPA has been reported in 5–20% of cases and is thought to be partially related to eosinophil-mediated neurotoxicity [60,61]. Among patients with AAV-related CNS hemorrhage, cytoplasmic ANCA (c-ANCA) positivity has been identified significantly more often than perinuclear ANCA (p-ANCA) staining [59]. Management of ANCA-associated CNS ischemic and hemorrhagic events parallels the therapeutic approach used for other severe, organ-threatening manifestations of GPA and MPA.

Posterior Reversible Encephalopathy Syndrome (PRES)

Case reports have documented PRES in patients with AAV [62,63]. Clinically, onset is typically acute, with symptoms most commonly including encephalopathy, seizures, headache, and visual disturbances [6]. PRES has been associated with hypertension, eclampsia, renal insufficiency, immunosuppressive medications, and connective tissue diseases [62]. Brain imaging characteristically demonstrates findings consistent with vasogenic edema, predominantly involving the bilateral parieto-occipital regions. In most cases, marked improvement occurs within days with supportive management alone.

Isolated Parenchymal Mass Lesion

In patients with GPA, intracranial parenchymal space-occupying lesions are rare [64]. Clinico-radiologically, they fall within the granulomatous phenotype (pachymeningitis, intracranial granuloma, hypophysitis) [7]. Parenchymal granulomas are thought to arise predominantly via vasculitis and disruption of the blood–brain barrier [13]. Clinical manifestations vary by lesion location, but seizures are the most common presenting feature [6,65]. On brain MRI, isolated parenchymal granulomas typically appear as a well-circumscribed mass, hyperintense on T2-weighted images with prominent enhancement on gadolinium-enhanced sequences [66].

Cognitive Impairment

Diffuse cerebral involvement has been reported in patients with small-vessel vasculitis and severe dementia and is considered a poor prognostic factor [67]. Cognitive deficits have also been described in AAV, and are thought to reflect underlying CNS involvement [6]. In patients with AAV, cognitive decline—most often subclinical and mild—may occur, with an estimated prevalence of ~30% [67]. On brain MRI, multiple white-matter lesions, typically located in the periventricular or juxtacortical regions, are frequently associated with these cognitive abnormalities [67].

Spinal Cord Involvement

Only a limited number of cases of ANCA-associated spinal pachymeningitis have been described, and available data suggest a female predominance, involvement of the cervical and thoracic segments, a nonspecific back-pain onset, and progression to motor and sensory deficits most consistent with thoracic myelopathy [68]. Three mechanisms may underlie spinal cord involvement: necrotizing inflammation of the spinal vasculature, compression of the cord by inflamed and thickened meninges, and the formation of primary spinal granulomas [69]. Li et al. [70] reviewed 12 AAV cases with spinal HP and reported that dural thickening was observed predominantly in the thoracic spine. Cases of myelopathy secondary to cord compression from thickened spinal dura have also been documented [12]. Contrast-enhanced spinal MRI has high diagnostic value, and biopsy is often required to confirm the diagnosis [6].

CONCLUSION

In summary, although CNS involvement in AAV is uncommon, it carries substantial morbidity, and its clinico-radiologic heterogeneity can delay diagnosis. By highlighting the leptomeningeal/dural axis (particularly hypertrophic pachymeningitis), pituitary disease, cerebrovascular events (ischemia/hemorrhage), isolated parenchymal granulomas, cognitive dysfunction, and the spectrum of spinal cord involvement, this review underscores the value of a phenotype-based approach. Induction with high-dose corticosteroids plus cyclophosphamide or rituximab, followed by prolonged maintenance immunosuppression, reduces the risk of relapse. Clinicians should remain mindful of the increased risk of vascular events and thromboembolism, antiplatelet refractoriness, and the possibility of hemorrhagic transformation after reperfusion. Finally, standardized diagnostic criteria, phenotype-specific treatment algorithms, and multicenter prospective cohorts are crucial for enhancing the quality of care and patient outcomes.

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acta medica

REVIEW

Pulmonary involvement in ANCA-associated vasculitis

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises systemic disorders, mainly GPA and MPA, characterized by small- and medium-vessel inflammation with frequent pulmonary involvement. Thoracic manifestations are diverse and include tracheobronchial disease, pulmonary nodules and cavitary lesions, diffuse alveolar hemorrhage, interstitial lung disease, bronchiectasis, and pleural involvement, each with distinct clinical and radiological features. Diagnostic evaluation requires integration of clinical findings, high-resolution CT, pulmonary function tests, bronchoscopy, and histopathology, while excluding infectious and malignant causes. Tuberculosis remains a major diagnostic challenge, particularly in endemic regions, due to overlapping clinical, radiological, and even serological features. Treatment typically involves high-dose glucocorticoids with cyclophosphamide or rituximab, with management tailored according to the extent and pattern of pulmonary involvement. Close monitoring is especially important in patients with MPO-ANCA positivity and interstitial lung disease, given the risk of progression to systemic vasculitis.

Keywords: ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, pulmonary involvement.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of systemic vasculitides that predominantly affect small and medium sized vessels [1]. AAV is classified into three main clinical subtypes, each characterized by distinct pathological, serological, and clinical features.

1. Granulomatosis with Polyangiitis (GPA), formerly known as Wegener's granulomatosis, frequently involves the kidneys as well as the upper and lower respiratory tracts.
2. Microscopic polyangiitis (MPA), which commonly affects the kidneys and lungs, is characterized by necrotizing vasculitis without granulomatous inflammation.
3. Eosinophilic Granulomatosis with Polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is typically characterized by asthma, peripheral blood eosinophilia, and multisystem organ involvement.

Each subtype exhibits a distinctive pattern of pulmonary involvement, which plays a pivotal role in establishing the diagnosis, guiding therapeutic strategies, and determining prognosis. This review discusses the main thoracic manifestations observed in GPA and MPA.

1. Tracheobronchial involvement

Tracheobronchial involvement is common in GPA and is characterized by inflammation of the tracheobronchial mucosa, which can lead to

ulceration, tracheo- and/or bronchomalacia, and subglottic stenosis. Mucosal lesions are typically segmental and focal, presenting with inflammation and mucosal ulceration, and may lead to fibrosis, stenosis, or airway malacia if cartilage is involved. Subglottic stenosis, defined as narrowing of the airway just below the vocal cords, is the most common tracheobronchial manifestation in GPA [2]. Symptoms such as stridor, hoarseness, and dyspnea require urgent evaluation and may necessitate tracheostomy in severe cases. Biopsy of tracheobronchial lesions often reveals non-specific mucosal inflammation and fibrosis, while overt vasculitis is rarely observed [3]. Treatment includes high-dose systemic glucocorticoids, cyclophosphamide, or rituximab. Airway obstruction secondary to fibrosis or scarring can be managed with balloon dilation, laser ablation, local steroid injections, cryotherapy, or rarely surgical interventions [3,4].

2. Pulmonary nodules, masses, and consolidations

Pulmonary nodules are common in GPA, although they may occur in all types of AAV. They are present in 40–70% of GPA patients at presentation, and are often bilateral, frequently associated with infiltrates or consolidations. Cavitation occurs in 20–50% of nodules [5,6]. These nodules are often subpleural, vary in size from a few millimeters up to 10 cm, and may cavitate as they enlarge. Cavities typically have thick, irregular walls and lack calcification. The halo sign, defined as ground-glass opacity surrounding a nodule, is frequently seen and indicates accompanying alveolar hemorrhage. Air bronchograms within nodules are also typical.

The differential diagnosis of pulmonary nodules and masses in GPA/MPA includes tuberculosis (TB), septic emboli, multiple abscesses, fungal infections, hematogenous metastases, lymphoma, and organizing pneumonia. Clinical, radiological, histopathological, microbiological, and serological findings are essential for establishing the correct diagnosis. Exclusion of malignancy is crucial before diagnosing AAV. Radiologically, the development of nodules and masses within days to weeks makes malignancy less likely. Importantly, TB and other infectious causes must be excluded to avoid misdiagnosis and inappropriate initiation of immunosuppressive therapy.

The diagnostic evaluation must encompass acid-fast bacilli (AFB) staining, fungal stains, and microbiological cultures [7]. In regions where TB is endemic, the differential diagnosis is particularly challenging due to overlapping clinical and radiological features of both diseases. In cases of large cavitary lesions, a negative sputum AFB smear may help rule out active TB. Detection of AFB in tissue samples is difficult, therefore real-time polymerase chain reaction (PCR) testing can be performed. However, clinicians should recognize that PCR results may remain positive for years in patients with a prior history of TB treatment, and a negative PCR result does not conclusively exclude TB [8]. Accurate diagnosis requires biopsy of pulmonary lesions, sputum microscopy, and a multidisciplinary evaluation. Interferon-gamma release assays (e.g., QuantiFERON-TB) and c-ANCA testing may aid in differentiating TB from GPA. Importantly, ANCA positivity can be observed in the context of TB infection, which may create a complex diagnostic dilemma [9].

The treatment of pulmonary nodules in AAV depends on the extent of disease involvement. Localized disease is typically managed with methotrexate and systemic corticosteroids, whereas systemic involvement requires a combination of high-dose glucocorticoids with either cyclophosphamide or rituximab. Although individual responses to therapy may vary, treatment should be continued as long as there is radiological evidence of lesion regression [1,3].

3. Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) can be defined as the leakage of blood into the alveolar spaces due to increased capillary wall permeability from capillaritis, resulting in impaired oxygenation. Clinical manifestations may include dyspnea, hypoxemia, and anemia, depending on the severity of organ involvement. Hemoptysis is often absent or scant. DAH can cause life-threatening hypoxemia, making early diagnosis and prompt management essential. In patients suspected of DAH, chest radiography can be performed as the initial imaging modality; however, up to half of these patients may have normal radiographic findings [10]. If clinical suspicion persists, thorax CT should be performed. Typical CT findings include bilateral alveolar opacities, intra- and interlobular septal thickening, ground-glass opacities, and a

crazy-paving pattern. In the differential diagnosis of DAH, it is essential to consider not only other immune-mediated diseases, such as anti-glomerular basement membrane disease and IgA vasculitis, but also non-immune-mediated causes, particularly infections, coagulation disorders, and, hemodynamic factors. Bronchoalveolar lavage (BAL) is considered the gold standard for diagnosis and is also crucial to identifying infectious processes included in the differential diagnosis [3].

The primary treatment regimen consists of high-dose glucocorticoids in conjunction with either cyclophosphamide or rituximab. Mechanical ventilation and admission to the intensive care unit (ICU) may be necessary in severe cases. Plasmapheresis is not advised for routine use per EULAR guidelines [1].

4. Interstitial lung disease

AAV-associated interstitial lung disease (ILD) represents a pulmonary involvement that most commonly develops during the course of MPO-ANCA-positive AAV. Clinically, patients often present with nonspecific respiratory symptoms, such as progressive exertional dyspnea and a chronic nonproductive cough, which may evolve gradually over weeks to months. ILD can be identified either prior to the diagnosis of AAV or during follow-up. High resolution thorax CT typically demonstrates ground-glass opacities, reticular opacities, interlobular septal thickening, consolidation, and honeycomb patterns. In MPO-ANCA–positive AAV patients, the most frequently observed radiological pattern of ILD is the usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) ,and, less frequently, desquamative interstitial pneumonia (DIP). Pulmonary function tests reveal a restrictive ventilatory defect accompanied by reduced diffusing capacity for carbon monoxide (DLCO) and decreased lung volumes.

At the time of diagnosis, ANCA positivity is detected in approximately 5–10% of patients with ILD [11]. In some patients, ANCA tests may be negative at diagnosis but become positive during follow-up. Notably, around 25% of MPO-ANCA positive ILD patients subsequently develop MPA [11-13]. Therefore, regular monitoring for systemic manifestations of AAV is strongly recommended in patients with MPO-ANCA positive ILD, even in the absence of extrapulmonary involvement.

There is currently no clear consensus regarding the use of immunosuppressive therapy in patients with positive MPO-ANCA and concomitant ILD. In cases of active MPA, immunosuppressive treatment should be initiated. However, in patients with ILD and positive ANCA, close monitoring for other organ involvement is essential, given the potential adverse effects of immunosuppressive therapy [13]. There are insufficient data regarding the efficacy of antifibrotic agents (nintedanib, pirfenidone) in AAV patients with interstitial fibrosis. In the recently published guideline on the treatment of progressive pulmonary fibrosis (PPF), antifibrotic therapy is recommended for PPF secondary to autoimmune ILDs, including vasculitides [14]. Nintedanib is the first-line agent recommended, whereas pirfenidone is considered a second-line option due to limited evidence.

5. Bronchiectasis

The association between bronchiectasis and AAV has been described in case reports and small case series [15,16]. The reported prevalence of bronchiectasis among patients with AAV varies considerably in the literature. A recent study reported a prevalence of 19% in patients with AAV [16]. In patients with MPA, the prevalence ranges between 16% and 37.9% [15-17]. Importantly, several studies have demonstrated a strong association between anti-MPO positivity and bronchiectasis [16].

Currently, there are no specific guidelines for the management of patients with both bronchiectasis and AAV. However, the presence of bronchiectasis should not preclude the use of intensive immunosuppressive therapies when clinically indicated [16,17]. Due to the high risk of respiratory infections, influenza and pneumococcal vaccinations are recommended. Even in patients without known airway colonization, bronchiectasis warrants careful monitoring for infection, especially during MPA follow-up. For patients with bronchial obstruction, bronchodilators may be used regularly. In cases of co-existing asthma, inhaled corticosteroids may be added. Airway clearance techniques should be taught by respiratory physiotherapists. Nebulized saline or sterile water can facilitate mucus clearance, especially if combined with pre-treatment using

bronchodilators in patients prone to bronchospasm. Regular use of mucolytics is not recommended, but intermittent use may be considered for patients with difficulty expectorating. If bacterial colonization (e.g., *Pseudomonas aeruginosa*) is detected, appropriate eradication therapy should be considered.

6. Pleural involvement

Pleural effusion or pleuritis is reported in approximately 5–20% of AAV patients, according to various case series [18]. Early recognition of pleural involvement may help prevent disease recurrence or progression to other organ systems.

Diagnostic Methods for Pulmonary Involvement in GPA/MPA

Diagnosis of pulmonary involvement in GPA/MPA requires a comprehensive approach that integrates clinical suspicion, serological testing, imaging modalities, fiberoptic bronchoscopy, and, when indicated, histopathological confirmation. The clinical spectrum is highly variable. While some patients may be asymptomatic, others may present with symptoms depending on the site of involvement, such as cough, dyspnea, hoarseness, stridor, sputum production, hemoptysis, and pleuritic chest pain, often accompanied by constitutional symptoms [19]. On physical examination, findings may range from subtle crackles, wheezes, decreased breath sounds in the presence of effusion, or overt signs of respiratory distress in severe cases.

Thorax CT plays a pivotal role in the evaluation of suspected AAV, allowing detailed assessment of pulmonary nodules, cavitations, subpleural lesions, airway inflammation, and stenoses, which conventional chest radiography often fails to detect [5]. It also provides more accurate visualization of ILD and DAH. A baseline CT scan is recommended prior to initiating immunosuppressive therapy to document the extent of pulmonary involvement. In patients with concomitant renal involvement, non-contrast CT is preferred to minimize the risk of contrast-induced nephropathy. Additionally, three-dimensional reconstruction of the tracheobronchial tree can further facilitate the evaluation of airway involvement, particularly in cases with stenotic lesions.

Pulmonary function tests provide valuable information in the assessment of respiratory involvement in AAV. Spirometry can help detect extrathoracic obstruction, such as subglottic stenosis, or intrathoracic obstruction in cases of tracheobronchial involvement. In patients with İLD, DLCO is typically reduced. For longitudinal monitoring of ILD, a combination of spirometry, DLCO measurement, and the six-minute walk test (6MWT) is recommended to assess functional impairment and disease progression [14].

Fiberoptic bronchoscopy is a useful tool in GPA patients with suspected tracheobronchial involvement, allowing targeted biopsies from inflamed mucosa or lung parenchyma. However, due to the small size of these samples, histopathological evidence of granulomatous vasculitis may not always be detected, and a negative result does not exclude the diagnosis of GPA. Although capillaritis can sometimes be observed in biopsies from patients with DAH, the invasiveness and associated risks of lung biopsy generally limit its use as a routine diagnostic procedure. In cases of suspected DAH, BAL from the affected segment can provide important diagnostic information. A progressively bloody return on sequential lavage aliquots is suggestive of DAH. Cytological analysis revealing ≥20% hemosiderin-laden macrophages is considered diagnostic [20]. In addition, BAL allows for microbiologic evaluation to help exclude infectious causes, which is essential in the differential diagnosis of pulmonary involvement in AAV.

Lung biopsy may be indicated in patients presenting with pulmonary nodules, masses, or consolidation. CT-guided percutaneous or thoracoscopic approaches can be utilized; however, small tissue samples obtained via percutaneous biopsy may limit the diagnostic yield. Targeted biopsies from active, non-necrotic areas increase the likelihood of obtaining a definitive diagnosis. In GPA, histopathological examination typically demonstrates necrotizing granulomatous inflammation. To exclude granulomatous infections such as TB, appropriate special stains and microbiologic cultures should always be performed. Histopathologic examination provides critical insight into the pulmonary manifestations of AAV. In GPA, granulomas typically begin as

neutrophilic microabscesses, which may cause partial or complete vascular occlusion. Unlike the well-formed granulomas observed in TB or sarcoidosis, GPA granulomas are irregular and consist of multinucleated giant cells surrounded by plasma cells, lymphocytes, and dendritic cells. Biopsies often reveal central necrosis, palisading histiocytes, and multinucleated giant cells, with necrosis evolving into liquefactive or coagulative forms. Necrotizing or granulomatous vasculitis may also be present in small arteries and veins, frequently leading to vessel occlusion from granulomas or thrombi. In contrast, MPA lacks granulomatous inflammation, with pulmonary capillaritis representing its characteristic histologic hallmark.

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acta medica

REVIEW

Evaluation of nutritional state and sarcopenia in patients with vasculitis

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ABSTRACT

Vasculitides are systemic rheumatic diseases characterized by chronic inflammation, predisposing patients to a polymorbid state and profound metabolic disturbances. Among the most clinically relevant complications are malnutrition and sarcopenia, which frequently coexist and contribute to frailty, disability, and mortality. Malnutrition arises from reduced dietary intake, treatment-related gastrointestinal side effects, and inflammation-driven metabolic imbalance, while sarcopenia is defined as the progressive loss of muscle mass, strength, and function, and develops as a secondary complication of chronic inflammation, glucocorticoid exposure, renal impairment, and physical inactivity. Their prevalence is high in patients with vasculitis, and they are strongly associated with adverse outcomes. Early recognition is essential and requires structured screening of nutritional risk with validated tools, complemented by systematic evaluation of muscle strength and body composition. Evidence emphasizes that intervention should begin once risk or probable sarcopenia is identified, rather than awaiting definitive confirmation. Management is multidisciplinary, integrating medical nutrition therapy with adequate protein and energy intake, oral or enteral supplementation when necessary, and individualized exercise programs, particularly resistance training, to stimulate muscle synthesis and restore function. This review highlights the underlying mechanisms, diagnostic approaches, and evidence-based strategies for addressing malnutrition and sarcopenia in vasculitis, underscoring the importance of proactive and coordinated care to improve functional outcomes, quality of life, and prognosis.

Keywords: Vasculitis, sarcopenia, malnutrition, muscle strength, nutritional therapy.

INTRODUCTION

Vasculitides are heterogeneous systemic rheumatic diseases characterized by inflammatory injury and, in some entities, necrosis of blood vessel walls [1]. The common feature of these diseases, chronic systemic inflammation that is prolonged and difficult to control, makes patients highly susceptible to a polymorbid state where multiple health problems coexist. Indeed, it has been shown that the risk of developing polymorbidity in patients with vasculitis, especially ANCA-associated vasculitides (AAV), is approximately 8 times higher than in the general population [2]. In this complex clinical picture, one of the most important and often overlooked problems that arises as a direct result of the systemic inflammatory response is sarcopenia [3]. Sarcopenia, defined as the progressive loss of muscle mass, strength, and function, is no longer considered to be solely related to aging (primary sarcopenia) but is now accepted as a significant complication of chronic inflammatory conditions like vasculitis (secondary sarcopenia) [4]. In patients with systemic inflammatory disorders, sarcopenia is highly prevalent and has been linked to increased morbidity, frailty, infectious complications and mortality [5,6].

PATHOPHYSIOLOGICAL MECHANISMS LEADING TO MALNUTRITION AND SARCOPENIA IN VASCULITIS

The development of sarcopenia and malnutrition in patients with vasculitis is a multifactorial process, fundamentally rooted in inflammation, treatment, and other disease-related complications. The fact that this process is a common feature of systemic rheumatic diseases is supported by findings in other conditions such as systemic sclerosis [7].

Catabolic Effects of Systemic Inflammation

Inflammatory processes lead to the production of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [8]. Systemic inflammation causes the body to redirect energy and nutrients for the immune response. In this process, muscle protein breakdown, insulin resistance, increased lipolysis, and an increase in energy expenditure are observed [9,10]. Particularly in muscle tissue, protein synthesis decreases while protein breakdown increases, depending on the severity of the inflammation. This situation is associated with the increased expression of two key genes that enhance muscle breakdown, atrogin-1 and MuRF-1, via the Ubiquitin-proteasome pathway [11]. Furthermore, the growth hormone/IGF-1 axis is suppressed during inflammation, which accelerates muscle atrophy [12].

Effects of Treatment on Nutritional Status

Glucocorticoids, the cornerstone of vasculitis therapy, are one of the most significant triggers for the development of sarcopenia. In high doses and long-term use, they lead to a condition known as "steroid myopathy" [13]. Glucocorticoids cause insulin resistance, impairing glucose utilization by muscle cells, and inhibit muscle protein synthesis. They also increase muscle protein breakdown. This condition leads to atrophy, especially in type II muscle fibers [14]. Certain genetic polymorphisms (e.g., ABCB1, PAI-1) may increase sensitivity to steroids [15]. It most commonly presents with weakness in the proximal muscles of the lower extremities, difficulty in climbing stairs, and rising from a seated position. Clinical findings are generally related to the cumulative dose and are usually reversible with dose reduction [16]. Other frequently used immunosuppressive drugs such as cyclophosphamide, azathioprine, and methotrexate can hinder adequate nutrient intake by causing gastrointestinal side effects like nausea, vomiting, anorexia, and mucositis [17,18].

Other Disease-Related Factors

Kidney involvement, which is common especially in ANCA-associated vasculitis, can lead to chronic kidney disease. Uremic toxins, metabolic acidosis, and inflammation play a significant role in the development of cachexia due to renal failure [19]. Additionally, general symptoms of systemic vasculitides such as chronic fatigue, pain, and depression severely restrict patients' physical activity levels, predisposing them to "disuse atrophy" [20].

CLINICAL ASSESSMENT: DIAGNOSING NUTRITIONAL STATUS AND SARCOPENIA

Early diagnosis of nutritional status and sarcopenia in patients with vasculitis is critical for intervention success and requires a multifaceted evaluation.

Assessment of Nutritional Status

In clinical practice, at-risk patients can be quickly identified with validated short screening tools such as NRS-2002 (Nutritional Risk Screening) or MNA-SF (Mini Nutritional Assessment-Short Form) [21].

The MNA-SF is a six-item instrument that evaluates recent changes in food intake, unintentional weight loss over the previous three months, mobility, recent psychological stress or acute illness, neuropsychological problems, and body mass index (BMI). Each item is scored, yielding a total score between 0 and 14. Scores of 12–14 indicate normal nutritional status, 8–11 denote risk of malnutrition and 0–7 indicate established malnutrition.

With the "Global Leadership Initiative on Malnutrition" (GLIM) criteria, established by the Global Clinical Nutrition Community, it is possible to make a definitive diagnosis and determine the severity of malnutrition in patients identified in the risk group by screening tools [22].

Anthropometric measurements provide practical and non-invasive information about body composition [23]. BMI, although used for general screening, cannot distinguish between muscle and fat mass. In conditions where inflammation and corticosteroid therapy coexist, such as in vasculitis, a patient may lose muscle mass while gaining fat mass. In this case, a serious underlying nutritional disorder may be overlooked even if the BMI remains normal or high. Therefore, BMI is not a reliable indicator on its own [24].

Low serum albumin and prealbumin levels may indicate malnutrition that should be interpreted in conjunction with an inflammatory marker such as C-reactive protein (CRP). Measurement of Vitamin D levels should also be standard due to the risk of osteoporosis and its effects on muscle function associated with steroid use [25].

Diagnostic Methods for Sarcopenia

The European Working Group on Sarcopenia in Older People (EWGSOP2) recommends the Find-Assess-Confirm-Severity (F-A-C-S) algorithm. This algorithm can be readily used in the follow-up of vasculitis [26].

Find: Identifying Risk

The first step is to identify patients at risk for sarcopenia. The SARC-F questionnaire is a brief, self-reported screening tool consisting of five domains: strength (difficulty lifting or carrying a moderate weight), assistance in walking, rising from a chair or bed, climbing stairs and history of falls in the previous year [27].

Each item is scored from 0 (no difficulty) to 2 (severe difficulty or inability), resulting in a total score between 0 and 10. A total score of 4 or more suggests a high probability of sarcopenia and indicates the need for objective muscle strength testing.

Assess: Evaluating Muscle Strength

In patients suspected after screening, muscle strength is evaluated. Low muscle strength is sufficient for a diagnosis of "Probable Sarcopenia." Muscle strength is the most reliable measure of muscle function.

Handgrip Strength: A simple, inexpensive, and powerful test for predicting outcomes. A calibrated hand dynamometer is used (Cut-off points: Male < 27 kg, Female < 16 kg) [28].

Chair Stand Test: An indicator of leg (quadriceps) strength. The time it takes for a patient to rise from a chair 5 times without using their arms is measured (Cut-off point: > 15 seconds for 5 rises) [29].

Confirm: Measuring Muscle Mass

If low muscle mass is also demonstrated in a patient with low muscle strength, the diagnosis is confirmed as "Definitive Sarcopenia".

Dual-energy X-ray Absorptiometry (DXA): One of the recommended methods for measuring muscle mass in clinical practice. It measures Appendicular Skeletal Muscle Mass (ASM).

Bioelectrical Impedance Analysis (BIA): A cheaper, portable, and practical alternative. However, it requires population-specific equations to validate the results.

Computed tomography (CT) and magnetic resonance imaging (MRI) are considered reference methods for non-invasive quantification of muscle mass and quality, but their use is usually limited by cost and availability. Nevertheless, in patients with vasculitis who frequently undergo imaging for other reasons (e.g., to assess disease activity or organ involvement), these scans can be used 'opportunistically' to evaluate muscle mass. For example, cross-sectional muscle area at the third lumbar vertebra (L3) strongly correlates with whole-body muscle mass and has prognostic value [30]. Therefore, CT and MRI are valuable tools for confirming a definitive diagnosis of sarcopenia, especially in research settings and specific clinical situations [31].

Physical Performance Tests: Determining Severity

If low physical performance is also detected in addition to a definitive diagnosis of sarcopenia, the condition is classified as "Severe Sarcopenia".

Usual gait speed measured over a short distance (e.g. 4 m) is a simple and informative test; a walking speed of ≤0.8 m/s indicates poor performance. Other validated tools such as the Short Physical Performance Battery (SPPB) and the Timed Up and Go (TUG) test may also be used to characterize functional limitation [4].

TREATMENT AND MANAGEMENT STRATEGIES

The modern approach to managing both malnutrition and sarcopenia emphasizes that one should not wait for a definitive diagnosis (e.g., completion of GLIM criteria or muscle mass measurement) to start treatment. Risk identified with screening tests (for malnutrition) or "Probable Sarcopenia" determined by low muscle strength are indications to investigate underlying causes and to begin treatment. This proactive approach is critical in preventing the progression of muscle loss and nutritional deficits [4,22]. Nutritional therapy should be initiated in patients who meet at least one of the criteria detailed in Table 1 [32].

When treatment is planned, it is aimed to start nutritional support within the first 48 hours of hospitalization and to reach at least 75% of the patient's needs. This approach has been proven to reduce mortality and the risk of adverse events [33].

The foundation of treatment consists of medical nutrition and exercise. Energy needs are adjusted according to the patient's clinical condition; while 25-30 kcal/kg/day is targeted for sedentary patients, this need can increase to 35 kcal/kg/day and above in cases of severe disease exacerbation or malabsorption [34]. Goals should be reached slowly to avoid refeeding syndrome.

To combat catabolic states, a protein intake of 1.2-1.5 g/kg/day is strongly recommended [35]. However, in patients with an eGFR <60 mL/min/1.73 m^2 who are not on dialysis, this target should be reduced to 0.8 g/kg/day [36].

If the oral route is feasible but spontaneous food intake remains insufficient, oral nutritional supplements (ONS), which have been proven to improve survival and be cost-effective, should be used [37]. In cases where oral intake is inadequate, enteral nutrition (EN) should be preferred to achieve nutritional goals. The timing of parenteral nutrition (PN) when oral/enteral intake is not possible is adjusted according to the patient's risk; it is not recommended before 7 days in low-risk patients, whereas it should be started immediately in those with severe malnutrition [38]. To improve functional status, healing of pressure ulcers and preserve muscle mass, specialized products containing β-Hydroxy β-Methylbutyrate (HMB) may be preferred [39].

Exercise is essential to maximize the effectiveness of nutritional therapy. While nutritional support provides the necessary building blocks for muscle tissue, exercise triggers the anabolic signal that enables the use of these building blocks. The targeted type of exercise in sarcopenia management is resistance exercise, which directly stimulates muscle protein synthesis and increases muscle strength. The exercise prescription must be individually planned and monitored by a physiotherapist, considering the patient's current disease activity and functional capacity. Ultimately, the success of the treatment depends on a multidisciplinary approach that combines nutritional and exercise interventions [40].

CONCLUSION

Sarcopenia and malnutrition are prevalent and clinically significant complications in patients with vasculitis, driven by a complex interplay of systemic inflammation, catabolic effects of treatment, and disease-related factors. Their presence is associated with poor clinical outcomes, including increased frailty and mortality. Therefore, routine screening for nutritional risk and sarcopenia should be an integral part of the clinical management of patients with vasculitis. The EWGSOP2 F-A-C-S algorithm provides a practical and systematic framework for diagnosis. A proactive management strategy

Table 1. Indications for initiating nutritional therapy

Category	Indication Criteria
Anthropometric Criteria	BMI < 18.5 kg/m^2
	Unintentional weight loss > 10% in the last 3-6 months, regardless of BMI
	Unintentional weight loss > 5% in the last 3-6 months if BMI is < 20 kg/m^2
Nutrient Intake Criteria	Starvation for more than three days (oral intake < 500 kcal/day)
	Anticipated inadequate oral intake (<60% of requirement) for more than 5-7 days
	Anticipated period of no oral intake for 5 days or more

is essential, where intervention is initiated upon identifying risk or probable sarcopenia, rather than waiting for a definitive diagnosis. The cornerstone of treatment is a multidisciplinary approach combining individualized medical nutrition therapy, with an emphasis on high protein intake, and a tailored resistance exercise program. Implementing these evidence-based strategies can mitigate the adverse effects of sarcopenia and malnutrition, thereby improving functional status, quality of life, and overall prognosis for patients with vasculitis.

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acta medica

REVIEW

Dentistry and rheumatology collaboration: dental health, treatment and measures for osteonecrosis of jaw for patients with vasculitis

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ABSTRACT

The relation between rheumatology and dentistry has increasing clinical importance, particularly in patients with systemic autoimmune diseases such as rheumatologic disorders and vasculitis. Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of periodontal supporting tissues, occurring from a dysbiotic shift within the oral microbiota. Although the primary etiological factor of periodontal disease is bacterial plaque, the main factor causing breakdown in the periodontium is the host-mediated immunoinflammatory response. Periodontal diseases can have both direct and indirect impacts on overall systemic health through possible remote effects of the inflammatory response caused by bacterial infection of the periodontium, and serving as a risk factor for systemic diseases or conditions affecting general health. Oral lesions may develop in patients with vasculitis during the course of the disease, and oral findings may even be the first clinical findings before the diagnosis. Bone-modifying agents (BMAs) such as bisphosphonates, used to prevent osteoporosis associated with various autoimmune and immune-mediated inflammatory disease, can predispose individuals to complications affecting bone metabolism and oral health, including medication-related osteonecrosis of the jaw (MRONJ). In such cases, effective prevention, early diagnosis and multidisciplinary management are essential to reduce morbidity and maintain oral function.

The present review aims to evaluate the potential interactions between periodontitis and rheumatological diseases; to assess the etiological/pathological basis of these diseases and the multidisciplinary approaches between periodontal and rheumatologic disciplines in promoting oral health and reducing the risk of osteonecrosis in patients with vasculitis.

Keywords: Periodontal diseases, rheumatic diseases, rheumatoid arthritis, vasculitis, autoimmunity.

INTRODUCTION

Periodontal diseases are a group of conditions that develop through an inflammatory process initiated by bacterial pathogens within complex polymicrobial interactions in the oral microbiome. In the United States, approximately 47% of adults aged 30 years and older (around 65 million adults) have periodontitis: 30% with moderate, 8.5% with severe, and 8.7% with mild periodontitis. Periodontal infections lead to substantial healthcare costs related to their local effects and are also associated with numerous systemic diseases [1]. Environmental, physical, social, and host-related factors can influence and modify the disease course in various ways. Certain systemic conditions may also affect the onset and progression of gingivitis and periodontitis. Systemic disorders that impair the function of neutrophils, monocytes, macrophages, and lymphocytes cause alterations in the production or activity of host inflammatory mediators. Clinically, these alterations may manifest as an earlier onset or a faster progression of periodontal destruction than would occur in their absence [2].

For many years, periodontal disease was regarded as an infectious disease; however, since the 1960s, autoimmune mechanisms have been demonstrated as determinant factors in addition to the host response to microorganisms responsible for infection. The presence of anti-collagen antibodies produced by plasma cells within the periodontal tissues of patients with periodontitis has been demonstrated [3]. Based on this, it has been suggested that a disease-causing destruction in periodontal tissues may involve a possible autoimmune process and influence other rheumatologic–immunologic mechanisms as well [4].

In recent years, numerous scientific studies have shown that periodontal health can have both direct and indirect effects on overall systemic health. The potential effects of inflammatory periodontal diseases on multiple organ systems can be evaluated under two main aspects: (1) the possible remote effects of the inflammatory response elicited by bacterial infection of the periodontium, and (2) the degree to which periodontal infection serves as a risk factor for systemic diseases or conditions affecting general health [2]. The epidemiologic relationship between periodontal diseases and various rheumatologic diseases has been demonstrated by many clinical studies [5].

The association between periodontitis and other systemic and rheumatologic diseases has been recognized since the early 20th century, particularly during the period dominated by the "focal infection theory." During that time, dental treatments were largely limited to tooth extractions. There are also early reports suggesting that non-extraction treatment approaches for periodontal disease could alleviate rheumatologic symptoms. One case report described a 45-year-old male patient presenting with severe rheumatoid arthritis, difficulty walking, and stiffness in the knee joints. Prior to dental intervention, he had received streptococcal vaccine therapy, but despite having apparently healthy teeth with no visible infection, his arthritis did not improve. A detailed periodontal examination revealed hard, brown calculus surrounding the tooth roots and periodontal pockets. The patient was treated with a protocol involving complete removal of calculus, root surface polishing, and ionization with zinc ions at each session. After treatment, the gingival tissues completely healed, and within three months, marked improvement in arthritis symptoms was observed. Ten months later, the patient was able to walk unaided [6]. Although this report presents only a single case and was published during a period when scientific journals lacked today's rigorous peer review processes, it remains noteworthy for illustrating the historical context of the relationship between periodontal and rheumatologic diseases.

To better understand the effects of periodontal diseases on rheumatologic conditions—and to clarify the role of dental practitioners in managing patients with rheumatologic diseases—it is essential to review the general characteristics of periodontal diseases and their treatment approaches.

Periodontal Diseases

Gingivitis presents inflammation limited to the soft tissue of the gingival epithelium and connective tissue, without the attachment loss or apical migration of the junctional epithelium observed in periodontitis. Depending on the duration of infection and etiology, the most common form is chronic plaque-induced gingivitis. The transition from gingivitis to periodontitis is a multifactorial process beginning with biofilm accumulation on tooth surfaces and progressing to tissue destruction due to dysregulation of the host immune response. Initially, dental plaque triggers a local inflammatory response characterized by increased vascular permeability, edema, and neutrophil infiltration. If plaque accumulation persists, the adaptive immune system becomes activated, dominated by T and B lymphocytes and plasma cells. At this stage, gingivitis develops, which is reversible with appropriate intervention.

If left untreated, inflammation activates more complex mechanisms, leading to periodontitis. Persistent microbial stimulation causes macrophages and T cells to release IL-1β, TNF-α, IL-6, PGE_2, and matrix metalloproteinases (MMPs), mediating connective tissue and bone destruction. Additionally, osteoclast activation through the RANKL pathway results in alveolar bone resorption [7].

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of microorganisms, resulting in progressive destruction of the periodontal ligament and

alveolar bone, accompanied by increased probing depth, gingival recession, or both." The principal clinical feature distinguishing periodontitis from gingivitis is clinically detectable attachment loss due to inflammatory destruction of the periodontal ligament and alveolar bone. This is often accompanied by periodontal pocket formation and changes in the density and height of the subjacent alveolar bone. Persistent bleeding on probing during sequential visits is a reliable indicator of inflammation and of increased risk for future attachment loss at the bleeding site. The attachment loss associated with periodontitis may occur in a cyclic pattern, progressing either continuously or in episodic bursts of disease activity [8].

The 2017 Classification of Periodontal and Peri-implant Diseases introduced a new staging and grading system, defining four stages of disease (1–4) and three progression rates or risk levels (A–B–C). The classification considers parameters such as clinical attachment loss, pocket depth, percentage of alveolar bone loss, and the number of teeth lost due to periodontal disease. Grading is based on annual attachment loss, bone loss-to-age ratio, and systemic risk factors such as smoking and HbA1c levels [9].

In contemporary dentistry, peri-implant diseases—inflammatory conditions around dental implants—share similar features with periodontal disease. These are categorized as peri-implant mucositis and peri-implantitis, as defined by the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions. Peri-implant mucositis refers to an inflammatory lesion confined to the peri-implant mucosa surrounding an osseointegrated implant, without accompanying bone loss. Peri-implantitis is characterized by inflammation in the peri-implant mucosa combined with progressive loss of supporting bone [9].

Periodontitis: Effects on Dysbiosis and Host Immune Response

Periodontitis is a disease characterized by progressive destruction of the periodontal tissues resulting from dysbiosis within the oral microbiota. In the pathogenesis of the disease, a crucial role is attributed not only to the anaerobic, Gram-negative bacteria known as the "red complex"—*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*—but also to *Aggregatibacter actinomycetemcomitans*. These microorganisms disturb the microbial balance essential for maintaining periodontal health, leading to a microbial shift that promotes pathogenic dominance. When the red complex bacteria establish stable colonization in the gingival sulcus—the natural space between the tooth and the gingiva—the host's innate immune system is activated.

However, these pathogens embedded in the dysbiotic biofilm develop resistance to host defense mechanisms such as phagocytosis, antimicrobial proteins and peptides, and reactive oxygen species, rendering their elimination extremely difficult. As a result, a chronic inflammatory process is sustained within the periodontal tissues [1].

In this process, tissue destruction is caused primarily not by the bacteria themselves, but by the dysregulated immune response of the host. Neutrophil infiltration, cytokine release (e.g., IL-1β, TNF-α, IL-6), and activation of matrix metalloproteinases (MMPs) contribute to the breakdown of connective tissue and resorption of alveolar bone. Thus, an immune response initially aimed at protection becomes pathogenic and self-destructive over time.

Although periodontitis manifests as a localized inflammatory disease, its effects extend beyond the oral cavity. Hyperactivated neutrophils and elevated levels of inflammatory mediators (such as cytokines and C-reactive protein) originating from periodontal pockets can enter the systemic circulation. This indicates that periodontitis should not be viewed solely as a local disease but as a pathology contributing to systemic inflammatory burden [10].

To quantify the systemic impact of periodontitis, researchers have proposed correlating it with the periodontal inflamed surface area (PISA)—the total inflamed epithelial area in the periodontal pockets. Based on this analysis, the inflamed gingival surface area has been calculated as approximately: 0.3 cm^2 in healthy individuals, 10 cm^2 in localized periodontitis, and 37 cm^2 in generalized severe periodontitis [11]. This model provides a measurable index of the systemic inflammatory load associated with periodontal disease.

Mechanisms of the Effect of Periodontitis on Autoimmunity

In the oral cavity, as in other mucosal systems exposed to the external environment, the immune system is continuously challenged by signals extending beyond simple commensal–epithelial interactions. This ongoing exposure contributes to immune system "education" through mechanisms that remain only partially understood. However, disruption of these localized responses is associated with a predisposition to tissue-specific autoimmune diseases.

Periodontitis serves as a prototype of such conditions, reflecting both local and systemic inflammatory processes and the activation of autoimmunity. It demonstrates a dysregulation of immune homeostasis that extends beyond local tissue pathology. Accordingly, the modern concept of periodontal disease has evolved: it is no longer attributed to a single pathogen but rather to polymicrobial dysbiotic communities that disturb tissue homeostasis and normal immune responses [12].

Animal studies have shown that *P. gingivalis*, recognized as a "keystone pathogen," can increase the overall virulence of the microbial community even when present in very low abundance (below 1%). Interactions between this bacterium and normally commensal microorganisms promote synergy and a transition toward pathogenicity, perpetuating dysbiosis. The resulting dysbiotic community sustains chronic inflammation and displays "inflammophilic" characteristics—bacteria thrive on tissue breakdown products as nutrient sources—further amplifying the cycle of destruction [1, 12]. From this perspective, periodontitis currently involves the dysbiosis of oral microbiota driven by inflammophilic bacteria. This process leads to impaired resolution of inflammation and failure to adequately regulate immune responses. Tissue destruction in periodontitis arises directly from immune activation due to the bidirectional imbalance between the microbiome and host inflammatory mechanisms. This dysregulation triggers both local and systemic autoimmune responses through multiple mechanisms, including: (A) Overproduction of autoantigens; (B) Microbial translocation; (C) Molecular mimicry; (D) Superantigen activation; (E) Dysregulation of immune checkpoints; (F) Bystander activation; (G) Dysregulation of Toll-like receptors (TLRs); (H) Excessive cytokine production; (I) Epitope spreading; (J) Complementarity of autoantigen [4].

Among autoimmune and rheumatic diseases influenced by periodontitis, the strongest evidence exists for rheumatoid arthritis (RA). Periodontal inflammation—particularly the role of *Porphyromonas gingivalis* in the citrullination process—has been implicated in the pathogenesis of RA. Additionally, increased prevalence of periodontitis has been reported in systemic lupus erythematosus (SLE), with overlapping inflammatory pathways. Periodontal disease is also observed more frequently in patients with juvenile idiopathic arthritis (JIA), ankylosing spondylitis, and other connective tissue disorders, and it may correlate with disease activity [13].

Periodontitis–Rheumatoid Arthritis Relationship

Over the past decade, a growing body of evidence has left little doubt that periodontitis and rheumatoid arthritis (RA) are closely interrelated. This association cannot be explained solely by shared pathogenic mechanisms or by overlapping environmental and genetic risk factors. Large cohort studies have demonstrated that periodontitis often precedes the onset of RA, and that individuals who develop RA exhibit a positive correlation between periodontitis and serum ACPA (anti-citrullinated protein antibody) levels. These findings provide strong support for a causal relationship between the two diseases. According to this model, the chronically inflamed periodontium serves as the site where immune tolerance to citrullinated epitopes is broken, initiating ACPA production. This theory has been validated in both animal and human models of periodontitis and RA and aligns with the paradigm suggesting that ACPAs are produced at mucosal surfaces years before clinical RA symptoms emerge [10].

Under inflammatory conditions, the mechanisms leading to hyper-citrullination occur predominantly at mucosal sites. In chronic inflammation of the periodontium, nearly all mechanisms contributing to the generation of citrullinated epitopes are triggered by periodontal pathogens. Thus, periodontal pathogens are considered direct initiators of autoimmune reactions that later give

rise to diseases such as RA. The mechanistic role of periodontitis and periodontal pathogens in RA development has been supported by case–control studies showing ACPA production at other mucosal surfaces, including the lungs and intestines. Collectively, these findings reveal a highly interconnected network of interactions capable of initiating the onset of RA [10].

Courbon et al. [14] investigated the specific role of *P. gingivalis* in the development of periodontitis and subsequent arthritis. In their experiment, rats were orally exposed for one month to either *P. gingivalis, Prevotella intermedia*, or a control gel, and monitored for eight months. Periodontitis development was assessed using serological analyses, gingival inflammation scores, and micro-CT imaging, while arthritis development was evaluated by measuring proinflammatory markers, anti-CCP, ACPA levels, and by histological and μCT analysis of ankle joints. The results showed that periodontitis developed exclusively in the *P. gingivalis* group, beginning one month after exposure. Both joint inflammation and systemic inflammation were detected only in this group at the 4th and 8th months. By the eighth month, ankle joints exhibited infiltration of inflammatory cells, cortical erosions, and overall bone loss. Additionally, anti-CCP2 antibody levels were found to correlate with both local and systemic bone loss.

Another study assessing citrullinated histones in inflamed periodontal tissue and sera of patients with RA and periodontitis demonstrated the presence of citrullinated histone H3 in periodontal tissue samples. Furthermore, sera from RA patients contained higher levels of autoantibodies against citrullinated histone H3 compared to healthy controls and periodontitis patients. These findings indicate that periodontitis contributes to the formation of antigens targeted by ACPAs [15].

In another in vivo mouse model, the arthritogenic effect of lipopolysaccharide (LPS) in periodontal disease was investigated. Periodontitis was induced in CD1 mice by injecting either 10 ng or 50 ng of LPS into the maxillary mucosa. Control mice were either untreated or injected with LPS at the tail. Mice receiving 50 ng LPS developed ankle swelling and inflammation after the fifth injection, which progressed until the end of the experiment. Micro-CT and histologic analyses revealed alveolar bone resorption, vascular proliferation, widening of joint space, leukocyte infiltration, synovial proliferation, and mild cartilage/bone destruction. Furthermore, increases in serum cytokine and ACPA levels were observed. Importantly, no arthritic changes developed in mice where LPS was injected in the tail, demonstrating that RA-like symptoms occurred only when LPS induced periodontitis locally [16].

A large-scale case–control study involving over 600 participants examined the prevalence of periodontitis among RA patients. It found that periodontitis was significantly more common in RA patients compared to controls and that the percentage of sites with probing depth ≥5 mm was markedly higher among RA patients [17]. Another cross-sectional study analyzed active matrix metalloproteinase-8 (aMMP-8) levels and periodontal bacterial profiles in gingival crevicular fluid of RA patients. Despite comparable periodontal and bacterial findings between the groups, RA patients exhibited significantly higher aMMP-8 levels correlated with the severity of periodontitis, suggesting a modulatory effect of RA on host immune response [18].

Epidemiological and cross-sectional data support a bidirectional relationship between periodontitis and RA. Numerous studies have evaluated how periodontal treatment influences RA disease activity and severity [10]. Meta-analyses of these studies confirm that periodontitis should be considered a modifiable risk factor for rheumatoid arthritis [5]. A clinical study evaluating the efficacy of non-surgical periodontal therapy in RA patients with periodontitis found that the treatment group exhibited significant reductions in DAS28-CRP, serum IgG levels against *P. gingivalis* hemin-binding protein (HBP35), and serum citrulline levels after eight weeks compared with untreated controls. Serum IgG levels against *P. gingivalis* HBP35 were positively correlated with anti-cyclic citrullinated peptide (anti-CCP) antibody levels, and a similar correlation was observed between *P. gingivalis*-specific IgG and rheumatoid factor (RF) levels [19].

Likewise, a recent study reported that in RA patients with periodontitis, scaling and root planing (SRP) significantly reduced DAS28-CRP, disease activity classification, ESR, and serum ACPA levels, demonstrating that non-surgical periodontal therapy can effectively reduce RA disease severity [20]. A simple, non-invasive, and cost-effective,

and procedure with predictable outcomes such as periodontal treatment can therefore contribute to lowering both local and systemic inflammatory load, potentially reducing the need for systemic pharmacologic therapy in RA and minimizing the risk of life-threatening complications, particularly cardiovascular events. Chemical mouthrinses containing various antimicrobial compounds and photodynamic therapy are currently being tested as adjuvants to SRP. Analyses of existing studies indicate that periodontal therapy exerts a more significant effect on reducing clinical disease activity indices than on ESR and CRP, as the latter are influenced by multiple factors—especially infections—which are more frequent in rheumatic patients chronically treated with glucocorticoids and immunosuppressants. The collective evidence strongly supports that routine periodontal examination should be incorporated into RA management guidelines, emphasizing early detection and treatment of periodontitis [5, 13].

Vasculitis and Periodontal Diseases

Vasculitis are a heterogeneous group of diseases characterized by chronic inflammation of blood vessels, which can lead to multi-organ involvement and serious systemic complications. According to the 1994 classification, vasculitis are primarily categorized based on the size of the predominantly affected vessels into four main groups: 1) Large-vessel vasculitis (e.g., giant cell arteritis), 2) Medium-vessel vasculitis (e.g., Kawasaki disease), 3) Small-vessel vasculitis—including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAVs), variable-vessel vasculitis (e.g. Behçet's disease) [21]. Although the etiopathogenesis of AAVs has not been fully elucidated, it is hypothesized that the formation of anti-neutrophil cytoplasmic antibodies triggers this autoimmune response. ANCAs target the cytoplasmic granules of neutrophils, initiating a systemic inflammatory cascade. Clinical symptoms vary considerably depending on the vascular bed involved, but the respiratory and renal systems are most commonly affected. In addition to organ-specific manifestations, patients frequently exhibit non-specific systemic signs of inflammation such as fever, headache, fatigue, loss of appetite, myalgia, arthralgia, constipation, and weight loss [21, 22].

Oral Manifestations in Vasculitis (Selected Entities)

Granulomatosis with polyangiitis (GPA) is a necrotizing systemic vasculitis primarily affecting the upper and lower respiratory tracts, but it may also involve the kidneys, skin, and nervous system. In most patients, the disease initially presents with head and neck symptoms [21]. The nasal septum, paranasal sinuses, ocular structures, larynx, ear, and oral cavity may all be affected. Approximately 10% of GPA patients develop oral lesions during the course of disease, and in 2% of cases, oral manifestations may be the first clinical sign before diagnosis. Moreover, oral lesions can serve as indicators of disease relapse or exacerbation. One of the most characteristic oral findings of GPA is gingival enlargement, classically described as "strawberry gingivitis." In this condition, the gingiva appears edematous, erythematous, and painful, with superficial petechiae giving the mucosa a strawberry-like appearance. Histopathologically, affected tissues may show fibrinoid necrosis of vessel walls, predominantly neutrophilic and non-specific lymphocytic infiltrates, and granuloma formation—although these features are not always present and are not pathognomonic. Diagnosis is based on clinical findings, systemic evaluation, and the presence of ANCA. Direct immunofluorescence may reveal IgM and/or C3 deposits surrounding vessel walls [21, 22].

Microscopic Polyangiitis (MPA)

Microscopic polyangiitis (MPA) is primarily characterized by a pulmonary–renal syndrome and differs from GPA by the absence of granuloma formation and eosinophilia [20]. Oral involvement is extremely rare and has been reported only in a few cases. In a cohort of ten female patients, oral ulcers were documented in two cases as part of extra-renal involvement. In one patient, gingival enlargement was observed and constituted the first clinical clue leading to the diagnosis of MPA following oral lesion evaluation. Histopathological features include fibrinoid necrosis of vessel walls with dense neutrophilic infiltration, sometimes accompanied by non-specific lymphocytic infiltrates. Direct immunofluorescence findings may be negative or show limited IgM and/or C3 deposition [21].

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Eosinophilic granulomatosis with polyangiitis (EGPA) is a type of vasculitis characterized by eosinophil-rich necrotizing inflammation, primarily affecting the lungs, and is typically associated with asthma and atopic conditions [21]. Oral involvement in EGPA is extremely rare, with only a few reports of ulcerative lesions. Some cases describe painful palatal ulcers developing about a week before the appearance of cutaneous lesions. Throughout the disease course, multiple small ulcers resembling aphthous stomatitis have been reported. The overall prevalence of oral ulcers among EGPA patients is estimated at around 2%, suggesting that such lesions may represent part of the broader clinical spectrum of EGPA. Histopathological examination shows vasculitis with fibrinoid necrosis and, occasionally, granulomatous lesions. A diagnostic hallmark is the presence of numerous eosinophils within the inflammatory infiltrate, accompanied by neutrophils, macrophages, and lymphocytes. Direct immunofluorescence may show IgM and/or C3 deposits in the vessel walls [22].

Medication-Related Osteonecrosis of the Jaws (MRONJ) And Rheumatic Diseases

Autoimmune and immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are associated with an increased risk of osteoporosis, falls, and fractures due to chronic inflammation, pharmacologic therapies, and reduced mobility. These conditions are commonly managed with conventional and biologic disease-modifying antirheumatic drugs (cDMARDs and bDMARDs) in combination with glucocorticoids. While these drugs effectively control disease activity, they can contribute to bone loss and heightened infection risk. To prevent osteoporosis, bone-modifying agents (BMAs) such as bisphosphonates and denosumab are widely prescribed in this patient group. However, long-term use of BMAs has been strongly associated with medication-related osteonecrosis of the jaws (MRONJ)—a rare but serious adverse effect, typically occurring after invasive dental procedures. Accordingly, the interaction among autoimmune disease, immunosuppressive therapy, bone-modifying agents, and oral health constitutes a critical clinical interface for both rheumatology and dentistry [23].

Definition and Pathophysiology

Medication-related osteonecrosis of the jaws (MRONJ), also referred to as osteonecrosis of the jaw (ONJ), is characterized by one or more necrotic bone lesions in the maxillofacial region, visible through intraoral or extraoral fistulae, and persisting over time. Although uncommon, it represents a serious clinical condition with potentially chronic consequences [24].

The diagnostic criteria for MRONJ include [25]: 1) Current or previous treatment with antiresorptive agents alone or in combination with immune modulators or anti-angiogenic drugs; 2) Exposed bone or bone that can be probed through intraoral or extraoral fistulae in the maxillofacial region persisting for at least 8 weeks; 3) No history of radiation therapy to the jaws or metastatic disease involving the jaws.

Among medications implicated in MRONJ, bisphosphonates (particularly intravenous forms) and denosumab are the most frequently associated drug classes. Other agents such as bevacizumab, romosozumab, and various tyrosine kinase inhibitors have also been linked to MRONJ in published case reports [25].

The pathophysiology of MRONJ primarily involves three mechanisms: 1) Suppression of bone remodeling, 2) Inflammation and/or infection, and 3) Impaired vascularization. Antiresorptive agents—including bisphosphonates and denosumab—exert direct effects on osteoclast formation, differentiation, and function. Because many teeth requiring extraction present with pre-existing periapical and/or periodontal infections, local inflammation and infection are major contributors in MRONJ pathogenesis. Additionally, bisphosphonates have been shown in vitro and in vivo to directly inhibit angiogenesis. Animal models demonstrate reduced vascularity and decreased micro vessel density in early bone healing phases within MRONJ lesions. Compromised angiogenesis following tooth extraction delays alveolar socket healing and increases the risk of secondary infection [24, 25].

Clinical Manifestations of MRONJ

Clinical manifestations of MRONJ typically begin with localized inflammation and progress to more pronounced soft and hard tissue changes.

In the early stages, patients may exhibit mucosal inflammation, non-healing extraction sockets, and sensory disturbances such as lip numbness. As the disease advances, purulent discharge, soft-tissue swelling, spontaneous loss of bone sequestra, tooth or implant mobility, severe dental pain, and trismus may develop. The presence of these findings indicates progression of osteonecrosis and the need for early intervention.

In advanced stages, both soft and hard tissues are affected by infection and necrosis. Clinically, abscess formation, bone exposure, intraoral or cutaneous fistulae, and nasal discharge may be observed. These conditions are often accompanied by halitosis and jaw pain originating from necrotic bone. In the late phases of MRONJ, pathologic mandibular fracture or segmental mobility, mandibular deformity, and widened periodontal ligament space may occur, leading to increased tooth mobility. These severe signs reflect the progressive and destructive nature of MRONJ and underscore the importance of early diagnosis, preventive strategies, and multidisciplinary treatment planning [24-26].

Risk Factors for MRONJ

Pharmacologic agents and therapeutic indications play a major role in MRONJ risk (Table 1).

For tyrosine kinase inhibitors (e.g., sunitinib), VEGF inhibitors (e.g., bevacizumab), fusion proteins (e.g., aflibercept), mTOR inhibitors (e.g., everolimus), and TNF-α inhibitors, methotrexate, and corticosteroids, MRONJ has been reported, though not consistently defined as a risk when used alone.

Local factors contributing to MRONJ include: dentoalveolar surgical procedures (e.g., extractions, implant surgery); poor oral hygiene or inadequate professional maintenance; periodontitis or peri-implantitis; dental trauma; and anatomical site (mandible carries approximately 3× greater risk). Demographic and systemic factors include smoking (×3 risk), diabetes mellitus, and hemoglobin levels <10 g/dL [24, 25]

Table 1. Risk of MRONJ for different medications and indications [25]

Drug / Indication	Reported MRONJ Risk
Zoledronate (IV) – Cancer therapy	<5%
Zoledronate – Osteoporosis therapy	<0.02%
Denosumab – Cancer therapy	6.5%
Denosumab – Osteoporosis therapy	0.04–0.3%
Alendronate	<0.05%
Romosozumab (osteoporosis)	0.03–0.05%

The most critical determinant of MRONJ risk is the dosage and frequency of bone-modifying/antiresorptive agents. High-dose (HD) intravenous bisphosphonates (e.g., 4 mg monthly zoledronate) and subcutaneous denosumab at oncologic doses (120 mg monthly) represent the highest risk. In contrast, low-dose (LD) antiresorptive therapies for osteoporosis (oral or parenteral BP, or 60 mg denosumab every 6 months) carry significantly lower risk. Patients receiving high-dose BMAs for multiple myeloma (MM) or bone metastases (BM) constitute the highest-risk group, with MRONJ incidence and prevalence ranging between 1% and >20%. Recent systematic reviews indicate that zoledronic acid carries a higher MRONJ risk than other bisphosphonates (e.g., pamidronate, ibandronate), and denosumab confers an even higher risk than zoledronic acid. MRONJ risk appears to increase with treatment duration. Kaplan–Meier survival analyses in MM/BM patients show a progressive rise in MRONJ risk with longer treatment years. It remains unclear whether treatment duration (drug exposure) or observation period (patient survival) is the more dominant factor; however, prolonged therapy and extended survival can raise cumulative incidence up to 30% over 8 years in certain metastatic cancer subgroups [25, 26]

Preventive Strategies and Dental Management in MRONJ Patients

Although recent updates have introduced new treatment strategies for MRONJ, predictability of treatment outcomes remains limited due to local factors and patient comorbidities. Therefore, preventive dental management is of paramount importance. The Italian position paper (SIPMO–SICMF, 2024) provided structured recommendations for the prevention and management of MRONJ, categorizing patients according to the dose and regimen of antiresorptive therapy and defining practical guidance for dental treatment planning [26] (Table 2).

Table 2. Antiresorptive Dose Groups and Subcategories [26]

Antiresorptive Dose Group	Definition
Low Dose (LD-AR)	R_0: Planned LD-AR therapy not yet initiated, or <3 years of LD-AR use without additional systemic risk factors. R_x: Ongoing LD-AR therapy >3 years, or <3 years with additional risk factors (i.e., concurrent systemic risk factors in patients on <3 years of LD-BMA therapy).
High Dose (HD-AR)	R_0: Planned HD-AR therapy not yet initiated. R_+: Ongoing HD-AR therapy without additional systemic risk factors. R_{++}: Ongoing HD-AR therapy with additional systemic risk factors, or in combination with anti-angiogenic drugs.

Table 3. Preventive Dental Care Strategies for MRONJ [25]

Stage	Strategies
During Antiresorptive Therapy (Non-malignant Disease)	- No changes to standard operative plans are required for most patients. - Evaluate medication type and duration, comorbidities, concomitant drugs (esp. chemotherapy, steroids, anti-angiogenics), baseline infection/inflammation, and extent of surgery. - Consider individualized "drug holidays." - Bone turnover markers are not reliable tools for MRONJ risk assessment.
During Antiresorptive / Targeted Therapy (Malignant Disease)	- Inform patients that MRONJ risk is higher in malignancy-associated AR therapy. - Educate patients on regular dental maintenance and preventive oral hygiene. - Avoid dentoalveolar surgery when possible. - Consider conservative techniques to avoid extractions. - Dental implants are contraindicated. - Discuss drug holidays when appropriate.

Table 4. Dental Treatment Recommendations According to BMA Dose Category [25]

Dental Treatment	High-Dose BMA (HD-BMA) – R_+ and R_{++}	Low-Dose BMA (LD-BMA) – R_x
Non-surgical Procedures		
Restorative Dentistry	Indicated	Indicated
Endodontic Treatment	Indicated	Indicated
Orthodontic Treatment	Conditional	Conditional
Periodontal Therapy	Indicated	Indicated
Prosthetic Rehabilitation	Conditional	Conditional
Surgical Procedures		
Dentoalveolar Surgery	Indicated	Indicated
Tooth Extraction	Indicated	Indicated
Pre-implant Bone Augmentation	Contraindicated	Conditional
Dental Implant Surgery	Contraindicated	Conditional
Periodontal Surgery	Indicated	Indicated
Endodontic Surgery	Indicated	Indicated

Dental interventions are classified as either necessary/emergency procedures—those aimed at eliminating infectious foci (e.g., pulpitis, pericoronitis, periapical or periodontal abscesses, peri-implantitis, dental trauma, pain, or tissue damage caused by prostheses) or elective procedures such as esthetic restorations, orthodontic treatments, elective periodontal or endodontic procedures, and prosthetic rehabilitations [24, 25] (Table 3).

The SIPMO–SICMF Expert Panel proposed a traffic-light classification system to help clinicians balance the risk–benefit ratio of dental procedures in patients receiving bisphosphonates or other BMAs. Treatments are categorized as: Indicated (Green light): all essential and emergency procedures not associated with an increased MRONJ risk; Conditional (Yellow light): elective procedures with uncertain MRONJ risk, permissible under controlled conditions; Contraindicated (Red light): elective

surgical interventions with clearly unfavorable risk–benefit profiles (Table 4).

Drug Holiday Practices

In patients without clinical signs of MRONJ, the concept of a prophylactic "drug holiday"—temporary suspension of bisphosphonate therapy prior to oral surgical procedures—has been proposed over the past two decades for patients with osteoporosis or multiple myeloma, in an effort to enhance wound healing. However, the duration of the drug holiday varies widely in the literature, ranging from a few weeks to several months, depending on published protocols. Evidence from both clinical and animal studies does not provide strong support for the routine use of drug holidays to prevent MRONJ. Thus, such interruptions are considered theoretical measures, based on pharmacokinetic reasoning rather than solid empirical data [25, 27].

Given current evidence, the SIPMO–SICMF Expert Panel advises that prophylactic suspension of denosumab should be approached cautiously, especially in patients at elevated MRONJ risk. Treatment planning should be individualized, depending on the type of pharmacologic agent and dosage regimen (Table 5).

Therapeutic and Preventive Outlook

Conservative and preventive therapy constitutes the cornerstone of MRONJ management and is applicable in the vast majority of cases. For refractory MRONJ cases unresponsive to conservative treatment, surgical intervention remains the primary approach. Teriparatide (TPTD) has emerged as a potentially promising conservative option in osteoporotic patients, though its efficacy—as well as that of other proposed therapies—requires further validation [24, 28].

In rheumatology, newer-generation DMARDs are increasingly used and, unlike glucocorticoids, do not negatively affect bone metabolism, potentially contributing to a lower prevalence of drug-induced osteoporosis. Moreover, the targeted anti-inflammatory effects of these new biologics may indirectly reduce MRONJ risk. However, risks associated with older therapies persist, and the long-term safety profiles of newer drugs must continue to be evaluated.

The overall benefits of antiresorptive therapy far outweigh the potential risks, offering substantial reductions in skeletal-related events among oncology patients and fracture risk in osteoporosis patients [29]. Nevertheless, MRONJ remains a condition that can severely affect quality of life. It is therefore essential to communicate individual MRONJ risk to patients and caregivers clearly, to ensure long-term adherence to medical and oral health programs. Given the continual introduction of new and potentially high-risk medications, healthcare professionals must keep the literature up to date and integrate new data into clinical decision-making [26].

CONCLUSIONS AND RECOMMENDATIONS

The management of periodontal diseases in patients with rheumatologic disorders requires a multidisciplinary approach, focusing on both control of systemic inflammation and prevention of drug-related complications. In autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and vasculitis, regular periodontal screening should be integrated into routine care. Gingival health should be monitored as a potential indicator of disease activity. Simple, low-cost, and repeatable interventions—such as plaque control and scaling and root planing (SRP)—

Table 5. Recommended Discontinuation and Resumption Timing of Antiresorptive and Anti-angiogenic Drugs [26]

Patient Group	Drug	Discontinuation Timing	Resumption Timing
High-Dose AR (R_+ and R_{++})	Bisphosphonates	1 week before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Denosumab (Xgeva®)	3 weeks before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Bevacizumab	5–8 weeks before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Sunitinib	1 week before surgery	After wound healing (4–6 weeks post-op)
High-Dose AR (R_+ and R_{++})	Everolimus	1 week before surgery	After wound healing (4–6 weeks post-op)
Low-Dose AR (R_+)	Bisphosphonates	1 week before surgery	After wound healing (4–6 weeks post-op)
Low-Dose AR (R_+)	Denosumab (Prolia®)	No drug holiday required	—

can significantly reduce systemic inflammation and potentially decrease glucocorticoid requirements.

In vasculitic conditions like granulomatosis with polyangiitis (GPA), characteristic findings such as "strawberry gingivitis" or ulcerative oral lesions should be carefully evaluated, as they may serve as early diagnostic clues or markers of disease relapse.

For patients at risk of MRONJ, surgical decision-making must consider antiresorptive drug dosage and regimen. In cases of high-dose (oncologic) therapy, procedures such as implant placement or bone augmentation should be avoided. In contrast, for low-dose osteoporosis regimens, surgical procedures may be safely performed under atraumatic techniques, with primary closure and antiseptic support protocols. The implementation of drug holidays should be individualized, considering patient-specific risk factors and pharmacokinetic properties of the medications—particularly denosumab, where timing is critical.

Looking ahead, more randomized controlled trials are needed to evaluate the impact of periodontal therapy on rheumatologic disease activity and bone mineral density. Longitudinal studies investigating the correlation between periodontitis-related biomarkers (such as aMMP-8, citrullinated proteins, and *P. gingivalis* load) and systemic inflammation would provide valuable diagnostic and prognostic insights. Moreover, clinical trials comparing the effects of traditional versus biologic DMARDs on alveolar bone metabolism could guide the development of personalized treatment strategies.

Finally, the implementation of personalized preventive and therapeutic protocols, combined with prospective evaluation of emerging pharmacologic agents, is essential. A strong communication bridge between rheumatology and dentistry, supported by patient education, will not only reduce oral complications but also improve the overall management and quality of life of patients with rheumatologic diseases.

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acta medica

REVIEW

Rational use of immunosuppressive drugs in vasculitis treatment

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ABSTRACT

Immunosuppressive drugs are essential for the treatment of inflammatory and autoimmune diseases, such as vasculitis. A complete understanding of pharmacological profiles, interaction potentials, and patient-specific variables is necessary for rational drug use. Azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide and glucocorticoids are common immunosuppressants that have complex pharmacokinetics and are linked to a variety of interactions between drugs, nutrients, and supplements, which may increase the toxicity or change the therapeutic response. Their safety and effectiveness are greatly influenced by metabolic polymorphisms, cytochrome P450 enzymes, and P-glycoprotein transporters. Serious side effects such as nephrotoxicity, myelosuppression, or decreased treatment response might result from inappropriate combinations. Therefore, therapeutic drug monitoring and individualization of therapy by a multidisciplinary approach becomes important. This review emphasizes the importance of rational use of these drugs, patient monitoring and management of drug interactions to ensure safe and effective immunosuppressive therapy, while minimizing preventable risks and maximizing patient outcomes.

Keywords: Rational drug use, immunosuppressives, drug interactions, pharmacist.

INTRODUCTION

Vasculitis refers to a heterogeneous group of rare disorders characterized by inflammation and necrosis of blood vessel walls, which can lead to tissue ischemia and organ dysfunction. The overall prevalence depends on the subtype and geographic region [1]. Although etiology-based disease classification is frequently the preferable method, most vasculitides cannot be classified in this way since the etiology is unclear [2]. Timely diagnosis and initiation of immunosuppressive therapy are critical for improving outcomes and preventing irreversible organ injury, as highlighted by the EULAR recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [3-5].

The pathophysiology of vasculitis and inflammatory processes are actively influenced by the endothelial injury through mechanisms, such as abnormal T-cell activation, autoantibody production (e.g., ANCA), and pro-inflammatory cytokine release [e.g., Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-6] [6]. Immunosuppressive drugs target these pathways at different levels: calcineurin inhibitors (e.g., tacrolimus, cyclosporine) inhibit T-cell activation by blocking IL-2 transcription; mycophenolate mofetil suppresses lymphocyte proliferation via inosine monophosphate dehydrogenase inhibition; azathioprine interferes with purine synthesis; methotrexate inhibits dihydrofolate reductase, reducing pro-inflammatory immune cell turnover and cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis and exerts its immunomodulatory effect via T cells regulations and rituximab, as a monoclonal antibody, suppresses the immune response by targeting the

CD20 receptor on the surface of B lymphocytes. Glucocorticoids suppress the immune response mainly by reducing the production of pro-inflammatory cytokines and limiting the movement of white blood cells to sites of inflammation. As these drugs exert immunosuppressive effects through distinct pathways, significant interindividual variability, and potential drug–drug and drug–nutrient interactions, their use requires careful consideration to balance efficacy and safety [2, 7, 8].

Treatment Strategy

The complex classification systems and largely unknown etiologies of vasculitides have complicated disease management; nevertheless, treatment strategies have continued to evolve with the use of various immunosuppressive drugs and the introduction of novel approaches, including biologic therapies. When administered with or without immunosuppressive medications, glucocorticoids are the first-line treatment for individuals with vasculitis. The selection of immunosuppressive medications is based on the type of vasculitis [9]. Among the different types of vasculitis, ANCA-associated vasculitis is considered the one that most clearly requires immunosuppressive treatment. It is followed by conditions such as Giant Cell Arteritis (GCA), Polyarteritis Nodosa (PAN), Takayasu Arteritis (TAK), Immunoglobulin (Ig) A vasculitis, and cryoglobulinemic vasculitis [4, 5, 10-12].

Treatments for various types of vasculitis have included the use of methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), rituximab (RTX), intravenous immunoglobulin, plasma exchange, and others [6]. It is imperative to determine the most appropriate immunosuppressive treatment for each patient, with the objective of enhancing treatment outcomes while mitigating the risk of adverse effects. Since these drugs are widely used and often involve complex regimens, a clear understanding of potential drug interactions and implementation of principles of rational drug usage is inevitable [13].

Rational Use of Immunosuppressive Drugs

The rational use of immunosuppressive drugs aims to achieve optimal therapeutic outcomes by ensuring appropriate indications, dosing, and treatment duration. These drugs are primarily employed in managing serious conditions such as vasculitis, organ transplantation, and autoimmune diseases. However, due to their immunosuppressive effect, they have risks of severe complications, including infections, malignancies, and organ toxicities. Therefore, comprehensive assessment of individual factors (such as comorbidities, age, renal and hepatic function, immune status, and medication adherence), consideration of indications, management of drug interactions, and close monitoring of treatment response are critical components of their rational use [4, 5, 7]. For example; elderly patients have an increased risk of hematologic toxicity with drugs like MMF, while AZA metabolism may be impaired in those with hepatic insufficiency [14, 15].

Therapeutic drug monitoring (TDM) is a strategy employed to ensure the rational use of immunosuppressive drugs, however, it is commonly used for calcineurin inhibitors such as tacrolimus and cyclosporine. Mycophenolate mofetil and azathioprine do not have widely established TDM protocols, but measurement of mycophenolic acid levels or metabolites may be considered in selected cases [8]. Drug information leaflets, clinical guidelines, and patient-specific pharmacokinetic calculations support the evidence-based dose adjustments.

Glucocorticoids remain the mainstay of rational immunosuppressive therapy in vasculitis due to their potent and rapid anti-inflammatory effects. When administered at immunosuppressive doses that are tailored to the severity of the disease, it enables effective control of vascular inflammation. Nevertheless, given their substantial side effect profile, particularly in cases of long-term, high-dose usage, meticulous dose optimization, gradual tapering and close monitoring of signs and symptoms are paramount to ensure their judicious utilization [10, 12].

Risk of Drug Interactions

Immunosuppressive drugs are susceptible to a range of pharmacological interactions. The most immunosuppressive drugs have the potential to interact through hepatic metabolism [mainly via cytochrome P450 (CYP) enzymes], renal elimination, and modulation of the immune system [13, 16].

Drug interactions are generally classified into two main categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions result from alterations in the absorption, distribution, metabolism, or excretion pathways of a drug once concomitantly used with the other. Concomitant administration of medications can result in interactions that influence the plasma levels of each drug, potentially leading to sub-therapeutic (inefficacy) or supra-therapeutic (toxicity) levels of either or both medications. For example, the absorption of mycophenolate mofetil can be impaired with antibiotics such as cephalosporins or rifampin, which leads to decreased plasma levels. Cyclosporine, mycophenolate mofetil and cyclophosphamide are metabolized via the CYP enzymes and P-glycoprotein system; therefore, the plasma concentrations can reach the toxic levels when co-administered with azole antifungals, calcium channel blockers, or macrolide antibiotics [8, 17, 18]. On the other hand, pharmacodynamic interactions involve the direct or indirect enhancement or reduction of drug effects at the site of action, which occur as additive, synergistic or antagonist mechanisms. For instance, concurrent use of methotrexate and nonsteroidal anti-inflammatory drugs (NSAIDs) may accelerate impairment of renal function, thereby increasing methotrexate toxicity. Similarly, a combination of azathioprine with myelotoxic drugs, such as co-trimoxazole or allopurinol increases the risk of pancytopenia [19]. Such interactions are particularly critical in serious conditions like vasculitis, where they can disrupt the balance between therapeutic efficacy and toxicity; therefore, close clinical monitoring (including therapeutic drug monitoring) and avoidance of drugs with interaction risk (where appropriate) are essential. Azathioprine is metabolized via the xanthine oxidase enzyme; therefore, concomitant use with xanthine oxidase inhibitors such as allopurinol significantly increases 6-mercaptopurine levels, markedly increasing the risk of bone marrow suppression. If this combination is unavoidable, the azathioprine dose should be reduced by 25–50%, and hematological parameters must be closely monitored [19]. Mycophenolic acid, the active metabolite of MMF, undergoes enterohepatic recirculation; consequently, antibiotics such as rifampin, ciprofloxacin, and amoxicillin-clavulanate have the potential to reduce the levels of mycophenolate, thereby diminishing its therapeutic efficacy. Therefore, it is crucial that antibiotic preferences are given particular consideration in patients at risk of sepsis during vasculitis flare-ups [20]. Methotrexate is eliminated primarily via renal tubular secretion. Concomitant drugs such as, NSAIDs, proton pump inhibitors (PPIs) like omeprazole and lansoprazole, and trimethoprim can reduce methotrexate (particularly with high-dose) clearance and increase the risk of toxicity, including hepatotoxicity and bone marrow suppression. When such combinations are required, using lower doses and close monitoring is recommended. Similarly, the risk of adverse effects of cyclophosphamide may increase by concomitant use of allopurinol, antifungals, barbiturates, linezolid and thiazide diuretics [21]. Since the metabolism of rituximab is mainly by various proteases and its elimination is mediated by the reticuloendothelial system, there are limited drug interactions when administered concomitantly, with the exception of concurrent use with cidofovir and talimogene laherparepvec, which are absolute contraindications [22]. However, as is applicable to all immunosuppressive drugs, co-medication with other immunosuppressives may enhance this effect and lead to pronounced myelosuppression.

Pharmaceutical incompatibility refers to drug stability and incompatibilities, which indicates the formation of precipitates or acid-base reactions resulting from physicochemical changes associated with the administration of certain parenteral drugs or mixtures together. In contrast to pharmacokinetic and pharmacodynamic interactions, drug incompatibilities occur prior to the drugs entering the body and can arise between drugs, drugs and solvent solutions, drugs and infusion system materials, or medical devices [23]. Therefore, a clear distinction should be made between the terms of drug stability, incompatibilities and drug interactions when using drugs concomitantly.

Not only with the drugs, but also certain foods may affect the outcome of drug treatment [24]. Antiproliferative drugs such as MMF can also interact with nutrients; its absorption may be delayed by high-fat meals; however, its overall bioavailability is not significantly affected. In contrast, the enteric-coated form, mycophenolate sodium, is generally preferred to be taken after meals. Additionally, supplements containing aluminum and magnesium (e.g., antacids) may

impair the absorption of MMF [25]. High-dose folic acid supplementation during methotrexate therapy may reduce the drug's efficacy; therefore, folic acid supplementation should be carefully planned with respect to dose and timing specific to the treatment regimen [26].

Furthermore, the efficacy and safety of immunosuppressive drugs may be affected by herbal supplements. It is well-known that St. John's Wort (*Hypericum perforatum*) is a potent CYP3A4 inducer, which may decrease the level of cyclosporine or glucocorticoids. Supplements includes Ginseng (*Panax ginseng*) or *Echinacea (Echinacea purpurea)* have been observed to stimulate the immune system, thereby reducing the effectiveness of drugs such as azathioprine, mycophenolate mofetil, and tacrolimus. Additionally, ginseng may affect their metabolism via CYP3A4 and P-glycoprotein [27].

Although commonly used interaction checker programs offer a helpful insight in identifying potential drug interactions, their clinical relevance, especially in patients receiving immunosuppressive therapy often requires careful interpretation. For drugs with a narrow therapeutic index, such as tacrolimus or cyclosporine, even minor changes in metabolism can lead to significant toxicity or treatment failure. This is where clinical pharmacists take an active role by not just recognizing interactions, also by evaluating their clinical significance and real impact on the treatment outcomes and consequently help to maintain safe and effective drug treatment [28].

CONCLUSION

The rational use of immunosuppressive drugs demands a collaborative approach, aimed at achieving a balance between adequate immunosuppression and the minimization of adverse effects. Therapeutic drug monitoring, individualized patient assessment of (e.g., age, organ function, comorbidities, antigen-related factors), and adherence to clinical guidelines are all practices undertaken to ensure safety and efficacy. It is therefore vital to emphasize the importance of multidisciplinary collaboration, increased vigilance among healthcare providers, and patient education regarding self-use of supplements in order to improve outcomes and reduce the incidence of preventable complications associated with immunosuppressive drugs.

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REVIEW

Male infertility and erectile dysfunction in patients with vasculitis

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ABSTRACT

Erectile dysfunction and male infertility are increasingly recognized complications in patients with vasculitis, arising from both disease-related mechanisms and treatment effects. Chronic inflammation, vascular involvement, and hormonal dysregulation may impair erectile function and reproductive capacity. Furthermore, commonly used medications such as steroids and immunosuppressants can negatively impact semen quality and may exert teratogenic effects. Studies have also demonstrated high rates of hypogonadism and sexual dysfunction in specific vasculitis subtypes, including granulomatosis with polyangiitis and Behçet's disease. Given the limited evidence base, multidisciplinary evaluation and proactive counseling regarding sexual health, fertility intentions, and treatment risks are essential.

Keywords: erectile dysfunction, male infertility, vasculitis.

INTRODUCTION

Male infertility and erectile dysfunction in patients with vasculitis

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance. The prevalence of ED increases with age; approximately 40% of men in their fifth decade are affected, while the prevalence at the age of 80 is between 30–40%. According to the Massachusetts Male Aging Study conducted in the USA, UK, and Australia among men aged 40–70 years, the prevalence of minimal ED is 17.2%, moderate ED 25.2%, and severe ED 9.6% [1].

It should be emphasized that the attainment of an erection depends on a complex interplay of multiple factors. These include vascular (arterial and cavernosal), neurological (sensory, motor, or autonomic), hormonal (testicular, pituitary, thyroid), systemic, pharmacological, and psychological components.

In clinical practice, a detailed medical and sexual history should be obtained from each patient, including previous and current sexual status, emotional state, duration of symptoms, and any previous treatments. The International Index of Erectile Function (IIEF) and its shortened version, the Sexual Health Inventory for Men (SHIM)—a five-item questionnaire—should be administered to all patients presenting with ED [2,3]. These standardized tools are valuable for both diagnosis and follow-up during treatment.

The first-line treatment for ED typically involves phosphodiesterase type 5 (PDE5) inhibitors, which are widely available and easy to use. Sildenafil, tadalafil, vardenafil, and avanafil have been used for many years and have success rates of up to 70%. Chronic sildenafil use has been shown to improve erectile function and enhance endothelium-dependent cavernosal relaxation [4].

Infertility is defined as the inability of a sexually active couple to achieve pregnancy after one year of regular, unprotected intercourse [5]. It affects approximately 15% of couples, with male factors accounting for nearly 50% of cases, often due to abnormal sperm parameters. Male infertility may result from endocrinological or systemic disorders, spermatogenic or transport defects, or idiopathic/unexplained causes. Abnormal sperm parameters are frequently observed in infertile men and may also be influenced by pharmacological treatments used for other diseases.

Steroids, immunosuppressants, and immunomodulatory drugs frequently used in patients with vasculitis may impair semen parameters and, in some cases, exert teratogenic effects. Clinicians should inform patients and their partners of these risks. Although the level of evidence regarding drug effects is generally low, the potential impact can be significant. For example, Clowse et al. reported increased rates of pregnancy loss and miscarriage among partners of male patients with vasculitis [6]. In clinical practice, cryopreservation and contraception should be discussed with patients receiving treatments known to impact fertility, such as sirolimus, ipilimumab, or dabrafenib. [7].

Beyond treatment, vasculitis itself can contribute to urological complications. For instance, Richter et al. reported hypogonadism in 50% of patients with Granulomatosis with Polyangiitis (GPA), independent of treatment response [8]. Androgen deficiency has also been associated with fatigue and reduced health-related quality of life in patients with ANCA-associated vasculitis [9]. Several studies have demonstrated a relationship between Behçet's syndrome and ED, with lower IIEF scores in affected patients compared to controls, independent of disease activity [10–12]. A systematic review by Talarico et al. concluded that multidisciplinary care is essential to address the significant impact on sexual health in Behçet's syndrome [13].

Although several studies have addressed the effects of vasculitis and its treatments on sexual function, the current literature remains limited. Further research is required to better understand the relationship between vasculitis and ED and to develop interventions that improve sexual function in this patient group. Until more evidence is available, a multidisciplinary approach to sexual health should be integrated into routine clinical practice. This should include assessment of pre- and post-disease sexual status, evaluation of drug side effects, hormonal influences, and fertility intentions. Such an approach can help preserve sexual function and improve overall quality of life.

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REVIEW

Biopsychosocial approach in vasculitis: BETY

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ABSTRACT

Rheumatic diseases cause biopsychosocial effects such as chronic pain, fatigue, social isolation, functional impairments, anxiety-depression, and sleep problems. National and international guidelines emphasize the importance of physical activity and exercise planning, patient education and self-management skills, and psychosocial interventions in the management of rheumatic diseases. Vasculitides are also a group of chronic diseases that can affect many organs and systems, impacting individuals biopsychosocially. Although comprehensive approaches are recommended in the literature for this disease group, as in other rheumatic diseases, studies in this field are quite insufficient. The Cognitive Exercise Therapy Approach (*Bilişsel Egzersiz Terapi Yaklaşımı - BETY*) is an innovative exercise approach developed on the basis of the biopsychosocial model for individuals diagnosed with rheumatological diseases. Developed based on the biopsychosocial model, the BETY exercise model is an example of a non-pharmacological exercise approach in the treatment of vasculitis.

Keywords: Biopsychosocial model, exercise, disease management, vasculitis.

INTRODUCTION

In the management of rheumatological diseases, determining biopsychosocial characteristics and recommending approaches that align with these characteristics is emphasized [1]. Among these characteristics, chronic pain, fatigue, social isolation, functional impairments, anxiety-depression, sleep problems, and cognitive impairments in sexuality have a crucial role. On the other hand, the concept of "*Exercise is medicine*" for all chronic diseases is becoming increasingly established, especially as the anti-inflammatory effects of exercise have been proven, and this information is being widely transferred to clinical practice [2]. Exercise approaches represent the most important parameter among coping skills for dealing with biopsychosocial characteristics. On the other hand, some long-standing myths persist. Among these are misconceptions such as "*Exercise should not be done while the disease is active*," "*Don't move when in pain*," and "*Exercise increases inflammation*." However, today, institutions that guide the field of rheumatology, such as EULAR (European Alliance of Associations for Rheumatology) and ACR (American College of Rheumatology), strongly emphasize both the necessity of a biopsychosocial approach and the value of exercise interventions [3,4].

Chronic inflammation can causes significant symptoms that require regular exercise. These represent periodic pain, chronic fatigue, decreased physical fitness, depression, inactivity, and, naturally, a decrease in quality of life. However, exercise's anti-inflammatory effects reduce cytokine release from adipose tissue, skeletal muscle, endothelial, and blood cells, thereby improving insulin sensitivity, endothelial function, and CRP (c-reactive protein) levels. It is known that IL-6, IL-1Ra, IL-10, and TNF-R are released from muscles, especially with exercise approaches lasting longer than 3 months. This leads to the pro-inflammatory properties of IL-6 being

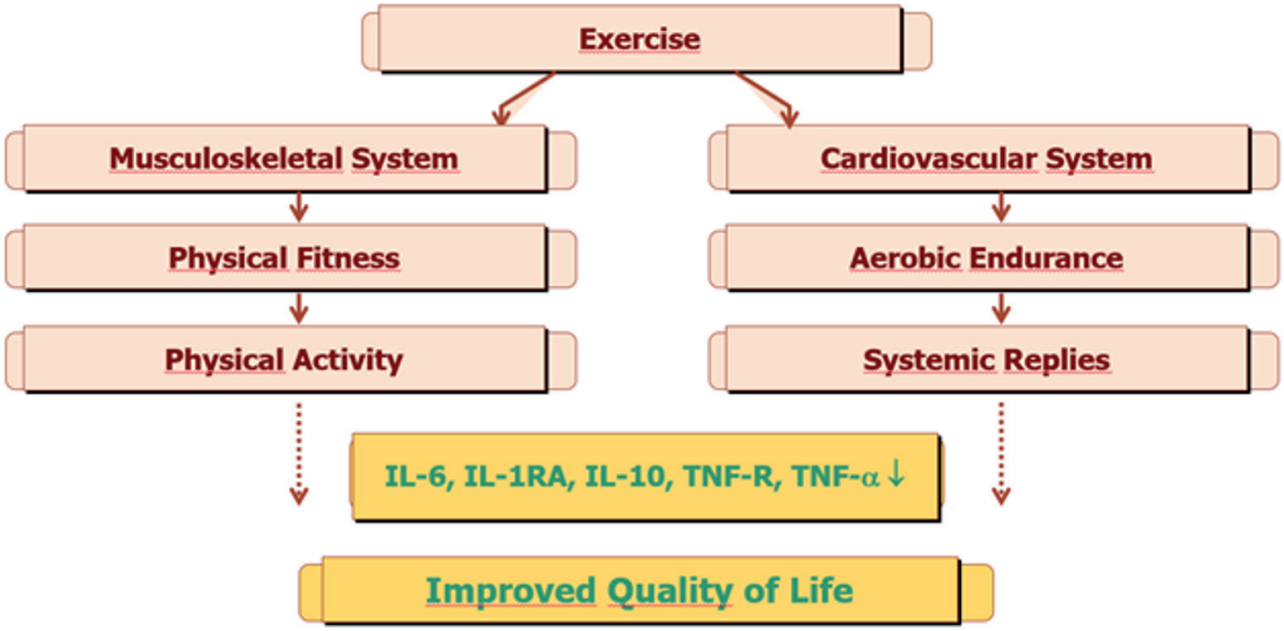

Figure 1. The effects of exercise on quality of life [9]

converted to anti-inflammatory properties due to the effect of exercise on cytokines (Figure 1) [5-8].

In other words, exercise approaches are also effective in counteracting potential side effects of medical treatment, such as low muscle function, low aerobic fitness, and low bone and muscle mass [6].

While exercise has been adopted in the field of rheumatology since the 1970s, with the development of biological agents and radiological techniques in the 21st century, exercise has become an indispensable part of quality of life. EULAR recommends regular exercise and patient education as a non-pharmacological treatment approach based on the biopsychosocial model [1]. At this point, the fact that pain is also a biopsychosocial concept forms the basis (Figure 2).

On the other hand, reiterating the definition of pain established by the International Association for the Study of Pain (IASP) in 1979, a new definition including nociplastic pain was established in 2020 [10]. With this definition, nociplastic pain, in addition to nociceptive and neuropathic pain, has become an area of focus for clinicians in pain management. It has also been emphasized that chronic pain in all three categories must be included in patient education [11].

According to the 2018 guidelines published by EULAR, pain is influenced by many parameters, and its management emphasizes the substantial importance of physical activity and exercise planning, patient education, and improving self-management skills, as well as psychological and social interventions [1]. To define, physical activity encompasses energy consumption above the basal metabolic rate, while exercise is the regular, repetitive form of physical activity performed at a specific rhythm and frequency. The concept referred to in the guidelines is that physical activity should be restricted when the disease is active; however exercises for the affected body part should still be performed. For fatigue, a symptom frequently reported in rheumatological diseases, structured exercises known as aerobic exercise, which involve large muscle groups and increase respiration and heart rate, are recommended. In daily life, a structured walking session in its simplest form should always be recommended to individuals.

Although the significant role of the biopsychosocial approach in alleviating biopsychosocial symptoms observed in rheumatological diseases is emphasized, the lack of standardized assessment and treatment methods is also reported [12].

Vasculitides are a heterogeneous group of diseases that affect various organs and systems and, causing life-threatening deficiencies [13]. Different diseases that occur with the involvement of different types of vessels are included in this group, and each named disease manifests itself with many biopsychosocial symptoms (Figure 3).

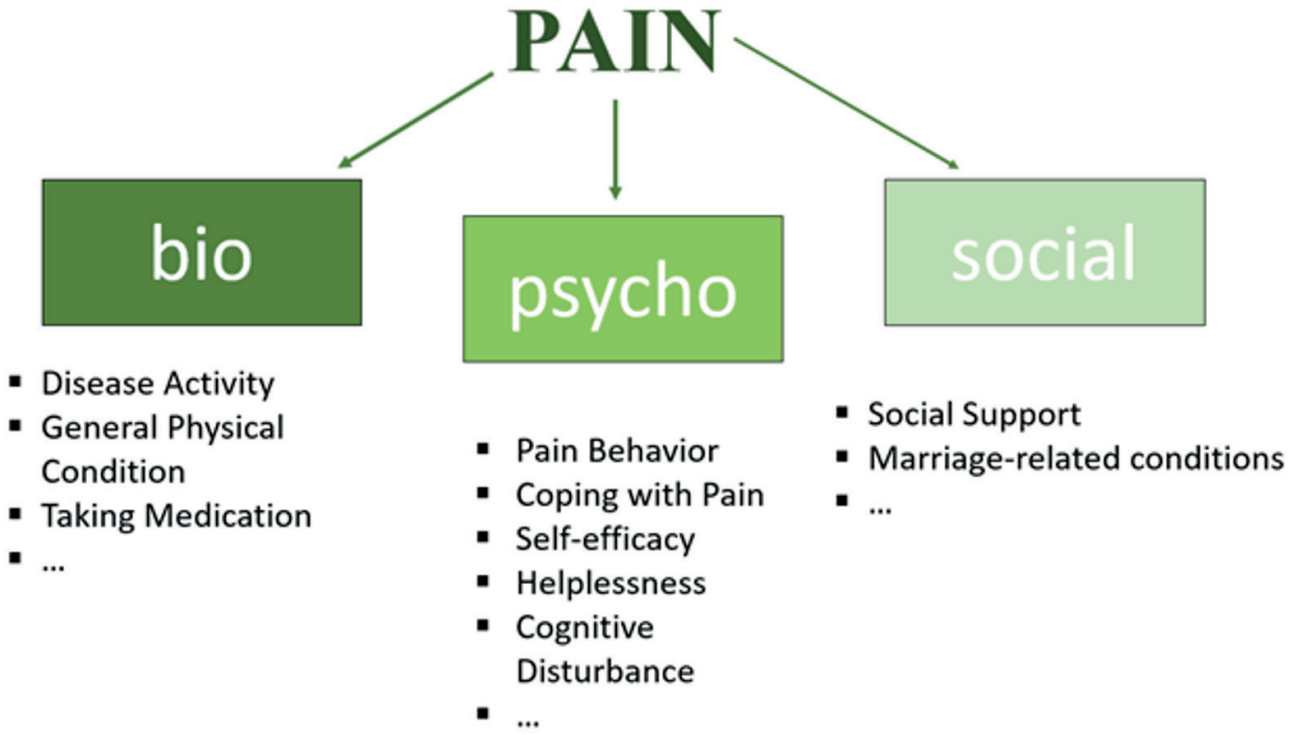

Figure 2. The biopsychosocial dimension of pain [1]

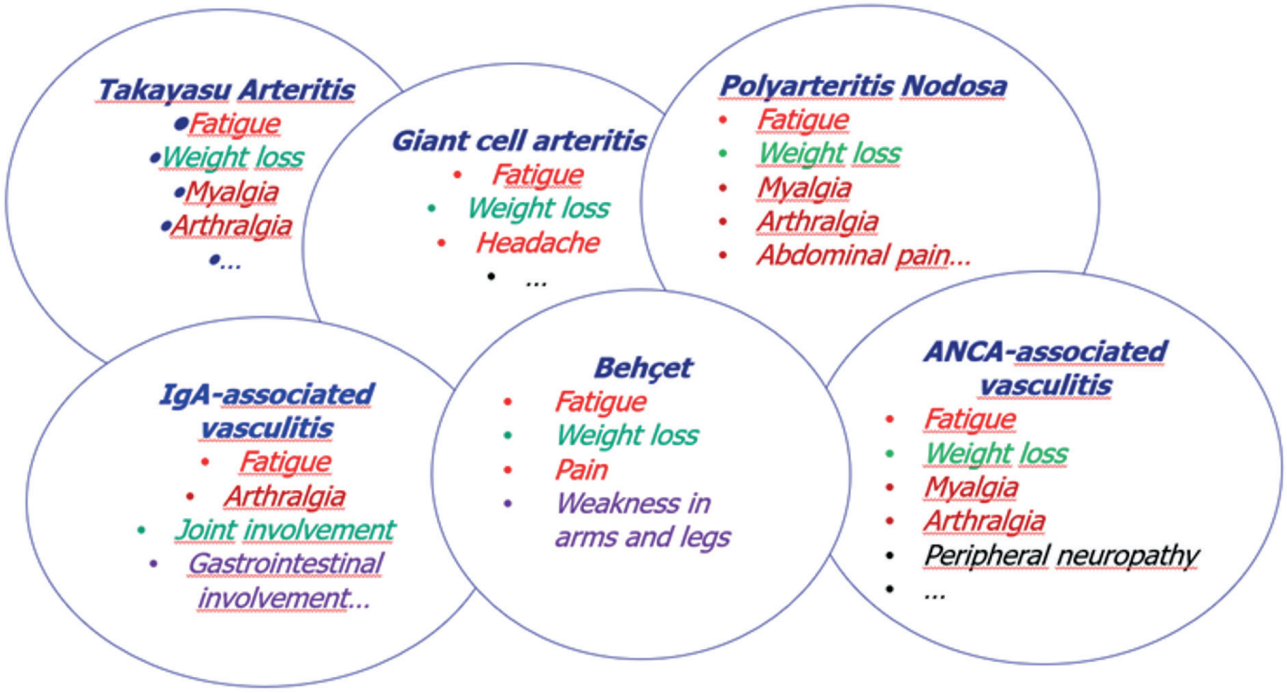

Figure 3. The biopsychosocial impairments seen in some types of vasculitides

The management of biopsychosocial characteristics (pain, fatigue, functional impairment, mood effects, social isolation, sexual problems, sleep problems) emphasizes the importance of exercise approaches. [14,15].

The importance of exercise approaches in cases of nerve and muscle involvement in vasculitis is also noted [16]. Furthermore, the 2022 EULAR update emphasizes the importance of a multidisciplinary approach, highlighting the necessity of patient education with the support of different disciplines to ensure lifestyle changes. It is particularly noted that screening for and treatment of cardiovascular risk factors are important. It has been emphasized that the disease management components recommended in the EULAR guidelines for

other rheumatological diseases should also be considered in vasculitides. However, despite all these requirements, it is stated that the evidence value in the literature is quite low [17-19]. The substantial importance of patient-reported outcome measures is also emphasized. However, when examining exercise recommendations in the field of vasculitis, studies incorporating exercise based on the biopsychosocial model mentioned in the guidelines are not found.

A Biopsychosocial Model-Based Exercise Innovation: BETY

The Cognitive Exercise Therapy Approach (*Bilişsel Egzersiz Terapi Yaklaşımı - BETY*) is an innovative exercise approach developed based on the biopsychosocial model for individuals diagnosed with rheumatic diseases. BETY aims to change the negative cognitions of individuals with rheumatic diseases related to their illness through exercise. The BETY innovation is detailed under four main parameters: function-oriented core stabilization exercises, pain information management, mood information management, and sexuality information management [20]. The BETY innovation also has a unique scale called BETY-BQ (BETY-Biopsychosocial Questionnaire). This scale was developed by collecting feedback from individuals with rheumatism who participated in BETY exercise sessions three days a week over many years, expressing the improvement they experienced through participating in the exercise sessions. During the process, the same items were applied to rheumatic individuals who did not participate in BETY sessions, and the scale was structured by adjusting the items with repeated statistics analysis, resulting in a final version with 30 items. BETY-BQ assesses individuals from a biopsychosocial perspective with items evaluating pain, functionality, fatigue, mood, social participation, sexuality, and sleep [21].

The efficacy of BETY innovation has been proven in terms of the well-being it creates in individuals diagnosed with axial spondyloarthritis (AxSpA), systemic sclerosis (SSc), and rheumatoid arthritis (RA). In AxSpA, it has a synergistic effect with medication in anti-inflammatory [22] and anti-TNF-naive individuals [23]; In SSc, it has a positive effect on functionality, muscle strength, vascularization, anti-inflammatory markers, and biopsychosocial status, as measured by objective and subjective outcome measures [24]; In Sjögren's Syndrome (SjD), research on the effectiveness of group and individual BETY sessions has shown improvements in fatigue, pain, mood, swallowing, and quality of life [25] and positive effects on knee joint muscle strength and proprioception, functional capacity, and biopsychosocial outcomes in RA through telerehabilitation [26]. Furthermore, qualitative and quantitative analysis results, including the perspectives of individuals who have participated in BETY exercise sessions for many years, have been presented in the management of various rheumatological diseases [20].

CASE REPORT

Case 1

A 64-year-old female patient diagnosed with IgG4-related vasculitis (Height: 165 cm, Weight: 75 kg, BMI: 27.55 kg/m^2) reported complaints of back pain, difficulty walking, and fatigue. After listening to the individual's complaints, the recovery goals were determined. The patient stated her recovery goals as "staying alive, walking without a cane, running."

She was taught BETY function-oriented core stabilization exercises for her complaints. She was given walking education. She then received BETY-Nosiplastic Pain Management (BETY-NPM) education for her pain complaints. She was subsequently encouraged to take responsibility for managing her illness.

For fatigue complaints, a walking program was recommended 3-5 days a week, including at least a 15-minute warm-up phase. The individual was included in the BETY exercise group.

After being included in the BETY exercise group, the individual achieved their recovery goals and reported the following recovery characteristics:

- *My fatigue complaint has decreased.*

- *I can use my leg properly.*

- *I can adapt coping strategies from the BETY Nosiplastic Pain Management Strategy to my life.*

- *Thanks to the exercises, I am holding on to life, and my energy is increasing.*

- The exercises are as important as my walking stick, my medication, and the food I eat on my recovery journey.

Case 2

A 50-year-old female patient diagnosed with Behçet's disease (Height: 164 cm, Weight: 61 kg, BMI: 22.67 kg/m^2) reported back pain and severe fatigue. After listening to the individual's complaints, the recovery goal was determined. The patient stated that her recovery goals were to wake up without pain, have a comfortable day, and be able to eat comfortably.

BETY function-oriented core stabilization exercises were selected for her complaints and taught to the patient. Subsequently, BETY-Nosiplastic Pain Management (BETY-NPM) education was provided. The relationship between pain and the limbic system was explained to raise awareness about mood, pain, and exercise. A conceptual change and recovery agreement was made to ensure that the patient took responsibility for their recovery journey.

A walking program was recommended for fatigue complaints, consisting of at least 3 days a week of at least 15 minutes of loading phase – increasing breathing and heart rate – structured with warm-up and cool-down periods.

After being included in the BETY exercise group, the individual achieved their recovery goals and reported the following recovery characteristics:

- I use a combination of medical treatment and exercise to get results in chronic pain management.

- I am healthier and happier after adapting the pain management strategy to my life.

- I have learned to say no.

- I value myself.

The importance of the biopsychosocial model in managing rheumatic diseases has been increasing in recent years. As is the nature of chronic diseases, the biopsychosocial problems experienced by individuals with rheumatic diseases have created this need. Vasculitides are also a group of chronic diseases that can affect many organs and systems, impacting individuals from a biopsychosocial perspective. Although guidelines recommend holistic approaches for this disease group, research in this area is notably insufficient. BETY, as an exercise innovation developed within the biopsychosocial model, should be used as a non-pharmacological exercise approach for vasculitis disease management that will be elevated to the level of evidence through further studies.

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