Adrenocortical dysfunction in rheumatoid arthritis: A narrative review and future directions

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Abstract
Background: Iatrogenic adrenal insufficiency (AI) secondary to long-term treatment with exogenous glucocorticoids (GC) is common in patients with systematic rheumatic diseases, including rheumatoid arthritis (RA). Moreover, a proportion of these patients is always in need of even small doses of glucocorticoids to maintain clinical remission, despite concomitant treatment with conventional and biologic disease-modifying drugs.

Methods: We conducted a literature review up to December 2020 on (a) the incidence of AI in both long-term GC-treated and GC-treatment naïve RA patients; (b) the potential effects of increased levels of circulating proinflammatory cytokines, as well as of chronic stress, in adrenocortical function in RA; (c) the circadian cortisol rhythm in RA; and (d) established and evolving methods of assessment of adrenocortical function.

Results: Up to 48% of RA patients develop glucocorticoid-induced AI; however, predictors are not established, while adrenocortical dysfunction may also occur in GC-treatment naïve RA patients. Experimental and clinical data have suggested that inadequate production of endogenous cortisol relative to enhanced clinical needs associated with the systemic inflammatory response, coined as the ‘disproportion principle’, may operate in RA. Although the underlying mechanisms are unknown, both proinflammatory cytokines and chronic stress may contribute the most in the adrenals hyporesponsiveness and the target tissue glucocorticoid resistance that have been described, but not systematically studied. A precise longitudinal assessment of endogenous cortisol production may be needed for optimal RA management.

Conclusion: Apart from iatrogenic AI, an intrinsically compromised adrenal reserve in RA may have a pathogenetic role and interfere with effective management, thus deserving further research.

KEYWORDS
adrenal androgens, adrenal insufficiency, circadian rhythm, DHEAS, endogenous cortisol, glucocorticoids, hypothalamic-pituitary-adrenal axis, rheumatoid arthritis, salivary cortisol
1 | INTRODUCTION

Adrenal insufficiency (AI) is a serious clinical condition characterized by deficient production or action of glucocorticoids (GC), accompanied by deficiency of mineralocorticoid and/or adrenal androgens secretion. Diagnosis of AI remains a clinical challenge for every physician due to the wide range of its clinical presentation, which varies from ‘nonspecific’ symptomatology of fatigue, reduced appetite, weight loss and dizziness to a life-threatening acute adrenal crisis, if left untreated.1 Classically AI is subdivided into three types according to the site of dysfunction: (a) primary or Addison disease, when adrenocortical insufficiency is present; (b) secondary, when pituitary diseases hamper the release of adrenocorticotropic hormone (ACTH); and (c) tertiary, when a dysfunction in the hypothalamus is involved.2

Rheumatoid arthritis (RA) is a chronic (auto)immune-mediated inflammatory systemic disease affecting 0.5%-1.0% of the population worldwide.3 Breach of tolerance to modified self-proteins and inflammation of the synovium, the main target tissue, are hallmark features of RA; eventually resulting in transformation of synovial fibroblasts into an aggressive hyper-proliferative and invasive tissue that leads to articular destruction and disability.4 RA is more prevalent in women, and the incidence increases significantly with age.5 Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), mainly methotrexate and leflunomide, are currently considered the gold standard for long-term treatment of RA, while biological agents or targeted/synthetic DMARDs are added in patients with inadequate response to csDMARDs. Notably, many patients require prolonged glucocorticoid administration to maintain remission.6 Although glucocorticoids are efficient in alleviating joint swelling, stiffness and pain, they are frequently associated with multiple adverse effects including bone loss, diabetes mellitus and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to adrenocortical hypotrophy and iatrogenic AI.7

Iatrogenic AI due to either prolonged treatment or high daily and/or high cumulative dose of glucocorticoids is considered the main cause of AI in the Western countries8 and is commonly found in patients with RA. In addition, however, a suboptimal response to stress and inflammation, termed ‘relative or functional’ AI, has been reported in patients with RA even in the presence of an apparently intact HPA axis.9 In earlier studies by Chrousos et al, the HPA axis response to stress was found compromised in RA rat models10 and in patients with RA,11 suggesting that a possible genetic background could contribute to the reported HPA axis hyporesponsiveness.12 Coexistence of Addison disease has also been reported, albeit rarely, in patients with RA.13-15

Here, we review published data on the prevalence of clinically overt GC-induced AI along with potential predictors in RA, as well as data on the role of a compromised adrenocortical function in disease-onset and management of these patients. We also discuss the role of chronic stress and of circulating cytokines in the integrity of the HPA axis in RA as well as the introduction into the clinical practice of novel, noninvasive methods, that can be used to identify even subtle deficits of the adrenal reserve in these patients.

2 | MATERIAL AND METHODS

This is a narrative review including the most relevant articles of both basic and clinical research focusing on (a) the presence of a compromised adrenal function in patients with RA, either on long-term treatment with GC or GC-treatment naïve; (b) the effect of chronic stress and circulating cytokines on adrenocortical function at the onset and during the course of the disease; (c) the circadian cortisol rhythm in RA; and (d) the use of novel, more sensitive methodologies of assessing adrenocortical reserve in clinical practice. Relevant articles were selected among those deposited on PubMed, EMBASE, Cochrane Central Register of Controlled Trials and clinicaltrials.gov up to December 2020. Reporting of the review conforms to broad EQUATOR guidelines.16

3 | RESULTS

3.1 | Glucocorticoid-induced adrenal insufficiency in rheumatoid arthritis

The prevalence of GC-induced adrenal insufficiency in RA is hard to estimate due to the significant heterogeneity among the published studies, based on different populations, variety of therapeutic courses used, and different measurements or cut-off values used to assess the functional integrity of the HPA axis (Table 1, Figure 1). According to current literature, the prevalence of GC-induced AI in patients with chronic rheumatic diseases can reach up to 50% after long-term, low-dose GC treatment.17 In RA specifically, the proportion of patients who develop GC-induced AI varies greatly, ranging between 10% and 28% in earlier studies,18,19 and being up to 45% in more recent ones.20

In the early study by Bacon et al, although 28% of patients with RA under long-term GC treatment developed secondary AI, the proportion of patients who failed to discontinue GC was significantly higher (more than 65% of the entire cohort), the main reason being the sustained reactive arthritis with localized joint swelling and tenderness rather than the AI per se.18 Similarly, in the study by Hicklin et al, 10% of the patients with RA who were on long-term GC treatment with a mean dose of 5 mg prednisone/d, developed AI.19
| Study                  | Population size (N) | Mean age (years), Males (%) | Mean GC dose | Mean GC treatment duration | Measurement/Method/Definitions | Main results                                                                                                                                 |
|-----------------------|---------------------|-----------------------------|--------------|---------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Bacon et al (1966)18  | N = 35 RA patients  | 51.3 y 29% males           | Mean total Prednisone dose 24.8 g | 6 mo-16 y (average 7.5 y) | Plasma cortisol at intervals of prednisone tapering (1 mg/mo) Synacthen test/ insulin hypoglycaemia test | 1. 28.5% (n = 10) of patients had successful withdrawal (average rate=1 mg/3.5 mo)  
2. Reasons of failure to withdrawal:  
   • RA flare in n = 23: (8/23 laboratory signs of adrenal insufficiency)  
   • AI in n = 1  
   • n = 1; withdrawal                                                                 |
| Hicklin et al (1968)19| N = 59; 39 RA patients, 20 controls | N/A | 5 mg prednisone/d (mean cumulative dose 2169.5 mg) | 8 wk-8 y (mean: 62.5 mo) | Synacthen test (250 μg) (12 h withdrawal of GC) | 1. AI in 4/39 patients (10%)  
2. No clear association between total dose, duration of treatment and development of AI.                                                                 |
| Kirwan et al (2006)21 | N = 139 Active RA | 55 y 29% males             | 1. Budesonide 3 mg/d 2. Budesonide 9 mg/d 3. Prednisolone 7.5 mg/d 4. Placebo | 12 wk (prospective study) | Synacthen test 250 μg at baseline and at 12 wk (24 h withdrawal of GCs)  
Abnormal response: P-cortisol > 2 SD below the pretreatment measurement | 1. Abnormal response to Synacthen:  
   a. 34% of patients taking budesonide 9 mg/d  
   b. 46% of patients taking prednisolone 7.5 mg/d  
2. Dose-dependent reduction in the HPA axis response to Synacthen test                                                                 |
| Borresen et al (2017)20| N = 42 RA patients | 65.3 y 31% males           | 5 mg prednisolone/d Oral GC in n = 33 Multiple GC formulas in n = 9 | 66 mo (6-444 mo) | Synacthen test (250 μg) (48 h withdrawal of GC)  
30’ P-cortisol normal when >420 nmol/L | 1. AI in 20 patients (48%)  
2. Abnormal test response in 7/9 patients with concomitant glucocorticoid therapy. Particularly in:  
   a. 4/4 with intra-articular injections  
   b. 3/4 with intra-muscular injections  
   c. 0/1 with GC cream  
3. Low ACTH levels within reference range (<1-28 pmol/L)  
4. Negative anti-adrenal antibodies (secondary AI)  
5. No association between adrenal function and duration of prednisone treatment, gender or seropositivity (RF) in RA |
| Burmester et al (2020)22| RCT (SEMIRA) | 54.4 y 23% males           | TCZ+prednisone 5-15 mg/d for ≥24 wk & at randomization: 5 mg/d prednisone for ≥4 wk with stable low disease activity for 4-6 wk | 24 wk | 1. Continue 5 mg/d for 24 wk.  
2. Taper prednisone reaching 0 mg/d in 16 wk. Delta-DAS28-ESR≥0.6 from baseline to 24 wk (clinically relevant) | 1. Successful treatment (low disease activity, no RA flares, no AI for 24 wk) in:  
   a. 99 (77%) continuous  
   b. 85 (65%) tapered  
2. Serious adverse events in:  
   a. 7 (5%) tapered  
   b. 4 (3%) continuousSafe and better results in disease control with 5 mg/d continued-prednisone treatment than tapered-prednisone regimen for 24 wk |

Abbreviations: AI, adrenal insufficiency; GC, glucocorticoids; h, hour; HPA, hypothalamic-pituitary-adrenal axis; N/A, not available; RA, rheumatoid arthritis; RF, rheumatoid factor; TCZ, Tocilizumab.
However, these early studies failed to demonstrate a robust relation between prednisone dose and duration of treatment on the development of HPA axis suppression, indicating a wide individual variation.

Kirwan et al compared the effect of 12 months treatment with either budesonide (two doses of 3 and 9 mg/d) or prednisone (7.5 mg/d) in adrenocortical function, in a prospective double-blind placebo-controlled trial in RA patients (n = 142). The proportion of patients who developed AI was significantly higher in patients receiving prednisone (46%) than those taking a high dose of budesonide (9 mg) (34%).

The suppressive effect of even low doses of GC on the HPA axis was further demonstrated by Borresen et al who studied the incidence of secondary AI in 42 patients with RA receiving 5 mg prednisone/d for a median of 5.5 years. In this study, secondary AI reached up to 48% of RA patients, while no association with total dose, duration of treatment, gender or seropositivity of the patients was observed. This study confirmed earlier observations that even in patients receiving low doses of prednisone, such as 5 mg/d, the risk of adrenal suppression remained high if GC were administered for a long period. As a result, although the daily dose of 5 mg prednisone (equivalent to 20 mg/d of hydrocortisone) equates to normal cortisol production under nonstressful conditions, patients with established AI on treatment with 5 mg prednisone or equivalent synthetic steroids are not sufficiently covered during stress.

The European League Against Rheumatism (EULAR), acknowledging the critical issue of GC-induced complications, suggested for patients on sustained clinical remission tapering of oral GC treatment at the earliest feasible time point of the therapeutic course and to the lowest daily dose possible, preferably <7.5 mg/d (prednisone equivalent), until the final target of full withdrawal is attained. In clinical practice, these guidelines are often difficult to follow due to the high risk of disease flares after tapering or stopping GC administration. The SEMIRA (Steroid EliMination In Rheumatoid Arthritis) study, a double-blind, multicentre, randomized controlled trial, compared oral glucocorticoid tapering with the continuation of low-dose oral glucocorticoids. The population study consisted of 259 patients with low disease activity RA on treatment with 5 mg/d prednisone and tocilizumab, an anti-interleukin (IL)-6 receptor antibody. The study demonstrated that, at least for the period of 24 weeks, the continued-prednisone regimen provided better maintenance of disease remission than did the tapered-prednisone treatment, with no symptoms suggestive of AI. The study protocol, however, did not include biochemical assessment of adrenocortical function.

It seems, therefore, that despite the introduction of highly effective DMARDs in the management of RA over the last decades, removing GC from the main therapeutic regimen remains a major clinical challenge, underlining the potential role of an intrinsically compromised adrenocortical function in the pathogenesis of RA. The optimal timing of low-dose tapering is thus crucial to prevent AI. This requires a detailed individual risk assessment and, where possible, regular monitoring of adrenocortical function, to ensure the timely adjustment of GC therapy.
glucocorticoid withdrawal in patients with RA with low disease activity receiving effective biological therapy is yet to be determined. Additionally, the potential role of hydrocortisone replacement therapy in the success of prednisone discontinuation is also investigated currently (NCT02997605). Nevertheless, until further data are available, the inability of tapering oral GC below 7.5 mg/d of prednisone or an equivalent synthetic GC is included in the recent definition of difficult-to-treat RA.23

3.1.1 Predictors of glucocorticoid-induced adrenal insufficiency

Mean and cumulative GC dose, duration and route of administration, and basal cortisol levels are considered prognostic factors of GC-induced AI.24 For every 5 mg increase in daily dose of oral GC, there is a 7% increased risk of AI.25 HPA axis functional integrity assessment is strongly recommended when prednisone >15 mg/d is administered for 6 months or >9.5 mg/d for 12 months, as these regimens have been significantly associated with a deficient adrenocortical response to ACTH stimulation.26 Studies on cumulative GC-dose and AI have produced conflicting results, showing either an increased risk of AI25,26 or no effect.19 Long duration of GC treatment is also considered a significant predictive factor for AI by most,26,27 but not all studies.20 Overall, it has been demonstrated that the risk of developing AI may increase with increased exposure to GC treatment.26,27 Regarding the route of GC administration, it appears that oral, intra-articular or a combination of routes affect the HPA axis functional integrity to a greater extent than those in response to inhaled or topically applied GC.24

A recent systematic review reported that AI persisted even after 3 years of GC withdrawal in almost 15% of patients with rheumatic diseases.28 Interestingly, when the results of this study were stratified according to the average dose, duration and cumulative dose of GC used within groups, no clear trends were identified, and AI was documented even in those who had the lowest exposure to GC.28

3.2 Intrinsic compromise of adrenocortical function in experimental arthritis

Chrousos et al studied HPA axis activation in a rat model which resembles human RA, demonstrating that the susceptibility to arthritis was strongly associated with a genetically determined HPA axis defectiveness.10 Lewis (LEW/N) rats treated with streptococcal cell wall (SCW) peptidoglycan polysaccharide to induce arthritis, showed blunted corticotropin-releasing hormone (CRH) and GC release upon stress or inflammatory stimuli, while administration of dexamethasone suppressed the progression of arthritis. As a mirror image experiment, treatment of congenic Fischer (F344/N) rats (which are normally resistant to the development of arthritis in response to SCW) with glucocorticoid receptor inhibitors in combination with SCW led to severe inflammatory arthritis10 (Table 2).

These early results were complemented by the discovery of a direct effect of cytokines on adrenal steroid hormone secretion. Tumour necrosis factor alpha (TNF-a) was shown to directly inhibit expression of key enzymes in the steroidogenic pathway in adrenocortical cells,29 while anti-TNF-a therapy allowed partial recovery of the suppressed HPA axis.30 In line with these in vitro studies, injection of proinflammatory cytokines into healthy subjects induced a strong initial reaction of the HPA axis that was gradually diminished after repeated injections over 3 weeks.31,32

A more recent study showed that the adrenal cortex of a collagen-induced arthritis rat model of severe human arthritis displayed a higher number of major histocompatibility complex class II (MHC-II+) cells than the cortex of control rats, associated with suppression of ACTH-induced secretion of GC by adrenocortical cells33 (Table 2, Figure 2). In addition, treatment of adrenocortical cells with IL-1b further reduced ACTH-stimulated GC secretion, suggesting that local inflammation of the adrenal glands in arthritic rats may be a key mediator of reduced corticosterone production through MHC-II+-expressing cells and IL-1b secretion.

3.2.1 Adrenocortical dysfunction in GC-treatment naïve patients with rheumatoid arthritis: the disproportion principles

The suspicion that newly diagnosed patients with RA may have a subclinical defect of HPA axis was initially raised in the 1950s based on the immediate and successful clinical response of these patients to GC treatment.34 However, in contrast to experimental data (Table 2), the results from clinical studies investigating an intrinsically compromised HPA axis in patients with RA have demonstrated variable results that require further investigation (Table 3, Figure 2).

Several studies that assessed basal or stimulated circadian activity of HPA axis in RA failed to demonstrate significant differences between patients with RA and controls.35 A critical step that changed the methodological approach of the HPA axis assessment in RA was the observation that the ‘normal’ levels of cortisol and/or ACTH secretion were inappropriate for the high inflammatory status, indicated by the increased pro-inflammatory cytokine levels of TNF-a, IL-1b and IL-6, in these patients. This condition, described as the disproportion principle,36 reflects the presence of a relative hyporesponsiveness of HPA axis to cytokines and may explain the failure of a subgroup of RA patients to successfully
withdraw from GC, despite the use of novel and highly efficacious treatments. Whether this compromised adrenocortical function pre-exists contributing to disease pathogenesis or whether it is developed as a secondary phenomenon due to high circulating cytokines within the first years from arthritis onset remains to be elucidated.

Straub et al supported the hypothesis that maintenance of low levels of cortisol/ACTH in chronic adrenal stimulation is an evolutionary adaptation that has prevailed to optimize temporal energy requirements and allow the human body to defend itself in case of acute stress and infections. Subsequently, substitutional exogenous glucocorticoid administration is required to compensate for this endogenous cortisol inherent or inflammation-induced ‘downregulation’ in chronic inflammatory diseases. Compromised adrenocortical function or ‘adrenal suppression’ reflects endogenous daily glucocorticoid production lower than the basal resting state secretion of 7-10 mg cortisol/m² body surface area per day (approximately equivalent to 2.5 mg/d of prednisolone).

In addition, increased circulating levels of pro-inflammatory cytokines during chronic stress and inflammation increases the extra-adrenal concentration of cortisol, through enhanced expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). This enzyme catalyses the conversion of inactive cortisone to biologically active cortisol, known as the cortisone-to-cortisol shuttle which, in turn, further suppresses pituitary secretion of ACTH through negative feedback regulation. Increased 11β-HSD1 expression in the inflammatory joints could exert beneficial effect by increasing active cortisol presence at tissue level; however, its action may be limited by the increased expression of 11β-HSD2 by macrophages and activated T cells. As a net result, 11β-HSD2 degrades active cortisol at the inflamed tissues further fuelling tissue destruction.

Moreover, glucocorticoid receptor gene polymorphisms that decrease the sensitivity of glucocorticoid receptors at target tissues were also identified in patients with RA, further supporting the notion that a defective HPA axis plays a critical role in the pathophysiology of this disease.

Although recent advances in molecular biology and genetics have increased dramatically our understanding of the pathophysiological interactions between the inflammatory process, the immune system response and the HPA axis in the pathogenesis of RA, still many critical points remain unanswered.
3.2.2 | Adrenal androgens versus glucocorticoids in rheumatoid arthritis

The female predisposition to develop RA in reproductive ages and the later disease incidence in older males suggest that sex steroids may also play a role in the pathogenesis of the disease. Adrenal androgens (AA), such as dehydroepiandrosterone (DHEA) and androstenedione, constitute important precursors of peripheral androgens, which act as natural immunosuppressors and anti-inflammatory molecules. Anti-inflammatory effects of DHEA include inhibition of oxygen radical secretion, resulting in decreased tissue destruction, while adrenal androgen metabolites downstream of DHEA also exert anti-inflammatory effects.

Early studies by Masi et al had shown that female patients with RA had significantly lower excretion of urinary metabolites of AAs (ie 11-deoxy-17-ketosteroids) and lower serum levels of dehydroepiandrosterone sulphate (DHEAS) compared to healthy controls, independently of the GC metabolite secretion status. In addition, decreased serum levels of DHEA and androstenedione were also found in young premenopausal females compared to healthy controls, 4-20 years before the clinical onset of RA, indicating that a potential adrenocortical defect may influence RA risk under the age of 50 (Table 3).

The exact molecular mechanisms that lead to low androgen levels before the onset of an inflammatory disease are currently unknown, but a chronic subclinical inflammatory process would be expected to inhibit the secretion of androgens in three different ways. First, inflammatory cytokines could block androgen production from precursors in both gonadal and adrenal glands through inhibition of the 17-α-hydroxylase/17,20-lyase (P450c17) enzyme system. Second, cytokines, such as TNF-α, IL-1α, IL-1β and IL-17, could enhance CYP7B-induced conversion of DHEA into the proinflammatory metabolite 7α-hydroxy-DHEA in collagen type-II arthritic animals and in RA patients. As a result, precursors would not be available for conversion to androgens. Third, there may be an excessive conversion of androgens to oestrogens in inflamed tissues in both sexes.

Alterations in the production of AAs and GCs in chronic inflammatory diseases do not always follow the same pattern and several studies have demonstrated a dissociation between cortisol and DHEA circulating levels, dependent on the age of RA onset. Serum DHEAS and cortisol concentrations were inversely associated in premenopausal women who developed RA before the age of 50, whereas the association was positive in premenopausal women who developed RA after the age 50.

The mechanisms behind these differential alterations are still unclear, but it appears that the immunomodulatory effects of both steroids may be contributory. Glucocorticoids and DHEA affect the same immunomodulatory genes, but in opposite direction. For instance, DHEA can prevent GC-induced lymphocyte and thymocyte apoptosis, reducing the susceptibility to viral infections, whereas GCs can increase the likelihood of opportunistic infections. As with GCs, AA production is initially stimulated in acute stress or infection but suppressed and often dissociated with the production...
### TABLE 3  Clinical studies investigating a possible intrinsic adrenocortical dysfunction in rheumatoid arthritis

| Studies                          | Study design                                                                 | Main results                                                                                                                                 |
|---------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Masi et al (1984)               | N = 16; 8 ambulatory GC treatment-naïve females with RA, 8 HC                 | 1. RA patients showed lower excretion of adrenal androgenic-anabolic metabolites on baseline (*P* < .001), and after ACTH (*P* < .005) and metyrapone (*P* < .02)-stimulation tests compared to HC.  
2. Lower excretion of glucocorticoid-derived metabolites was observed at baseline (*P* < .05), but not after ACTH/metyrapone stimulation tests in RA patients. This study suggests an impaired synthesis or metabolism of adrenal androgens and a greater relative deficiency in DHEA rather than androsterone or etiocholanolone in patients with RA that may predispose to disease onset. |
| Chikanza et al (1992)           | N = 30; 10 RA patients, 10 patients with OM, 10 patients with noninflammatory arthritis Measurements:  
1. Diurnal serum cortisol and TNF-α, IL-1, IL-6 levels  
2. Cortisol secretion in response to surgery  
3. ACTH and cortisol response to CRH test | RA patients compared to OM patients demonstrated:  
1. Lower diurnal cortisol levels (albeit within normal range)  
2. Inability to increase endogenous cortisol secretion after surgery despite increased IL-1, IL-6 levels. |
| Crofford et al (1997)           | N = 10; 5 with newly diagnosed RA, 5 HC  
Assessment of ACTH and cortisol circadian rhythms and HPA axis response to CRH stimulation test | In RA patients:  
1. Normal circadian rhythms of ACTH and cortisol  
2. Increased plasma IL-6 levels  
3. No differences between plasma ACTH levels, cortisol responses to CRH and ACTH/cortisol ratio between RA patients and HC |
| Cutolo et al (1999)             | N = 17; 10 premenopausal RA females, 7 HC  
Measurements of serum DHEA, DHEAS, cortisol, IL-6 and IL-12 at baseline and after CRH and ACTH stimulation | Baseline, RA patients compared to HC:  
1. Significantly lower levels of DHEA and DHEAS  
2. Significantly higher levels of IL-6, IL-12  
Low dose ACTH test and CRH stimulation in RA patients compared to HC:  
1. Significantly lower total secretion of DHEA (calculation of area under the curve)  
2. Normal plasma cortisol levels despite the level of inflammation |
| Masi, Chatterton and Aldag, (1999) | Serum collected from pre-RA cases (4-20 y prior the RA onset) and HC (1:4 ratio)  
Pre-RA patient subgroups based on:  
• Entry menopausal status (EMS)  
• Age at the beginning of the prospective study or age when RA developed.  
Measurement of adrenal steroid hormones | Significantly lower serum levels of DHEA in premenopausal, younger women (RA onset before the age of 50) compared to HC.  
**Marker or contributor to disease onset?**  
**Proposed Hypothesis:** Subtle adrenocortical dysfunction, as assessed by adrenal androgen deficiency, may predispose to younger-onset RA. |
| Kanik et al (2000)              | N = 64; 32 with newly onset synovitis (of whom 15 with RA) and 32 HC  
Collection of fasting morning blood to assess:  
• ACTH, cortisol, adrenal androgens, testosterone, CRP, ESR, RF  
• Cortisol every 20’, in total of 3 samples | 1. No significant differences between patients and HC in the 1st year of disease.  
2. Accelerated age-associated decline of adrenal androgens in the patient group. |
| Derijk et al (2001)             | N = 94; 30 RA patients, 40 SLE patients, 24 HC  
Single stranded conformation polymorphism (SSCP) and direct sequencing of hGR gene  
COS-1 cell transfection: mRNA stability assay (actinomycin D treatment) | 1. Identification of a certain polymorphism in hGR gene in exon98 (‘ATTTA’ to ‘GTATTA’ transition).  
2. G allele frequency in HC: 6%, RA: 18%, SLE: 20%  
3. The identified polymorphism led to increased stability of hGRß mRNA in COS-1 cells. |

(Continues)
| Studies                  | Study design                                                                 | Main results                                                                                                                                                                                                 |
|-------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Straub et al (2002)107  | N = 192; 34 early onset RA, 46 Reactive arthritis (ReA), 112 HC              | RA patients compared to ReA patients and HC:  
1. Higher levels of IL-6, TNF-α  
2. Higher levels of cortisol, DHEA, but relatively low in relation to the inflammation status  
3. Similar ACTH, DHEAS levels  
4. Alteration of steroidogenesis greater in RA than in ReA patients |
| Imrich et al (2005)108  | N = 29; 15 premenopausal women with RA (mean aged 41.2 y), 14 HC             | RA patients compared to HC at baseline:  
1. Lower DHEAS ($P < .05$)  
2. Borderline lower DHEA ($P = .067$)  
RA patients compared to HC after insulin-induced hypoglycaemia:  
1. Similar levels of cortisol, ACTH, ASD, 17OHP  
2. Lower EPI levels ($P = .005$), lower NE levels ($P < .001$) |
| Masi et al (2013)55     | N = 180; 36 Female pre-RA patients, 144 HC                                  | 1. Lower androstenedione levels in pre-RA patients vs. HC  
2. DHEAS levels were not significantly different between groups |
| Masi et al (2014)53     | Serum adrenocortical steroid levels and intercorrelations in RA females      | 1. Decreased serum levels of DHEAS in females with premenopausal-onset RA.  
2. Decreased levels of ASD in pre-RA women compared to HC associated with either the lowest quintile DHEAS or lower cortisol values.  
3. Negative correlation of serum cortisol with DHEAS at baseline in pre-RA females with premenopausal-onset disease compared to HC and the pre-RA subjects with postmenopausal-onset disease. Adrenocortical androgenic steroid deficiency and adrenal androgen-to-cortisol steroid imbalance in a minority of premenopausal-onset RA women. |
| Masi et al (2015)66     | The RA Precursors Study (RAPS) Neuroendocrine Immune Database: 90 males (18 pre-RA, 72 HC), 180 females (36 pre-RA, 144 HC) | 1. ASSA and sIL-2Ra significantly higher in females ($P < .010$) in pre-RA, HC and the total sample compared to males.  
2. sTNF-R1 significantly higher in males ($P < .001$) in pre-RA, HC and the total sample compared to females. Adrenal androgens (DHEA and ASD) were significantly associated with the sexually dimorphic cytokine receptors (sIL-2Rα and sTNF-R1), in both pre-RA and HC subjects. |
| Stark et al (2015)68    | N = 842; 521 RA patients, 321 HC SNPs (TaqMan) Ex vivo (synovial fibroblasts) | 1. CYB5A SNP rs1790834 was associated with reduced risk of RA in women [OR (95%CI): 0.63 (0.46-0.86)], in RF-positive patients [OR (95%CI): 0.53 (0.37-0.75)] and in anti-CCP+patients [OR (95%CI): 0.58 (0.41-0.83)].  
2. The minor (A) allele of the studied SNP in CYB5A was associated with 2-fold higher CYB5A mRNA expression, increased 17,20-lyase activity and 2.5-fold increased 7α-hydroxy-DHEA production in extracted synovial fibroblasts. |

(Continues)
of GCs in chronic inflammatory disorders, such as RA.\textsuperscript{63} Although the physiological significance of these events is still unclear, it remains to be established whether relatively inadequate, for the state of inflammation, AA and GC production by the adrenal cortex contributes to the onset of RA by failing to suppress the continuing inflammatory process. In line with these findings, more recent studies demonstrated significant associations between AA levels in RA patients and disease onset, severity and progression. A strong cross-talk between AAs and sexual dimorphic cytokine receptors, such as soluble IL-2Ra and soluble TNF R1,\textsuperscript{66} has been identified in both RA patients before symptomatic onset and in healthy controls. Moreover, in a generalized structural equation model that was used to identify multiple risk factors for RA onset and progression, AAs were strongly associated with improved survival rates in a subgroup of RA patients with disease onset before the age of 60\textsuperscript{67} (Table 3).

| Studies                  | Study design                                      | Main results                                                                 |
|-------------------------|---------------------------------------------------|------------------------------------------------------------------------------|
| Ren et al (2020)\textsuperscript{67} | RAPS subcohort: N = 270; 54 pre-RA subjects (36 females, 18 males), 216 matched HC (4:1) | Increased baseline androgenic-anabolic steroid z-scores were significantly correlated with increased total survival, but only in earlier onset (<60 y) HC subjects (mean entry and onset age, 37 and 48 y respectively) |
|                         | A generalized structural equation model (GSEM) was used to identify risk factors for incident RA cases and to evaluate long term survival. | Overall mortality (1974-2017) was 72.2\% for RA and 52.8\% for HC. Mortality increased with: 1. Increased age at cohort entry (for all subjects) [OR (95\%CI): 1.1 (1.1-1.2)] 2. RA onset (vs. non-RA) [OR (95\%CI): 2.2 (1.3-3.8)] 3. Cigarette smoking (>21 cigarettes daily) [OR (95\%CI): 2.1 (1.2-3.7)] 4. Decreased androgenic-anabolic steroids z-score [OR (95\%CI): 2.6 (1.6-4.1)] |
|                         |                                                   | Increased risk of incident RA onset: 1. RA family history [OR (95\%CI): 7.2 (2.3-22.4)] 2. Cigarette smoking (>21 cigarettes daily) [OR (95\%CI): 5.0 (1.8-13.6)] 3. RF immunoglobulin M (IgM) [OR (95\%CI): 2.0 (1.4-2.8)] 4. Higher baseline overall latent activity of immunoreactive proteins * [OR (95\%CI): 1.3 (1.0-1.8)] |

*Derived from CRP, sIL-2Ra, and sTNF-R1

Abbreviations: 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; and sIL-2Ra, soluble interleukin 2 receptor A; anti-CCP, antibody against cyclic citrullinated peptide; ASD, D4-androstenedione; ASSA, acute serum amyloid a; CRH, corticotrophin-relasing hormone; CRP, C-reactive protein; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; EPI, epinephrine; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; h, hour; HC, healthy control; hGR, human glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal axis; ILs, interleukins; NE, norepinephrine; OM, osteomyelitis; Pre-RA, before the clinical onset of symptoms; RA, Rheumatoid Arthritis; RAPS, rheumatoid arthritis precursors study; RF, rheumatoid factor; SLE, Systemic Lupus Erythematosus; SNP, single-nucleotide polymorphism; sTNF-R1, soluble tumour necrosis factor receptor 1; TNF-a, tumour necrosis factor a.

3.3 | Chronic stress and compromised adrenocortical function in rheumatoid arthritis

Stress is defined as the state of threatened or perceived as threatened homeostasis,\textsuperscript{70} and several studies have supported the involvement of psychological and physical stress in the development and/or perpetuation of autoimmune diseases, such as RA.\textsuperscript{71-73}

The integrity of the HPA axis and the autonomic nervous system (ANS) is considered of vital importance for the adaptive response against stressor(s) to be effective.\textsuperscript{74} Chronic stress induces dysregulation of the HPA axis mainly through the release of hypothalamic CRH and arginine-vasopressin (AVP). Under nonstressful conditions, CRH and AVP are secreted into the portal system in a circadian and pulsatile pattern.\textsuperscript{75} These circadian secretions are in turn expressed in the systemic secretion of ACTH and cortisol, which are also circadian and pulsatile. Interestingly, the presence of circulating
cytokines in the blood also follows a circadian pattern, which is inverse, almost the mirror image, to that of the HPA axis.

During acute stress, the amplitude and synchronization of CRH and AVP secretory pulses is increased, and this is reflected in the levels of ACTH and cortisol in the systemic circulation. Similarly, during an acute activation of the immune system, as when an inflammatory reaction takes place, the circulating levels of proinflammatory cytokines, such as TNF-α, IL-1 and IL-6, are elevated. Once a threshold level is exceeded, the HPA axis is stimulated and circulating levels of GC increase starting to exert suppressive effects on the inflammatory reaction, finally controlling the immune response and helping the organism to reach the prior healthy homeostasis.

Chronic stress and chronic inflammation are a different ball game. Although a colloquialism this prose may be, it accentuates an important difference between the well-orchestrated, physiologic, acute stress and inflammation reactions that lead to resolution, and the pathologic, protracted changes in the activity of the stress system and the inflammatory response that allow survival at the expense of health and life expectancy (allostasis or cacostasis). Chronic stress causes a form of mild systemic inflammation that provides no benefit to the organism, and, if anything, it damages tissues and, hence, was recently called ‘para-inflammation’. It is associated with a blunted circadian cortisol rhythm, a suppressed inflammatory response, and a shift from T helper 1 to T helper 2 and a T helper reg to T helper 17 immunity. It is obvious that in chronic stress, endogenous glucocorticoids fail to terminate the stress response and, in fact, cause body composition changes reminiscent of hypercortisolism, such as visceral adiposity, sarcopenia and osteopenia/osteoporosis (Figure 2).

Apart from the central role of hypothalamic CRH in the interaction between acute or chronic stress and HPA axis changes, a negative effect of chronic stress may be exerted via changes in the sensitivity of target tissues to glucocorticoids (Figure 2). Exposure to a major stressful life event may result in glucocorticoid receptor resistance, which, in turn, interferes with the suppressive effects of the HPA axis on proinflammatory cytokines. Thus, without appropriate cortisol regulation, the organism fails to downregulate inflammatory processes contributing to a vicious cycle where stress, inflammation and a compromised HPA axis function may result in the development of chronic immune-mediated inflammatory diseases, such as RA.

4 | FUTURE DIRECTIONS

Until today, the most used HPA axis tests to recognize whether hormone production is sufficient are the low-dose (1 μg) and standard-dose (250 μg) ACTH-stimulation tests. The standard-dose ACTH test causes a ‘supraphysiologic’ response in critically ill patients and, thus, has a relatively low sensitivity. On the other hand, the low dose ACTH test can be influenced by technical parameters and has a relatively low specificity, and, therefore, the standard dose ACTH test is the preferred procedure. Moreover, decreased levels of DHEAS for a given age and gender may unmask decreased adrenal function, even in subjects with normal baseline or ACTH-stimulated cortisol.

The introduction into the clinical practice of novel, easy to apply, noninvasive and low-cost methods to assess adrenal function have provided valuable additional information regarding even subtle changes of the adrenal secretory capacity. Saliva offers a noninvasive and stress-free alternative to plasma and serum biological fluid that is being increasingly used for steroid analysis. In this context, measurement of salivary cortisol is a reliable indicator of locally available cortisol in target tissues. Although salivary and serum cortisol are highly correlated in healthy subjects, salivary cortisol is more sensitive when examining the HPA axis function in RA patients. However, correlation of serum and salivary cortisol after pharmacological stimulation in RA is yet to be investigated. In addition, salivary DHEA, which is a lipid-soluble unconjugated steroid, enters saliva mainly through an intracellular route and reflects the unbound, biologically active fraction in the general circulation. Therefore, DHEA concentrations can be easily assessed as single or repeated sampling measurements in the saliva. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has garnered increased interest over the last years regarding assessment of steroids in human saliva. Several studies have proved LC-MS/MS as a more accurate, reliable alternative to the widely used immunoassay approach in detecting even subtle changes in DHEA and cortisol concentrations.

Analysis of hair cortisol concentrations (HCC) is another relatively novel method that reflects cumulative long-term cortisol exposure and is currently under intense investigation for defining cut-off values to evaluate subtle disturbances of the HPA axis in disease states, such as cyclical Cushing syndrome or adequacy of hydrocortisone replacement therapy. HCC has also been shown to increase with psychological stressors, including major life events, as well as physical stressors, such as endurance exercise, shift work and aging. Since HCC provides the advantage of evaluating time integrated HPA axis activity during an extended period, its role in evaluating HPA axis activity in RA is promising. In patients with other autoimmune diseases, such as systemic lupus erythematous (SLE), Sjögren syndrome and systemic sclerosis, HCC values were higher compared to healthy individuals.

Nevertheless, any attempt to critically assess the adrenal function in RA so far has been limited by two parameters. First, in most cases patients have already been treated with...
GC and may thus have a compromised adrenocortical function; this means that the intrinsic activity of the axis could not be thoroughly evaluated. Second, earlier studies that evaluated HPA axis in GC-treatment naïve patients with RA were mainly based on single hormonal parameters without evaluating the functional integrity of the adrenals under circadian regulation or pharmacologic stimulation.

Another issue concerning HPA axis assessment in RA is the circadian fluctuation of endogenous cortisol secretion. In RA, the circadian rhythms impact on immune cellular functions, including synthesis and release of pro-inflammatory cytokines and chemokines, which are peaking at late night-early morning, driving the early morning clinical joint symptoms that characterize RA patients. In line with the disproportion principle, however, the nocturnal hyperactivation of the immune system in RA is not followed by the anticipated increase in the amplitude of the circadian rhythm of the anti-inflammatory endogenous cortisol. In fact, it has been shown that the circadian rhythm of serum cortisol is similar in healthy controls and in RA patients. In contrast, serum concentrations of IL-6 are almost 10 times higher in RA, and the circadian rhythm is different in RA patients from that of controls.

As a result, this relatively reduced—for the level of circulating pro-inflammatory cytokines secretion—cortisol levels may allow the onset of RA to occur and contribute to the progression of the disease.

Treatment with GC remains an important part in the management of RA despite the use of much more effective and disease-specific medications, such as csDMARDs and biologic agents. Future research on neuroendocrine-immune relations in RA is needed to determine whether a compromised adrenocortical function pre-exists or subsequently develops and to define the role of exogenous GC administration and/or intrinsic adrenocortical function in the management and long-term remission of such patients. In addition, emerging evidence has shown that assessment of HPA axis activity in RA patients cannot be performed without considering the concentration of circulating cytokines, the disease state, the stress degree of the patient and the basal and stimulated response of the HPA axis. Activation of the immune system with increased cytokine and chemokine production and immune cell alterations occur very early in RA development. Whether subtle changes in the HPA axis are part of these very early processes of RA development and whether these processes are reversible remains to be elucidated. Future prospective cohort studies that would assess the adrenocortical function in early RA GC-treatment naïve patients (or even in pre-RA patients) at their 1st visit and during the progression of the disease are urgently needed. Assessment of adrenocortical function must now reflect a holistic approach with the aid of all the currently available methods, including (a) morning and diurnal variation of salivary cortisol and DHEA; (b) estimation of adrenocortical functional reserve through endogenous or exogenous provocative stimulation of the HPA axis (exercise stress test, CRH and ACTH tests, etc); and (c) assessment of time-integrated long-term cortisol secretion by measuring hair cortisol.

Given the advanced research of the last decades in the field of steroid assessments, a combination of novel methods (using human saliva or hair) and techniques (eg LC-MS/MS) is anticipated to give a greater insight in the critical but not yet delineated interaction between RA pathophysiology and adrenocortical function.

5 | CONCLUSIONS

Current knowledge implicates the potential role of a compromised adrenocortical function in the pathogenesis and progression of immune-mediated and inflammatory diseases, such as RA. It remains to be elucidated whether this pre-exists disease onset in predisposed individuals or is related to a suppressive effect of certain inflammatory cytokines on adrenocortical function and/or stress-induced functional alterations. It is also possible that this may represent a combination of events, where a defective HPA axis is unable to produce adequate cortisol levels to downregulate the initial inflammatory trigger, thus permitting the overproduction of pro-inflammatory mediators that further suppress adrenocortical reserve to a critical point, beyond which clinically overt RA ensues.

While these possibilities are not mutually exclusive, they could operate at different levels in predisposed individuals, ultimately developing a chronic inflammatory disease with a common phenotype such as RA. Regardless of the possible underlying molecular mechanisms, it is imperative to readily recognize an underlying compromised adrenocortical function in patients with RA and its potential implications. It is expected that new methods of adrenocortical assessment will help obtaining a more accurate, mechanistic insight into the role of adrenal function in the pathogenesis and progression of RA.

CONFLICT OF INTEREST

None.

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