

## Review

# Adrenal insufficiency in Patients with Rheumatoid Arthritis: Prevalence, Clinical Implications, and Management Strategies

Maram Al Jehani<sup>1</sup>, Abdullateef Almagsoodi<sup>2</sup>, Ayedh Al junaybi<sup>3</sup>, Bushra Alshahrani<sup>4</sup>, Yasser Halabi<sup>5</sup>, Maymunah Alibrahim<sup>6</sup>, Anhar Gazzaz<sup>7</sup>, Zainub AL Jaffer<sup>8</sup>, Abdulelah Almalki<sup>9</sup>, Munirah Alohaymid<sup>10</sup>, Nada Alata<sup>11</sup>.

<sup>1</sup> Department of Endocrinology, East Jeddah Hospital, Jeddah, Saudi Arabia

<sup>2</sup> Department of Internal Medicine, Rijal Alma Hospital, Rijal Alma, Saudi Arabia

<sup>3</sup> Department of Internal Medicine, King Abdullah Hospital, Bisha, Saudi Arabia

<sup>4</sup> College of Medicine, King Khalid University, Abha, Saudi Arabia

<sup>5</sup> College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

<sup>6</sup> Department of Internal Medicine, King Fahad Hospital, Al Ahsa, Saudi Arabia

<sup>7</sup> Medical Center – Al Faysaliya Branch, University of Jeddah, Jeddah, Saudi Arabia

<sup>8</sup> Department of Internal Medicine, Dammam Medical Complex, Dammam, Saudi Arabia

<sup>9</sup> Department of Internal Medicine, King Fahad General Hospital, Al Baha, Saudi Arabia

<sup>10</sup> Department of Internal Medicine, King Abdulaziz Hospital, Al Ahsa, Saudi Arabia

<sup>11</sup> Department of Internal Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia

**Correspondence** should be addressed to **Maram Al Jehani**, Department of Endocrinology, East Jeddah Hospital, Jeddah, Saudi Arabia. Email: [maram.Jehani@gamil.com](mailto:maram.Jehani@gamil.com)

Copyright © 2023 **Al Jehani**, this is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 16 July 2023, Revised: 18 July 2023, Accepted: 19 July 2023, Published: 20 July 2023

### Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune-inflammatory disease that affects a significant proportion of the global population. It is characterized by synovial inflammation and joint destruction, leading to disability. The treatment of RA often involves the use of glucocorticoids, which can result in adrenal insufficiency (AI) due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The prevalence of AI in RA patients varies but is generally higher compared to the general population. The diagnosis of AI can be challenging due to its nonspecific symptoms and overlap with RA manifestations. Delayed recognition and inadequate management of AI can lead to adrenal crises, which are life-threatening emergencies. Regular monitoring of adrenal function, glucocorticoid replacement therapy, optimization of RA treatment, and patient education are crucial in the management of AI in RA patients. Future research should focus on risk stratification, the development of novel biomarkers, the exploration of alternative treatment strategies, and the evaluation of long-term outcomes to enhance our understanding and improve the management of AI in RA patients.

**Keywords:** *rheumatoid arthritis, adrenal insufficiency, glucocorticoids, management*

## Introduction

Rheumatoid arthritis (RA) is a persistent autoimmune-inflammatory disease that affects approximately 0.5%-1.0% of the global population (1). It is characterized by a breakdown in tolerance to modified self-proteins and inflammation of the synovium, which is the primary target tissue. Over time, this leads to the transformation of synovial fibroblasts into highly aggressive, hyper-proliferative, and invasive tissue, causing destruction of the joints and resulting in disability (2). RA is more common in women, and its occurrence increases significantly with age (3).

Currently, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate and leflunomide, are considered the standard long-term treatment for RA. In cases where patients do not respond adequately to csDMARDs, biological agents or targeted/synthetic DMARDs are added to the treatment regimen. It is worth noting that many patients require prolonged administration of glucocorticoids to maintain remission (4).

Although glucocorticoids effectively relieve joint swelling, stiffness, and pain, they are often associated with various adverse effects, including bone loss, diabetes mellitus, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This suppression can lead to adrenocortical hypotrophy and iatrogenic adrenal insufficiency [AI] (5, 6).

AI is a significant medical condition characterized by the inadequate production or function of glucocorticoids (GC), along with deficiencies in mineralocorticoid and/or adrenal androgen secretion. The diagnosis of AI poses a clinical challenge for physicians due to its diverse range of clinical presentations. These symptoms can vary from nonspecific signs such as fatigue, reduced appetite, weight loss, and dizziness, to a potentially life-threatening acute adrenal crisis if left untreated (7).

Traditionally, AI is classified into three types based on the site of dysfunction: (a) primary or Addison's disease, which occurs when there is insufficiency in

the adrenocortical function; (b) secondary AI, where pituitary disorders impair the release of adrenocorticotrophic hormone (ACTH); (c) tertiary AI, involving dysfunction in the hypothalamus (5).

Iatrogenic AI, which is primarily caused by prolonged treatment or high daily and/or cumulative doses of glucocorticoids, is considered the primary factor contributing to AI in Western countries (8). This condition is commonly observed in patients with RA. However, in addition to iatrogenic AI, a suboptimal response to stress and inflammation, known as "relative or functional" AI, has been reported in RA patients, even when the HPA axis appears to be intact (9). Furthermore, there have been rare reports of co-existing Addison's disease in patients with RA (10).

The purpose of this review is to explore the prevalence, clinical implications, and management of AI in patients with RA, with the goal of enhancing our comprehension and informing clinical practices in this regard.

## Review

The etiology of AI in RA is multifactorial. The underlying autoimmune process in RA can contribute to adrenal gland dysfunction. Inflammatory cytokines and autoantibodies associated with RA may target and damage the adrenal glands, leading to impaired cortisol production (1).

Furthermore, chronic use of exogenous glucocorticoids, such as prednisone, which is commonly prescribed to manage RA, can suppress the adrenal glands' natural cortisol production. Prolonged exposure to exogenous glucocorticoids can lead to hypothalamic-pituitary-adrenal (HPA) axis suppression and subsequent AI. The duration, dose, and route of glucocorticoid administration can influence the risk of AI development. In addition to RA and chronic glucocorticoid use, concomitant autoimmune conditions, such as autoimmune adrenalitis or autoimmune polyendocrine syndrome, may also contribute to AI in RA patients (11).

The prevalence of AI in patients with RA has been investigated in various studies, shedding light on the

frequency and significance of this comorbidity. While the prevalence rates vary across studies, there is a consistent trend indicating a higher prevalence of AI in RA patients compared to the general population.

Estimating the prevalence of GC-induced AI in patients with rheumatoid RA is challenging due to significant heterogeneity among published studies. These variations stem from differences in study populations, diverse therapeutic regimens, and variations in the methods and cut-off values used to assess the functional integrity of the HPA axis.

According to current literature, the prevalence of GC-induced AI in patients with chronic rheumatic diseases, including RA, can range up to 50% following long-term, low-dose GC treatment (12). Specifically in RA, the proportion of patients who develop GC-induced AI exhibits significant variability. Earlier studies have reported proportions ranging from 10% to 28% (13, 14), while more recent investigations have observed proportions as high as 45% (15).

In a study by Bacon et al., 28% of RA patients receiving long-term GC treatment developed secondary AI. However, it is noteworthy that a higher proportion of patients (more than 65% of the entire cohort) failed to discontinue GC treatment, primarily due to sustained reactive arthritis with localized joint swelling and tenderness rather than AI itself (13). Similarly, in a study by Hicklin et al., 10% of RA patients on long-term GC treatment with a mean prednisone dose of 5 mg/day developed AI (14).

These findings emphasize the complex nature of GC-induced AI in RA, with variations in prevalence rates influenced by factors such as disease characteristics, duration and dosage of GC treatment, as well as the specific manifestations of the underlying disease itself (11).

The criteria used for diagnosing AI can impact the reported prevalence rates. Different studies may employ varying diagnostic methods, such as morning cortisol levels, adrenocorticotropic hormone (ACTH) stimulation tests, or measurement

of other adrenal hormones. Variations in these criteria can affect the identification and classification of AI cases, potentially influencing the reported prevalence rates.

Several tests are employed to evaluate adrenal function and confirm the diagnosis. The most commonly used tests include measurement of cortisol levels, adrenocorticotropic hormone (ACTH) stimulation tests, and evaluation of other adrenal hormones (16). Measurement of morning cortisol levels can provide an initial screening for AI, with levels below the normal reference range indicating adrenal dysfunction. ACTH stimulation tests, such as the low-dose (1 µg) or high-dose (250 µg) test, assess the adrenal gland's ability to respond to ACTH stimulation and produce cortisol. In these tests, blood cortisol levels are measured before and after administration of synthetic ACTH, and a suboptimal cortisol response suggests AI. Additional tests may include measurement of other adrenal hormones, such as aldosterone or dehydroepiandrosterone sulfate (DHEAS), to assess the overall adrenal function. These laboratory tests, in conjunction with clinical assessment, aid in the diagnosis and management of AI. However, it is essential to consider patient-specific factors and consult with an endocrinologist for accurate interpretation of results and individualized patient care (5, 17).

To obtain a comprehensive understanding of the prevalence of AI in RA, further studies are warranted. These studies should consider factors such as disease characteristics, corticosteroid usage patterns, and consistent diagnostic criteria. Additionally, investigating the prevalence of subclinical AI, which may not present with obvious clinical symptoms, could provide valuable insights into the full spectrum of AI in RA patients.

AI in patients with RA can have significant clinical implications. AI often presents with nonspecific symptoms that can overlap with those of RA, posing challenges in differentiating between the two conditions. Common symptoms of AI include fatigue, weakness, weight loss, hypotension, and electrolyte imbalances (5).

The overlapping nature of these symptoms can lead to underdiagnosis and undertreatment of AI in RA patients, potentially resulting in adverse outcomes. Delayed diagnosis and inadequate management of AI can increase the risk of adrenal crises, which are life-threatening emergencies that require immediate medical attention. Adrenal crises occur when there is an acute deficiency of adrenal hormones, particularly cortisol, leading to severe manifestations such as hypotension, altered mental status, dehydration, electrolyte disturbances (e.g., hyponatremia, hyperkalemia), and even coma or death if not promptly recognized and treated (17, 18).

The challenge of recognizing AI in RA patients lies in differentiating between the symptoms of AI and those attributed to the underlying RA itself. Both conditions can contribute to fatigue, weakness, and weight loss. Additionally, RA itself can cause joint pain and inflammation, which may be mistaken as the primary cause of symptoms. Consequently, AI can often be overlooked, resulting in inadequate management and potentially exacerbating the symptoms and consequences of the underlying AI (19).

It is crucial for healthcare providers to maintain a high index of suspicion for AI in RA patients, particularly those on chronic corticosteroid therapy. Early recognition and appropriate management of AI can help mitigate the risk of adrenal crises and improve overall patient outcomes. Regular monitoring of adrenal function through biochemical tests, such as morning cortisol levels and ACTH stimulation tests, can aid in the early detection and diagnosis of AI in RA patients (20). Healthcare providers should maintain awareness of the possibility of AI in RA patients, especially those receiving chronic corticosteroid therapy, and consider appropriate techniques to ensure early detection and management of this condition.

Management strategies for AI in RA require a comprehensive and multidisciplinary approach. There are several steps of care that are implemented in clinical practice. Regular monitoring of adrenal function is essential in RA patients receiving

chronic corticosteroid therapy or suspected of having AI is the first crucial step. Biochemical tests such as morning cortisol levels and ACTH stimulation tests are commonly employed to assess adrenal function and guide treatment decisions (20).

In confirmed cases of AI, glucocorticoid replacement therapy is vital to maintain physiological cortisol levels. The choice of glucocorticoid, dosage, and administration route should be individualized based on adrenal function and clinical status. The goal is to replicate the normal diurnal cortisol rhythm while minimizing the risk of glucocorticoid-related adverse effects (17).

Optimizing RA treatment strategies can help reduce the reliance on long-term corticosteroid use, which is associated with AI. Rheumatologists should adopt an early and aggressive approach using disease-modifying antirheumatic drugs (DMARDs), biologic agents, or targeted therapies to control disease activity. This approach may reduce the need for corticosteroids and potentially mitigate the risk of AI development (1).

Patient education plays a critical role in the management of AI in RA patients. Patients should be educated about the signs and symptoms of AI, the importance of regular monitoring, and adherence to glucocorticoid replacement therapy. Patients should also understand the need to adjust glucocorticoid doses during periods of illness, stress, or surgical procedures (21).

Future perspectives in the management of adrenal insufficiency (5) in patients with RA involve several areas of research. Risk stratification is a key aspect that aims to identify specific risk factors associated with the development of AI in RA patients. This knowledge would facilitate risk assessment and targeted screening approaches to identify individuals at a higher risk of AI. Additionally, the development of novel biomarkers holds promise in enabling early detection and monitoring of AI in RA patients. Reliable biomarkers would improve clinical outcomes by allowing for timely interventions and individualized management strategies. Exploring alternative treatment strategies



is another important research direction, with a focus on immune modulatory agents or therapies targeting the adrenal glands. These approaches could potentially reduce the reliance on corticosteroid use and improve adrenal function in RA patients. Lastly, evaluating the long-term outcomes of AI in RA patients, including its impact on disease progression, joint damage, and mortality, would provide valuable insights into the clinical implications and prognosis of this comorbidity. Understanding the long-term effects of AI in RA is crucial for optimizing management strategies and improving patient outcomes (22). Further research in these areas will enhance our understanding of AI in RA and contribute to the development of personalized management strategies that optimize patient outcomes

### Conclusion

Adrenal insufficiency is a clinically relevant concern in patients with rheumatoid arthritis. The prevalence of AI in RA patients is relatively high, and its clinical implications can be significant. Early detection, close monitoring of adrenal function, appropriate glucocorticoid replacement therapy, and optimization of RA treatment strategies are crucial for the effective management of AI in RA patients. Further research is warranted to improve early detection, optimize management strategies, and evaluate the long-term outcomes of adrenal insufficiency in the context of rheumatoid arthritis.

### Disclosure

#### *Conflict of interest*

There is no conflict of interest

#### *Funding*

No funding

#### *Ethical consideration*

Non applicable

#### *Data availability*

Data that support the findings of this study are embedded within the manuscript.

### *Author contribution*

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

### References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023-38.
2. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. *Lancet*. 2017;389(10086):2328-37.
3. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376(9746):1094-108.
4. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-99.
5. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet*. 2014;383(9935):2152-67.
6. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther*. 2002;96(1):23-43.
7. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 2015;3(3):216-26.
8. McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. *Curr Opin Rheumatol*. 2008;20(2):131-7.
9. Imrich R, Vlcek M, Aldag JC, Kerlik J, Radikova Z, Rovensky J, et al. An endocrinologist's view on relative adrenocortical insufficiency in rheumatoid arthritis. *Ann N Y Acad Sci*. 2010;1193:134-8.
10. Robinson CE. Addison's disease and rheumatoid arthritis. *Ann Rheum Dis*. 1957;16(1):82-3.
11. Filippa MG, Tektonidou MG, Mantzou A, Kaltsas GA, Chrousos GP, Sfrikakis PP, et al.

Adrenocortical dysfunction in rheumatoid arthritis: Alpha narrative review and future directions. *Eur J Clin Invest.* 2022;52(1):e13635.

12. LaRochelle GE, Jr., LaRochelle AG, Ratner RE, Borenstein DG. Recovery of the hypothalamic-pituitary-adrenal (HPA) axis in patients with rheumatic diseases receiving low-dose prednisone. *Am J Med.* 1993;95(3):258-64.

13. Bacon PA, Myles AB, Beardwell CG, Daly JR. Corticosteroid withdrawal in rheumatoid arthritis. *Lancet.* 1966;2(7470):935-7.

14. Hicklin JA, Wills MR. Plasma "cortisol" response to Synacthen in patients on long-term small-dose prednisone therapy. *Ann Rheum Dis.* 1968;27(1):33-7.

15. Borresen SW, Klose M, Baslund B, Rasmussen Å K, Hilsted L, Friis-Hansen L, et al. Adrenal insufficiency is seen in more than one-third of patients during ongoing low-dose prednisolone treatment for rheumatoid arthritis. (1479-683X (Electronic)).

16. Arlt W, Allolio B. Adrenal insufficiency. *Lancet.* 2003;361(9372):1881-93.

17. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(2):364-89.

18. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *Eur J Endocrinol.* 2010;162(3):597-602.

19. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med.* 2008;36(6):1937-49.

20. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal

Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(11):3888-921.

21. Ndosi M, Adebajo A. Patient education in rheumatoid arthritis: is the needs-based approach the way forward? *Clinical Rheumatology.* 2015;34(11):1827-9.

22. Dineen R, Martin-Grace J, Thompson CJ, Sherlock M. The management of glucocorticoid deficiency: Current and future perspectives. *Clinica Chimica Acta.* 2020;505:148-59.