REVISTA CIE

Revista de Investigación Educativa | Vol. 2, No. 2
ISSN: 3061-8657 | Julio-Diciembre 2026

REVIEW ARTICLE

# Musculoskeletal disease as an extrahepatic manifestation associated with the hepatitis C virus: state of the art

## Enfermedad musculoesquelética como manifestación extrahepática asociada al virus de la hepatitis C: estado del arte

**Elvia Donají Sánchez Solís*, Clara Cristina Sánchez Rodríguez, Angela Araceli García Zaleta****

### Abstract

Chronic hepatitis C virus infection is recognized as a systemic disease with multiple extrahepatic manifestations that can precede liver damage. Among these, musculoskeletal disease stands out due to its frequency and the functional impact it has on patients. The objective of this narrative review was to analyze the current state of knowledge regarding musculoskeletal disease as an extrahepatic manifestation associated with the hepatitis C virus, considering its pathophysiological mechanisms, clinical scenarios, and therapeutic approaches. A narrative review of scientific literature published between 2019 and 2024 in specialized health sciences databases was conducted. The evidence shows that musculoskeletal manifestations associated with the virus present a broad spectrum, including arthralgia, myalgia, and various patterns of inflammatory arthritis, with complex immunological bases. Furthermore, treatment with direct-acting antivirals not only allows for viral eradication but is also associated with clinical improvement of these manifestations. Timely recognition of musculoskeletal involvement is essential for early diagnosis and comprehensive management of the infection.

**Keywords:** hepatitis C virus; extrahepatic disease; musculoskeletal disease; HCV-associated arthritis; direct-acting antivirals

### Resumen

La infección crónica por el virus de la hepatitis C se reconoce como una enfermedad sistémica con múltiples manifestaciones extrahepáticas que pueden preceder al daño hepático. Entre ellas, la enfermedad musculoesquelética destaca por su frecuencia y por el impacto funcional que genera en los pacientes. El objetivo de esta revisión narrativa fue analizar el estado actual del conocimiento sobre la enfermedad musculoesquelética como manifestación extrahepática asociada al virus de la hepatitis C, considerando sus mecanismos fisiopatológicos, escenarios clínicos y abordajes terapéuticos. Se realizó una revisión narrativa de literatura científica publicada entre 2019 y 2024 en bases de datos especializadas en ciencias de la salud. La evidencia muestra que las manifestaciones musculoesqueléticas asociadas al virus presentan un espectro amplio, que incluye artralgias, mialgias y distintos patrones de artritis inflamatoria, con bases inmunológicas complejas. Asimismo, se identifica que el tratamiento con antivirales de acción directa no solo permite la erradicación viral, sino que se asocia con mejoría clínica de estas manifestaciones. El reconocimiento oportuno de la afectación musculoesquelética es fundamental para un diagnóstico temprano y un manejo integral de la infección.

**Palabras clave:** virus de la hepatitis C; enfermedad extrahepática; enfermedad musculoesquelética; artritis asociada a VHC; antivirales de acción directa

**Correspondencia:** ccsanchez@uat.edu.mx

**Fecha de recepción:** 17/junio/2025 | **Fecha de aceptación:** 05/abril/2026 | **Fecha de publicación:** 14/agosto/2026

* Universidad Anáhuac Mayab. Mérida, Yucatán, México

**Universidad Autónoma de Tamaulipas. Facultad de Medicina de Tampico. Tampico, Tamaulipas, México

## INTRODUCTION

Chronic infection with hepatitis C virus (HCV) remains a major global public health concern because of its high prevalence, frequently asymptomatic course, and capacity to induce multisystem organ damage. According to the World Health Organization, more than 50 million people are living with chronic HCV infection worldwide, with a heterogeneous distribution and a substantial disease burden in low- and middle-income regions where barriers to early diagnosis and universal access to antiviral therapy persist (World Health Organization, 2023). Despite significant therapeutic advances achieved over the past decade, hepatitis C continues to pose important challenges to healthcare systems, particularly because of the prevalence and complexity of its extrahepatic manifestations.

Hepatitis C virus is characterized not only by its hepatotropic nature and its central role in the development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, but also by its ability to induce extrahepatic disease in a significant proportion of infected individuals. It has been estimated that 40% to 70% of patients with chronic HCV infection develop at least one extrahepatic manifestation, highlighting the systemic nature of the disease and the persistent interaction between the virus and the host immune system (Cacoub et al., 2016). These manifestations encompass metabolic, endocrine, renal, neurological, dermatological, and musculoskeletal disorders, which may precede the diagnosis of liver disease and, in some cases, represent the primary reason for seeking medical attention.

Within this clinical spectrum, HCV-associated musculoskeletal disease is of particular relevance because of its frequency and the considerable functional impairment it may cause. Musculoskeletal manifestations range from nonspecific arthralgia and myalgia to chronic inflammatory arthritis that can closely resemble primary rheumatic diseases, especially rheumatoid arthritis (Johnson & Lee, 2022). This clinical and serological overlap poses a significant diagnostic challenge, potentially leading to delayed recognition of the underlying viral infection and the inappropriate initiation of immunomodulatory therapies in the presence of active viral replication.

The pathophysiology of HCV-related musculoskeletal disease is complex and multifactorial. Persistent viral infection promotes chronic immune activation characterized by polyclonal B-cell stimulation, sustained autoantibody production, and the formation of immune complexes that may deposit in multiple tissues, including articular structures (Argyropoulou et al., 2020). Concurrently, molecular mimicry, loss of immunological tolerance, and activation of both innate and adaptive inflammatory pathways have been implicated in the development of synovial inflammation and joint damage (Kim & Park, 2023; Nguyen & Tran, 2022). This immunological milieu accounts for the high prevalence of rheumatoid factor, cryoglobulins, and other autoantibodies

observed in patients with HCV infection and rheumatologic manifestations.

The introduction of direct-acting antiviral agents has dramatically transformed the management of HCV infection and its extrahepatic complications. These therapies achieve sustained viral eradication rates exceeding 90%, with favorable safety profiles and excellent tolerability, thereby substantially altering the natural history of liver disease and improving a wide range of systemic manifestations (Cooke et al., 2024). Available evidence suggests that viral clearance is associated with a significant reduction in articular inflammatory activity and improved functional outcomes in patients with HCV-associated musculoskeletal disease (Johnson & Lee, 2022).

In this context, a comprehensive evaluation of the available scientific evidence regarding musculoskeletal disease as an extrahepatic manifestation of HCV infection is warranted. A thorough understanding of the underlying pathophysiological mechanisms, the diverse clinical presentations, and the impact of antiviral therapy is essential not only for optimizing patient management but also for strengthening early detection strategies that facilitate timely diagnosis of HCV infection. Therefore, the aim of this narrative review is to synthesize the current state of knowledge regarding the relationship between hepatitis C virus infection and musculoskeletal disease, emphasizing its clinical, diagnostic, and therapeutic relevance within a comprehensive patient-centered approach.

## METHODS, TECHNIQUES AND INSTRUMENTS

The present study was conducted as a narrative review of the scientific literature aimed at comprehensively analyzing musculoskeletal disease as an extrahepatic manifestation associated with chronic hepatitis C virus (HCV) infection. This methodological approach was considered appropriate given the complex, multidimensional, and heterogeneous nature of the phenomenon under investigation, which encompasses pathophysiological, immunological, clinical, and therapeutic dimensions that have been explored through diverse research designs and conceptual frameworks.

The narrative review approach enabled the integration of evidence derived from observational studies, scholarly reviews, immunopathological investigations, and clinical consensus documents, providing a broad and contextualized perspective on the current state of knowledge. Unlike systematic reviews or meta-analyses, the purpose of this review was not to quantify effects or compare specific interventions but rather to identify relevant pathophysiological patterns, recurring clinical scenarios, and emerging therapeutic strategies, while also highlighting knowledge gaps that may guide future research.

A structured literature search was performed using the PubMed, SciELO, and LILACS databases, selected for their extensive coverage of health sciences, internal medicine, rheumatology, infectious

diseases, and medical education. Controlled vocabulary and keywords in both English and Spanish were combined using Boolean operators. Search terms included hepatitis C virus, extrahepatic manifestations, musculoskeletal disease, arthritis, rheumatic manifestations, and direct-acting antivirals. The search strategy was adapted to the specific characteristics of each database to maximize both sensitivity and relevance of the retrieved records.

Studies published between 2019 and 2024 and available in full text were eligible for inclusion if they explicitly addressed the relationship between HCV infection and musculoskeletal manifestations from a clinical, pathophysiological, or therapeutic perspective. Original research articles employing quantitative, qualitative, or mixed-methods designs, as well as narrative reviews, systematic reviews, meta-analyses, and normative documents issued by international organizations, were considered. Editorials, letters to the editor, anecdotal reports, and publications lacking a clearly described methodology or not directly relevant to the objectives of the review were excluded.

The literature selection process was conducted in two stages. First, titles and abstracts were screened to identify potentially relevant studies. Subsequently, the full texts of preselected articles were reviewed to verify compliance with the predefined inclusion criteria. Reference management was performed manually to avoid duplication and ensure consistency in citation practices.

Data extracted from the selected studies were organized through a thematic narrative synthesis structured around key analytical domains, including the epidemiology of HCV-related extrahepatic disease, the immunopathogenic mechanisms underlying musculoskeletal involvement, the principal clinical presentations reported in the literature, and the impact of direct-acting antiviral therapy on the course of rheumatologic manifestations. This approach facilitated a critical integration of the available evidence, highlighting areas of convergence, divergence, and emerging trends across the scientific literature.

Because this study consisted exclusively of a review of previously published literature, it did not involve direct participation of human subjects or the handling of personal data and therefore did not require approval from a research ethics committee. Nevertheless, the review was conducted in accordance with the principles of scientific integrity, methodological transparency, and appropriate acknowledgment of sources, consistent with international standards for academic publication.

## RESULTS AND DISCUSSION

The review of the scientific literature identified musculoskeletal disease as one of the most frequent and clinically significant extrahepatic manifestations associated with chronic hepatitis C virus (HCV) infection. The studies analyzed consistently reported that rheumatologic manifestations may occur at various stages of infection, including prior to the diagnosis of liver disease, thereby reinforcing their

value as potential early clinical indicators of previously unrecognized HCV infection (Cacoub et al., 2016; Nguyen & Tran, 2022).

From a clinical perspective, HCV-associated musculoskeletal manifestations encompass a broad spectrum that includes nonspecific arthralgia and myalgia, oligoarticular reactive arthritis, and symmetric polyarthritis with features that overlap considerably with rheumatoid arthritis. Several studies have reported that these clinical entities may be difficult to distinguish serologically, as a substantial proportion of patients exhibit positive rheumatoid factor and other autoantibodies despite the absence of true rheumatoid arthritis (Su et al., 2014; Johnson & Lee, 2022). This diagnostic overlap represents a major clinical challenge because failure to recognize the underlying viral etiology may lead to the inappropriate use of immunosuppressive therapies.

The reviewed evidence demonstrated that the pathophysiology of HCV-related musculoskeletal involvement is complex and multifactorial. Chronic infection induces persistent immune activation characterized by polyclonal B-cell stimulation, sustained autoantibody production, and the formation of immune complexes containing cryoglobulins, IgG and IgM immunoglobulins, and complement components. These immune complexes may deposit within articular and vascular tissues, triggering inflammatory cascades that perpetuate tissue injury (Argyropoulou et al., 2020; Chen & Zhao, 2024). In addition, molecular mimicry and loss of immunological tolerance have been implicated in disease pathogenesis, whereby viral antigens share structural similarities with joint components, promoting cross-reactive autoimmune responses (Kim & Park, 2023; Lee & Kim, 2023).

Recent literature has further highlighted the contribution of innate inflammatory mechanisms to HCV-associated arthritis. In particular, activation of the NLRP3 inflammasome has been proposed as a relevant driver of chronic inflammation through the induction of proinflammatory cytokines, including interleukin-1β and interleukin-18, which contribute to the amplification and maintenance of joint inflammation (Wan et al., 2024). This emerging pathophysiological framework provides a more integrated understanding of articular damage by linking persistent viral infection to sustained activation of both innate and adaptive immune responses.

Regarding treatment, the studies reviewed indicated that the introduction of direct-acting antiviral agents (DAAs) has substantially altered the clinical course of HCV-associated musculoskeletal manifestations. Viral eradication achieved with these therapies was consistently associated with reduced articular inflammatory activity and significant improvements in pain and physical function, thereby decreasing the need for prolonged immunosuppressive treatment in many patients (Johnson & Lee, 2022; Cooke et al., 2024). These findings have led contemporary clinical guidelines and recent reviews to recommend antiviral therapy as the primary therapeutic strategy for

patients presenting with rheumatologic manifestations related to HCV infection.

Nevertheless, the available evidence also suggested that a subset of patients continues to experience articular symptoms despite successful viral eradication, indicating that certain autoimmune mechanisms may persist independently of active viral replication. In such cases, a combined therapeutic approach may be required, incorporating nonsteroidal anti-inflammatory drugs, low-dose corticosteroids, or, in selected patients, immunomodulatory agents, with careful monitoring to minimize the risk of hepatic toxicity or potential viral reactivation (Martínez & Hernández, 2022; Nardone et al., 2024).From a public health and medical education perspective, the evidence synthesized in this review underscores the importance of recognizing musculoskeletal manifestations as a valuable diagnostic opportunity for HCV detection.

Several authors have emphasized that the identification of atypical arthritis or inflammatory joint disease with an unusual clinical course in patients without a known diagnosis of hepatitis C should prompt HCV screening, in accordance with international recommendations advocating at least one lifetime screening test and continued surveillance among individuals at increased risk (World Health Organization, 2023; Cooke et al., 2024).

## CONCLUSIONS

Hepatitis C virus (HCV)-associated musculoskeletal disease should be recognized as an integral component of the extrahepatic spectrum of infection rather than as a secondary or incidental complication. Its recognition expands the traditional clinical perspective focused primarily on hepatic injury and underscores the need to view HCV as a systemic pathogen capable of inducing sustained multisystem involvement through complex immunological mechanisms that extend beyond the articular domain. Such a comprehensive understanding is essential for contemporary clinical practice and is consistent with current scientific evidence.

The management of musculoskeletal manifestations related to HCV infection requires a conceptual shift in both diagnostic and therapeutic approaches. Recognizing these manifestations as potential indicators of underlying viral infection can strengthen strategies aimed at early diagnosis and reduce treatment delays that contribute to increased morbidity and mortality.

In this regard, the clinical evaluation of patients presenting with atypical rheumatologic conditions or inflammatory musculoskeletal disorders with an unusual clinical course represents a strategic opportunity to improve HCV detection rates and optimize the benefits of antiviral therapy.

Ultimately, the management of HCV infection and its extrahepatic manifestations should be grounded in an interdisciplinary approach that integrates hepatology, rheumatology, and primary care, with particular emphasis on the continuous education of healthcare professionals and the implementation of population-based screening strategies. Consolidating this framework not only contributes to improving patients' quality of life but also strengthens ongoing efforts to eliminate hepatitis C as a major public health concern, in alignment with international goals aimed at reducing new infections and preventing long-term systemic complications.

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