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REVIEW ARTICLE

Parasitic infestations and their influence on joint inflammation

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ABSTRACT

Objective. The objective of this study was to conduct a bibliographic analysis of current data regarding the impact of parasitic infestations on immune status and the progression of osteoarticular diseases within the context of parasitic infections.

Material and methods. This was a qualitative analytical study presented as a narrative literature review. Relevant primary sources published between 2016 and 2022 were identified and selected using data extraction and analysis methods.

Results and discussion. The concept of "parasitic therapy" has generated considerable interest among researchers, the public, and patients for whom standard treatments have been ineffective or offered limited results. Although studies exploring the role of parasitic infections in arthritis are less common than in other fields, animal models suggest that parasitic infections may alleviate joint inflammation. However, further research is needed across different forms of arthritis, including clinical data collection and double-blind, controlled clinical trials.

Conclusions. While only a few studies have demonstrated that parasitic infections may worsen preexisting diseases, the scientific consensus is that parasitic infections can create an immunoregulatory environment, reducing the severity of coexisting conditions. Finally, more rigorous animal studies are required to thoroughly investigate immunomodulatory mechanisms and potential side effects of parasitic infections in the presence of other diseases.

Keywords: parasitosis, parasitic arthritis, parasitic immune status.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The mechanisms and systemic effects of parasitic therapy on joint inflammation are still unclear. More research is needed to assess its safety, long-term impact, and therapeutic potential in autoimmune diseases.

The research hypothesis

Parasitic infections can modulate immune responses and reduce joint inflammation, offering a potential therapeutic approach for autoimmune diseases, including rheumatoid arthritis.

The novelty added by the manuscript to the already published scientific literature

The manuscript provides novel insights by exploring the immunomodulatory effects of parasitic infections on joint inflammation, a relatively under-researched area. It suggests new perspectives on using parasitic therapy as a potential treatment for autoimmune diseases, particularly rheumatoid arthritis, while emphasizing the need for personalized approaches and identifying molecular pathways involved in immune regulation.

Introduction

Parasitosis represents a persistent global health challenge, with its prevalence being particularly high in developing countries. According to a World Health Organization report from 2010, there were an estimated 48.4 million cases of parasitic infections, with 59,724 deaths recorded [1, 2].

In the Republic of Moldova, parasitic infections hold a significant share among infectious diseases, following only acute respiratory infections and acute diarrheal illnesses in prevalence. In the first six months of 2015, 7,645 individuals were diagnosed with various helminthic infections, marking a 9.5% decrease compared to the same period in the previous year [3, 4].

While gastrointestinal, visceral, encephalic, and cutaneous manifestations are commonly associated with parasitic diseases, the musculoskeletal system can also be affected [5, 6].

The main types of parasites responsible for such conditions include:

- Cestodes (e.g., *Taenia spp.*, *Echinococcus spp.*);
- Trematodes (e.g., *Schistosoma spp.*, *Opisthorchis spp.*);
- Nematodes (e.g., *Toxocara spp.*, hookworms, *Strongyloides spp.*, filarial worms);
- Protozoa (e.g., *Giardia lamblia*, *Toxoplasma gondii*).

Involvement of the musculoskeletal system may present with various clinical features, such as:

- Arthritis, myositis, enthesitis, and tendinitis;
- Soft tissue swelling, trophic ulcers, and muscle necrosis;
- Elephantiasis, bone or muscle cysts, pathological fractures;
- Calcification of soft tissues;
- Migration of larvae through subcutaneous tissues;

Joint damage caused by parasitic infections occurs through three key mechanisms:

1. Direct invasion of the parasite into the joint, triggering an inflammatory response (arthritis). This inflammation may be further complicated by a secondary bacterial infection introduced either by microbial agents attaching to the parasite or entering the joint through pathways created by the parasite [2].
2. Periarticular deposition of parasites, leading to secondary joint inflammation [5].
3. Immune-mediated reactions resulting from the body's response to the presence of the parasitic agent [2, 6].

Over the past decade, significant progress has been made in parasitology research. New discoveries related to interleukins and immune cell networks have reshaped our understanding of how parasites interact with the human immune system. These insights demonstrate how parasites may either evade immune responses to persist in the host or modulate immune reactions to prevent reinfection. However, despite these advances, many challenges remain. Weaknesses in infection control systems continue to impact public health and diminish the quality of life, especially in underprivileged populations.

Many parasitic worms thrive at the expense of children's development, particularly in areas with poor living conditions and limited healthcare access. Additionally, diarrheal diseases caused by parasites such as *Entamoeba histolytica*, *Giardia lamblia*, *Cryptosporidium parvum*, and *Cyclospora cayetanensis* remain a persistent burden, particularly in developing countries, where even basic sanitary measures are insufficient [5].

Though musculoskeletal complications from parasitic infections are more commonly associated with tropical regions, they are increasingly encountered in non-endemic areas, such as the Republic of Moldova, due to migration and seasonal travel. Although Moldova is not classified as an endemic zone for severe parasitic diseases affecting the musculoskeletal system, exotic infections have become more frequent.

The most reported parasitic infections in Moldova that have shown musculoskeletal involvement are:

- *Echinococcus granulosus*: The national morbidity rate for echinococcosis over the past decade averaged 4.3% [3, 7].
- *Giardia lamblia*: This infection exhibited an average prevalence of 4.86% in the same period [3, 4].

Despite numerous reports documenting musculoskeletal involvement in parasitic infections, there is still a lack of systematic research that can provide comprehensive insights. Such research is essential not only for national and international recognition but also for developing early intervention strategies in the diagnosis and treatment of musculoskeletal disorders related to parasitosis.

The aim of this study was to conduct a bibliographic analysis of the most recent data concerning the impact of helminthic infestations on immune function and the progression of osteo-articular diseases in the context of parasitic infections.

Material and methods

This qualitative and analytical study focused on primary research published between 2016 and 2022. The objective was to identify musculoskeletal biomarkers relevant to the diagnosis, disease progression, and complications associated with parasitic infestations.

To achieve the research goals, scientific databases such as PubMed, NCIB, Google Search, and Medscape were explored using the following key terms:

- Parasitic arthritis;
- Parasitic biomarkers;
- Diagnosis of parasitic infestation;
- Prediction of disease progression in parasitic infections.

A total of 74 reference sources were identified, out of which 19 studies were deemed most relevant and selected for detailed analysis.

Results and discussion

Modulating joint inflammation through parasitic infections

Chronic autoimmune conditions like rheumatoid ar-

thritis (RA) pose significant challenges to musculoskeletal health, requiring innovative treatments beyond conventional therapies. Parasitic infections, known to influence immune function in their hosts, have drawn considerable interest in parasite-mammal model studies. These models aim to uncover pathways and molecules that could inspire novel therapies for autoimmune and idiopathic diseases. Although much research has focused on mucosal inflammation in parasitic infections and gastrointestinal diseases such as inflammatory bowel disease (IBD), the impact of these infections on joint inflammation remains underexplored. This paper highlights the potential for parasitic infections to alleviate joint inflammation and reviews relevant literature supporting this hypothesis.

Immune modulation by parasitic infections

Parasitic infections trigger an immune response characterized by type 2 helper T cell (Th2) activation [8-11]. This response plays a regulatory role, often suppressing the more aggressive Th1-driven immune responses. As a result, individuals with parasitic infections may experience milder symptoms of Th1-mediated inflammatory diseases. Numerous studies have shown that parasites residing in mucosal tissues, such as trematodes, cestodes, and nematodes, can reduce inflammation in experimental models of colitis and airway hyperreactivity [5, 12-14]. However, limited research has investigated the systemic effects of parasitic infections on organs beyond the primary site of infection, including joints. This article discusses the potential for parasitic infections to regulate immune responses and alleviate joint inflammation.

The growing burden of autoimmune diseases

Over the last few decades, the prevalence of autoimmune diseases, including inflammatory bowel disease (IBD), multiple sclerosis, diabetes, and rheumatoid arthritis (RA), has increased substantially, especially in developed nations. RA, a chronic and progressive autoimmune disorder, affects approximately 1% of the North American population [15, 16]. The socio-economic impact of RA is significant; in 2003, arthritis and other related conditions cost the United States around $127.8 billion, equating to 1.2% of the national GDP [15, 16].

Limitations of current treatments for RA

Current treatments for RA rely on nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs). While NSAIDs reduce inflammation, they do not stop disease progression and often result in gastrointestinal, renal, and neurological side effects [17].

GCs are potent anti-inflammatory agents but carry significant risks with long-term use, including reduced bone mineral density, obesity, diabetes, and cataracts [17, 18]. DMARDs, such as methotrexate (MTX), are effective in slowing joint destruction but can cause severe toxic effects in the liver, respiratory system, gastrointestinal tract, and other organs [19].

Given the limitations and side effects of current treatments, there is an urgent need for alternative therapies. Advancing these therapies requires a thorough understanding of the immune mechanisms driving joint inflammation. Although animal models cannot perfectly replicate human RA, they provide valuable insights into the disease's immune processes. Notably, research on mice paved the way for the development of anti-TNFα therapies, now a cornerstone of RA treatment [18].

Parasitic therapy and immune regulation

Infections with parasites induce immune responses dominated by IL-4, IL-5, IL-9, IL-10, and IL-13 [6, 12, 20]. These responses are associated with mast cell hyperplasia, eosinophilia, and increased IgE production [21, 22]. Parasites also secrete molecules that can modulate the host's immune system by reducing inflammation or redirecting immune responses. Parasitic infections are believed to shift immune responses from a Th1-dominated state to Th2 pathways, potentially mitigating autoimmune inflammation.

For example, the ES-62 glycoprotein, derived from *Acanthocheilonema vitea*, has demonstrated anti-inflammatory properties. It inhibits the activation of pro-inflammatory cytokines and suppresses mast cell degranulation [23]. In murine models, ES-62 reduced the severity of collagen-induced arthritis by lowering levels of TNFα, IL-6, and IFNγ, while increasing IL-10 production [23, 24].

Research on parasitic infections and joint inflammation

Several studies have shown that parasitic infections can reduce joint inflammation. One early observation involved rats infected with *Syphacia obvelata*, which developed a milder form of arthritis after receiving CFA injections [23, 24]. In another study, mice infected with *Heligmosomoides polygyrus* and *Nippostrongylus* exhibited a reduced incidence of arthritis, although some joint damage persisted [25].

Recent research found that infection with *Schistosoma mansoni* reduced collagen-induced arthritis in mice by decreasing joint swelling and synovial hyperplasia [26]. Similarly, infection with the tapeworm *Hymenolepis diminuta* alleviated arthritis symptoms, with effects comparable to those of steroids and NSAIDs [5, 25].

Despite promising results, parasitic therapy faces significant challenges. Not all parasites are suitable for therapeutic use; for example, *Schistosoma mansoni* causes severe disease and is unsuitable for clinical application. The risk of iatrogenic infections and the potential for comorbid conditions also need to be carefully considered. Some studies have raised concerns that parasitic therapy might not be appropriate for patients with diseases characterized by eosinophilia [6, 26, 27].

Another challenge is the difficulty in isolating specific immunomodulatory molecules from parasites. However, advances in mass spectrometry and other technologies have improved our ability to extract and analyze these molecules. This progress offers hope for the development of new anti-inflammatory drugs based on parasitic molecules.

While research on parasitic therapy remains in its early stages, evidence suggests that parasitic infections can mod-

ulate immune responses and reduce joint inflammation. However, further studies, including clinical trials, are needed to confirm these findings and explore their potential for human treatment. The ultimate goal is to identify specific parasitic molecules that can serve as templates for developing novel therapies for autoimmune diseases.

Conclusions

Although a limited number of studies have indicated that parasitic infections may sometimes aggravate pre-existing conditions, the prevailing consensus is that parasitic infections can create an immunoregulatory environment that helps reduce the severity of concurrent diseases. While research on the impact of parasitic infections on arthritis remains limited, findings from animal models and concurrent parasitic infections suggest that "parasitic therapy" holds promise as a potential strategy for managing inflammatory joint diseases.

This field represents a fascinating area of translational research, with the potential to yield important discoveries about immunomodulatory mediators, anti-inflammatory cell functions, and pathological mechanisms. These insights could pave the way for the development of novel treatment strategies targeting autoimmune and idiopathic diseases in humans. The idea of using specific parasitic organisms as therapeutic agents, especially for individuals whose immune profiles have been carefully studied, aligns with the concept of personalized medicine. However, at present, this remains a theoretical possibility rather than a clinical reality.

It is important to highlight that individuals should not attempt to self-infect with parasitic organisms in pursuit of potential health benefits. Lastly, animal studies must be conducted with greater rigor to better understand all aspects of immunomodulation induced by parasitic infections and to assess potential adverse effects when such infections occur in conjunction with other diseases.

Competing interests

None declared.

Authors' contributions

Study conception and design: MG, LG, GP. Data acquisition: MG, GP. Analysis and interpretation of data: MG, ER. Drafting of the manuscript: MG, LG. Significant manuscript review with significant intellectual involvement: LG. Approval of the „ready for print" version of the manuscript: LG, MG, GP, ER**.**

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