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Circadian Rhythms and Arthritis

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Circadian (about 24 hours) rhythms exist at all levels of organization in the human body. For example, there are circadian rhythms in sleep and activity patterns, plasma cortisol levels, cytokine production, and body temperature.

It is well-known that some clinical signs and symptoms of rheumatoid arthritis (RA) vary within a day and between days; the morning stiffness that is observed in patients who have RA has become one of the diagnostic criteria of the disease (Fig. 1) [1]. The intensity of pain varies as a function of the hour of the day; pain is greater after awakening in the morning than in the afternoon or evening [2].

Circadian changes also are observed in joint swelling and finger circumference. The circadian pattern of joint stiffness of a patient who has RA is in phase with the circadian rhythm of pain. These rhythms differ inversely by approximately 12 hours from the circadian changes of left- and right-hand grip strength. Greater grip strength was demonstrated when joint circumferences and the subjective ratings of stiffness and pain were least and vice versa [3].

Sex hormones also seem to be involved in circadian rhythms of RA symptoms. Increased pain intensity and sleep disturbances are observed during the luteal phase in patients who have when estrogen and progesterone levels would be higher than during the follicular phase [4]. These rhythms are driven

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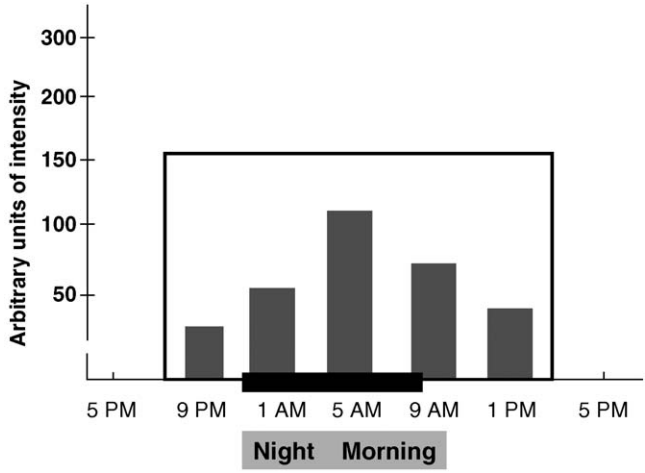

Fig. 1. Clinical signs and symptoms of articular inflammation in patients who have RA vary consistently as a function of the hour of the day. Pain and joint stiffness are greater awakening in the morning than in the afternoon or evening (*x-axis, wide black line*).

by biologic clocks and are endogenous in origin which suggest that clinical signs and symptoms in RA follow a biologic clock.

Biologic rhythms in experimental inflammation

Biologic rhythms have been observed with different animal models of inflammation. In one study, maximal inflammation occurred during the activity period of the animals (ie, between midnight and 8 AM) [4]. In humans, maximal activity was preawakening (see Fig. 1).

Biologic rhythms with a periodicity longer than 24 hours also have been detected in a rodent model. A circaseptan rhythm (almost 7 days) of paw edema, over a period of 30 days, was observed with peak inflammation every 6 to 7 days [5].

Furthermore, circannual variations have been identified in different models of inflammation and showed that maximal articular edema was significantly greater in spring and was lowest in winter [6]. A time-dependent change of blood flow to the inflammatory site also could explain the circadian variations in experimental edema and data in rats showed that the blood flow was greater in the night and lesser in the morning [2].

The mechanisms of the time-dependent variations of the inflammatory reaction are complex and include several systems of mediators (eg, histamine, bradykinin, prostaglandins, and mainly, pro- and anti-inflammatory cytokine production). The circadian changes in the metabolism or secretion of endogenous corticosteroids is certainly responsible, in part, for the time-dependent changes

that are observed in the inflammatory response. This assumption is supported by the fact that adrenalectomy abolished the circadian variation in the rate of formation of experimental edema and that this pattern was restored by hydrocortisone administration [7].

Other data indicate that the inflammatory response, produced by different agents, was in phase opposition with the corticosterone rhythm; less edema was observed when the plasma corticosterone levels were higher and vice versa [4,6]. More recently, melatonin (mLT), another circadian hormone that is the secretory product of the pineal gland, has been implicated in the time-dependent inflammatory reaction with effects that are opposite to those of cortisol [8].

In several species, pinealectomy—or any other experimental procedure that inhibits mLT synthesis and secretion–induces a state of immunodepression that is counteracted by mLT replacement [9–11]. In general, mLT displays an immunoenhancing effect [12]. mLT is able to activate T lymphocytes, monocytes, natural killer cells, neutrophils, and antibody-dependent cellular cytotoxicity and enhances antibody responses in vivo [10]. In animal models, humans, and in vitro experiments, mLT enhances inflammatory cytokine and nitric oxide (NO) production [13,14].

Cortisol and melatonin regulate circadian cytokine production

In adult primates, only visible light (400–700 nm) is perceived by the retina. This photic energy is transduced and delivered to the visual cortex and—by an alternative pathway—to the suprachiasmatic nucleus and then to the hypothalamic region that directs circadian rhythm. Visible light exposure also modulates the pituitary and pineal glands and leads to neuroendocrine changes. mLT, norepinephrine, and acetylcholine decrease with light activation, whereas cortisol, serotonin, γ-aminobutyric acid, and dopamine levels increase [15].

Ocular light appears to be the predominant time cue and major determinant of circadian rhythm for many neurohormones. Cortisol and mLT show an opposite response to light. The increasing light conditions in the early morning have a strong impact on the morning cortisol peak, whereas mLT is synthesized in a strictly nocturnal pattern. Direct inhibitory effects of light on pineal activity may contribute to phasing of the onset and termination of mLT production [9,16].

Recently, in healthy humans, a diurnal rhythmicity was found between cellular (T-helper lymphocyte 1 [Th1] type) or humoral (Th2 type) immune responses and related to immunomodulatory actions of cortisol and melatonin (Fig. 2) [17].

Specifically, lipopolysaccharide (LPS)- or tetanus-stimulated human whole blood interferon (IFN)-γ (type 1) and interleukin (IL)-10 (type 2) production, and the IFN-γ:IL-10 ratio exhibited significant diurnal rhythmicity. The IFN-γ:IL-10 ratio peaked during the early morning and correlated positively with plasma mLT, but negatively with plasma cortisol. IFN-γ, and to a lesser extent, IL-10 production were sensitive to inhibition by exogenous cortisone. The IFN-γ:IL-10

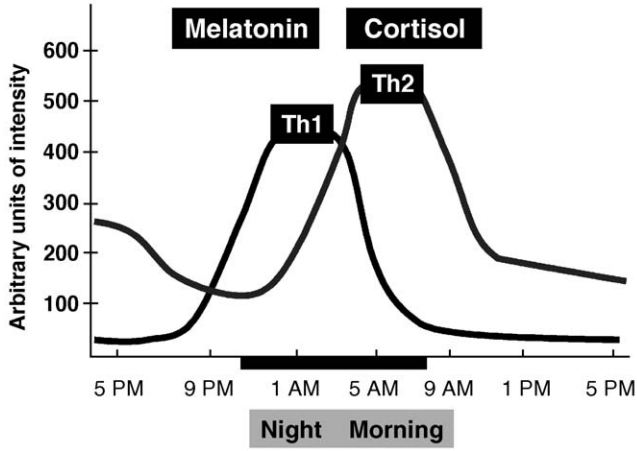

Fig. 2. The diurnal rhythmicity in healthy humans between cellular (Th1 type) or humoral (Th2 type) immune responses and its relation to immunomodulatory actions of cortisol and mLT. The wide black bar on the x-axis represents the period of pain and stiffness in RA patients.

ratio decreased by more than 70% after the administration of oral cortisone acetate (25 mg). These findings support the concept that plasma cortisol, and possibly, melatonin, regulate diurnal variation in the IFN-γ:IL-10 ratio. Because IFN-γ and IL-10 have opposing effects on cellular (type 1) immunity, changes in their balance would be anticipated to impose diurnal rhythmicity on cellular immunity.

In normal subjects, mLT peaks at approximately 3 AM, whereas cortisol peaks at approximately 9 AM [18]. IL-1, IL-6, and soluble IL-2 receptors peak between 1 AM and 4 AM and are decreased throughout the day [17].

mLT stimulates IL-1 and IFN-γ production by human monocytes and serum IL-2 increases during the night, concomitantly with the mLT increase. Also, mLT seems to enhance IL-2 immunomodulating effects [19–22]. mLT increases the production of IL-12 and NO by human synovial macrophages, enhances IL-2, IL-6, and IFN-γ production by human circulating $CD4^+$ lymphocytes, and up-regulates the level of gene expression of tumor necrosis factor (TNF)-α and macrophage-colony stimulating factor [14,23,24]. To the contrary, cortisol was correlated negatively with the IFN-γ:IL-10 ratio and cortisone administration markedly reduced the ratio with a clear causal relationship [17].

Besides IFN-γ and IL-1, TNF-α and IL-12 also exhibit distinct diurnal rhythms that peak in the early morning and are related inversely to the plasma cortisol rhythm [25]. Because IFN-γ and IL-10 might be considered to be markers of cellular (type 1) and humoral (type 2) immunity, respectively, these studies suggest a bias toward increased cellular immunity during the night and the early morning (peak of mLT) when the IFN-γ:IL-10 ratio is high. Conversely, a relative bias toward increased humoral (type 2) immunity is suggested during the day (see Fig. 2) [26].

Cortisol correlations with circadian rhythms in rheumatoid arthritis

The inflammatory cytokines (eg, IL-6, IL-1, TNF-α), as soluble products of the activated immune system, stimulate the production of corticotropin-releasing hormone (CRH) in the hypothalamus: CRH release leads to pituitary production of corticotropin, followed by glucocorticoid secretion by the adrenal cortex [27,28]. These components constitute the hypothalamic–pituitary–adrenocortical (HPA) axis.

Recently, intact corticotropin secretion, but impaired cortisol response in patients who had active RA, was described. This observation was consistent with a relative adrenal glucocorticoid insufficiency; the latter had been suggested 40 years earlier [29,30]. Increased HPA axis function is a normal response to the stress of inflammation and might be mediated by central and peripheral actions of circulating cytokines.

Besides IL-1 and TNF-α, IL-6 seems to be a major cytokine that mediates interactions between the activated immune system and the anterior pituitary cells and adrenal steroidogenesis. Recent studies in patients who had RA, however, showed that overall activity of the HPA axis remained inappropriately normal (or relatively low) and apparently was insufficient to inhibit on-going inflammation, at least in patients who had early, untreated arthritis [31,32].

In particular, in early morning hours, an earlier surge of plasma corticotropin and cortisol was observed in patients who had RA; significantly increased IL-6 levels and a pronounced circadian variation of plasma levels were detected when compared with healthy subjects (Fig. 3) [33]. In addition, a positive temporal correlation was found between plasma IL-6 levels and the corticotropin:cortisol ratio; elevated levels of IL-6, 1 and 2 hours, respectively, before the elevations of corticotropin and cortisol was found in patients who had RA [33]. In the same patients, a negative correlation of cortisol and IL-6 was found with a delay of 5 hours which indicated that the HPA function in RA apparently is insufficient to inhibit ongoing inflammation.

Another study showed a significantly altered secretion of adrenal androgens (AAs) in glucocorticoid-naive premenopausal patients who had RA [34]. Decreased plasma levels of the AAs—dehydroepiandrosterone (DHEA) and its sulfate metabolite—were found. Also, these levels were correlated significantly with decreased early morning cortisol concentrations and increased basal levels of IL-6 in patients who had RA [34].

Early morning IL-6 peak values were greater in patients who had RA than in controls, and correlated significantly to morning C-reactive protein (CRP) levels and the Ritchie's index [35]. Another observation of reduced DHEA production, combined with normal cortisol production during ovine corticotropin-releasing hormone (oCRH) and corticotropin testing, further supports the concept of adrenal–androgen hypofunction in patients who have active RA [36].

IL-6 had a strong central effect on steroid production and may be one of the factors that controls the long-term adrenal response to stress. This cytokine also is able to act synergistically with corticotropin on the adrenal cells to stimulate

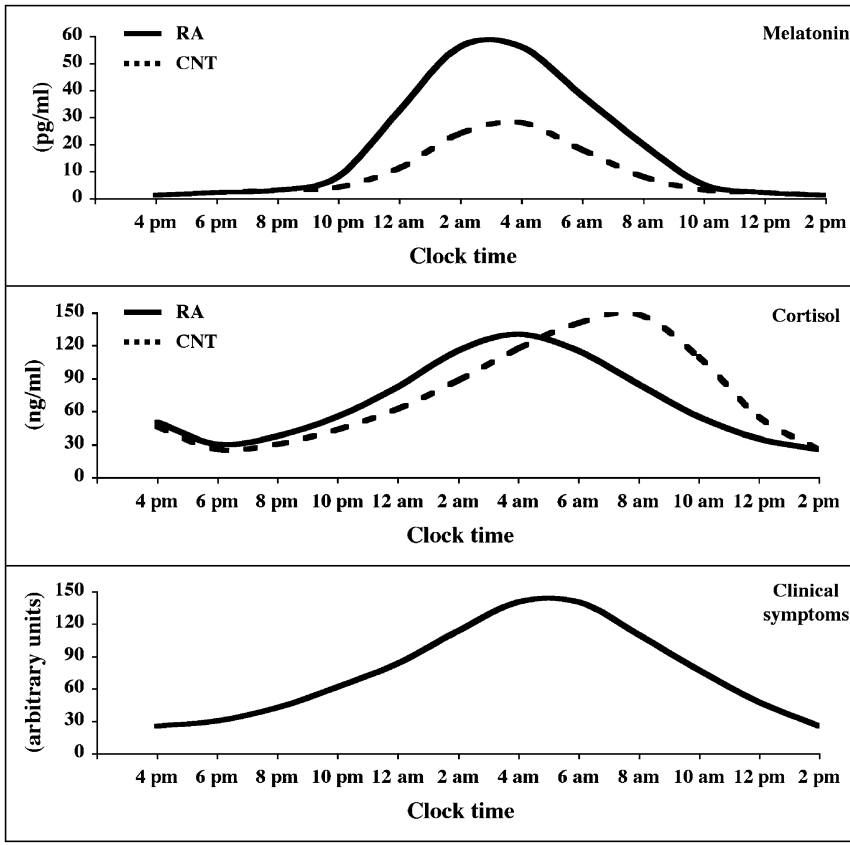

Fig. 3. In both RA patients (*solid line*) and control subjects (CNT, *dashed line, upper panel*), mLT levels progressively increase from 8 PM to the early hours of the morning, but RA patients reach an earlier peak level at 12 AM, at least 3 hours before controls. Cortisol levels (*middle panel*) reach an earlier peak in RA patients than in control subjects but showing slightly lower concentrations.

the release of corticosterone [37,38]. Accordingly, the reduced cortisol and AA secretions that are observed during testing in patients who have RA and are not treated with glucocorticoids may be regarded as "relative adrenal insufficiency" in the setting of a sustained inflammatory process, as shown by increased IL-6 levels [39].

In a recent investigation on salivary cortisol levels in patients who had early RA, afternoon concentrations in patients who had high disease activity did not decrease, as did the cortisol levels in healthy controls or patients who had RA who had low disease activity [39]. These findings and others [40] further indicate that activation of the HPA axis occurs in RA, but is insufficient. The observed, less than required production of cortisol supports the use of low-dosage corticosteroid "replacement therapy" in patients who have RA ([41] and see the article by Masi et al elsewhere in this volume).

Melatonin correlations with circadian rhythms in rheumatoid arthritis

Recent studies evaluated mLT levels in patients who had RA, with a focus upon the analyses of circadian variations [42]. mLT serum levels at 8 PM and 8 AM were significantly greater in patients who had RA than in controls ($P < .05$). The differences were more evident in patients who were older than 60 years.

In patients who had RA and in healthy subjects, mLT levels increased progressively from 8 PM to the early morning hours; however, they reached peak levels at midnight in patients who had RA, which was at least two hours earlier than in controls (see Fig. 3). Subsequently, mLT concentrations in patients who had RA reached a plateau that lasted for 2 to 3 hours; this was not observed in controls. After 2 AM, mLT levels decreased similarly in patients who had RA and in healthy subjects. The study confirmed that the nocturnal rhythm of mLT occurs in patients who have RA, but with an earlier peak level and a longer duration in the early morning [42].

IFN-γ, IL-1, IL-2, IL-6, IL-12, and TNF-α production (Th1 cytokines) reach their peak during the night and early morning, at the same time that mLT serum levels are highest and plasma cortisol is lowest. Accordingly, among the signs of joint inflammation in patients who have RA, the intensity of pain varies as a function of the hour of the day; pain is greater after awakening in the morning than in the afternoon or evening [2,3]. Circadian changes also are observed in joint swelling and finger size in the early morning in patients who have RA [1].

Therefore, mLT could be involved in activating the inflammatory response during the night—at least in RA—which is considered to be a Th1-cytokine–driven immune disease (Fig. 4) [43]. In addition, mLT was found in high

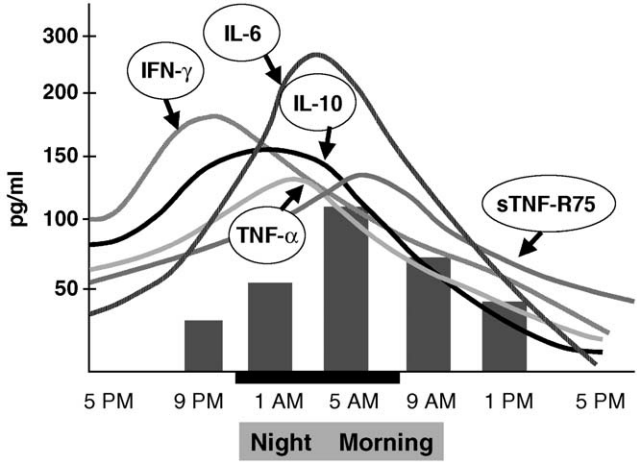

Fig. 4. Circadian clinical symptoms (bar graphs) in relation to cytokine levels, IFN-γ and IL-10. IL-6 and TNF-α production (Th1 cytokines) reach a peak during the night and early morning, at the time when mLT serum levels are highest and plasma cortisol lowest. sTNF-R75, soluble p75 tumor necrosis factor receptor levels increase slightly later.

concentration in synovial fluids from patients who had RA and binding sites for mLT have been detected in synovial macrophages [44,45].

Effects of latitude on circadian rhythms

Recent studies and reviews examined the epidemiologic evidence which suggests that ultraviolet radiation may play a protective role in RA. A gradient of increasing incidence of RA with latitude and seasonal variation also has been reported [46–48].

Therefore, we evaluated serum mLT, cortisol, TNF-α, and IL-6 circadian rhythm in patients who had RA from a northern European country (Estonia). In particular, we compared the mLT and cortisol levels in that group with patients from a southern European country (Italy), to detect a possible influence of different daily winter photoperiods [49]. Patients who had RA from Estonia and Italy were characterized by similar RA disease severity and duration and both were compared with age- and sex-matched healthy controls. Blood samples were obtained at 8 PM, 10 PM, 12 AM, 2 AM, 4 AM, 6 AM, 8 AM, and 3 PM during the months of January and February.

A significantly ($P < .01$) greater mLT concentration and an earlier peaking was observed in Estonian patients who had RA when compared with their age- and sex-matched controls, starting at 10 PM. mLT serum concentrations were

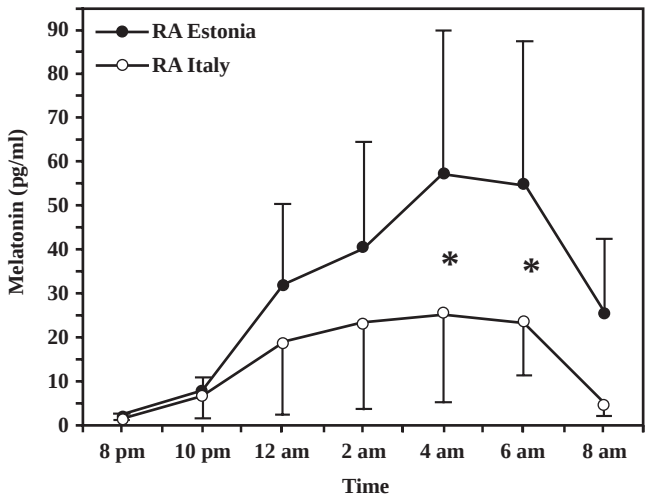

Fig. 5. mLT serum concentrations were found to be significantly higher in Estonian patients who had RA when compared with Italian patients, at midnight, and the difference was even greater over the study duration. Vertical lines represent ± SD; *, $P < 0.05$. (*Data from* Otsa K, Peets T, Maestroni G, et al. Circadian rhythms of melatonin in Estonian rheumatoid arthritis patients. Ann Rheum Dis 2004;63:S139; and Cutolo M, Maestroni GJM, Otsa K, et al. Circadian melatonin and cortisol levels in rheumatoid arthritis patients in winter time: a north and south Europe comparison. Ann Rheum Dis, in press.)

significantly higher in Estonian patients who had RA when compared with Italian patients, at midnight, and the difference was even greater over the study duration (Fig. 5). No significant difference was observed in serum cortisol levels between Estonian patients who had RA and their controls [49,50].

TNF-α serum levels were significantly higher in Estonian patients who had RA when compared with their controls. Significantly higher serum IL-6 and TNF-α concentrations were observed at 10 PM and midnight in Estonian patients who had RA when compared with Italian patients who had RA [49,50].

This study shows, for the first time, that in a northern European country (Estonia), the circadian serum concentrations of mLT and TNF-α are significantly higher than in matched patients who had RA from a southern European country (Italy). In addition, mLT and TNF-α concentrations were increased in patients who had RA. Reduced daily light exposure as observed in northern Europe—at least during the winter—might explain the higher and more prolonged mLT concentrations that were observed in northern patients who had RA. The increased prevalence of autoimmune diseases, such as RA, that is observed in northern Europe also may be related to the increased immunostimulatory effects that are exerted during the night by mLT and to a reduced neuroendocrine stimulation during the light phase of the photoperiod.

Circadian rhythms and timing for therapy

In RA, the circadian rhythm of cortisol and corticotropin are disturbed, particularly in patients who have greater inflammatory activity [51]. The mechanisms of dysregulation are complex, but are believed to result from effects of relative hypocortisolism in this disease [52; see also the article by Masi et al elsewhere in this issue] and increased cytokines.

Diurnal control of the HPA axis is regulated strictly to provide increased glucocorticoid production during the daytime hours in humans and other nonnocturnal animals and increased AA sex hormone precursors at night. In normals, serum levels of proinflammatory cytokines also display diurnal rhythms that peak in the early morning and tend to be related inversely to the rhythms of plasma cortisol [17]. The interaction and relations of serum cortisol and inflammatory cytokine levels are complex. Their relation is believed to be counterregulatory, but the full controlling factors are not well-defined in health or disease [17,33].

Data in humans indicate that elevation of plasma cortisol within the physiologic range—achieved by administration of cortisone acetate 25 mg at 9 PM—markedly suppressed IFN-γ and inflammatory cytokines [17]. The relative ability of cortisol to inhibit production of IL-1β, IL-6, and TNF-α is not established fully. One study of exercise-induced elevation of cortisol suppressed whole blood production of only TNF-α, without effect on IL-1β or IL-6 production [53]. In turn, the relative effects of individual and combined in-

flammatory cytokines on central stimulation of the HPA axis is not defined fully [28].

Normal response to chronic stressors requires appropriate stimulation of the adrenal cortex and maintenance of its appropriate organ size, including its components (ie, the zona glomerulosa [aldosterone synthesis], zona fasciculata [cortisol synthesis], and zona reticularis [AA synthesis]). Hypocortisolism has been reported in various stress-related bodily disorders, with the deficiency attributed mainly to adrenal cortical insufficiency [54]. Some data imply that hypocortisolism may result from stressors in humans and in animal models [54].

The mechanisms that permit normal activation of steroidogenesis and preserve the proper size and growth factor stimuli of the adrenal to maintain its structural integrity are highly complex and incompletely understood [55,56]. Normal adrenocortical responses to stress or inflammatory disease require sufficient corticotropin stimulation of steroidogenesis. In addition, maintenance of its structure requires growth hormones and accessory factors, which are less well understood [55,56].

Experimental studies of adrenocortical cell growth—using the Y1 mouse cell culture model—show that a brief pulse of corticotropin (up to 2 hours) stimulated adrenal cell proliferation, whereas continuous treatment with corticotropin (14 hours) inhibited cell cycle progress at the midpoint of the cell division cycle G1 period [57].

The possible relevance of such dual effects of corticotropin on cell cycle progress may apply to patients who have RA and their altered diurnal pattern of HPA function. Potentially, excessive corticotropin pulsing at night in patients who have RA may tend to inhibit the normal adrenal cell proliferation that is required for maintenance of organ competency, especially under stresses of inflammatory disease. Given the altered status of HPA function in RA, therapy with required glucocorticoids (GCs) should be provided in the optimal dosages and timing to normalize the functional and structural HPA axis dysregulations.

Under normal circumstances, corticotropin maintains the size and function of the adrenal cortex. Too little corticotropin—as would result from chronic pharmacologic administration of GCs—results in adrenal atrophy; increased corticotropin—as occurs in Cushing's disease—results in adrenal hypertrophy. Several studies of patients who had RA and Cushing's disease [58,59] or syndrome [60] demonstrated remission of RA in the setting of hypercortisolism [58] or flare after surgical treatment [59,60]. This indicated the important role of cortisol in suppressing inflammation.

Advantages and disadvantages exist for the particular timing of low daily dosage GCs that are administered as approximately physiologic replacement (ie, up to ~5 mg prednisone in women and up to 7.5 mg in larger men). A single morning dosing tends to induce less suppression of the normal diurnal corticotropin pulsing which peaks in the early morning before awakening (see Figs. 2 and 3) [61]. Conversely, evening and bedtime dosing may provide greater benefits in suppressing nocturnal peaks in proinflammatory cytokines [25,62] as well as improved symptomatic results (eg, better quality sleep) and decreased

joint stiffness and pain on awakening [63]. A single morning administration of GCs may be less inhibitory of pituitary function than split doses; however, critical studies have not been performed with such therapy in the near physiologic range [63].

One study described 12 patients who had RA who took a mean dosage of prednisolone, 5.6 mg daily, for 4 weeks as single doses at 1 AM, 8 AM, or 11 PM in a double-blind, within-patient control trial [64]. Similar effects on circadian rhythms of finger joint swelling, grip strength, and other objective assessments were found with all regimens. The investigators suggested that a single, morning-only regimen of prednisolone is reasonable because adrenopituitary suppression should be minimized [64].

The conventional indication for the use of low-dosage steroids in the treatment of RA is the amelioration of unacceptable morning stiffness that is unresponsive to other standard clinical measures [63]. A double-blind, cross-over study of the effect of timing (morning versus night) of low-dosage (mean 5.8 mg) prednisolone was performed in 41 patients who had RA. Two 1-month long sequences of active drug versus identical placebo tablets were assigned randomly; the active drug was administered on retiring (10 PM to 11 PM) or arising (6 AM to 7 AM), with subsequent cross-over to the alternate administration [63]. Significantly ($P = .0001$) less morning stiffness was observed with night administration and patients preferred ($P < .05$) the night therapy [63].

Another low-dosage prednisolone study provided rationale for a 2 AM dosing being the most effective means of suppressing diurnal peaking of IL-6 concentrations [62]. The short interval of 4 days of therapy and the temporal design of the study did not control strictly for the interval between GC dosing and assays of the outcome variables which limited the reliability of the results [61].

A recent study compared treatment of 30 patients who had active RA with prednisolone, 7.5 mg, that was administered at 2 AM or at 7:30 AM. Over the course of 6 months, significant clinical and laboratory improvements were observed in each group of 15 patients, beginning from the first month. Administration of the medication in the morning or at night did not affect the favorable results of the treatment. These investigators recommended that new studies should investigate the best timing of administration as well as optimal doses of glucocorticoids that are needed in RA patients, according to their levels of endogenous cortisol, corticotropin, and HPA axis function, and different circadian rhythms [65].

In our clinical experience, a subgroup of patients who has RA presents with a preponderance of nonarticular rheumatic symptomatology—that is analogous to polymyalgia rheumatica—rather than mainly having inflammatory joint manifestations. In such patients, low-dosage GC therapy is effective in relieving the fibromuscular manifestations [63]. The timing of our GC administration also is influenced by the patient's described patterns of symptomatology and quality of sleep. For example, more often, patients who have poor sleep that is due to generalized night pain and greater symptomatology in the mornings are administered the GC at night. Conversely, patients who describe increased pain

during their active daytime functions, with lessening in the evenings on resting, usually are prescribed GC on first arising. At times, a split-dosage is administered. Patients are advised to be aware of how the alternative administrations affect their symptomatology. With close physician–patient interaction, favorable dosages and timing of GCs usually are achieved.

Further examples of biologic rhythms

In healthy women, increased sensitivity to experimentally-induced ischemic pain has been reported in the luteal phase [67,68]. Therefore, sex hormone fluctuations also seem to be involved in circadian rhythms of RA symptoms. Increased pain intensity and sleep disturbances are observed during the luteal phase in patients who have RA; estrogen and progesterone levels would be higher than during the follicular phase [4].

In addition, circadian rhythms of pain, stiffness, and dexterity recently were described for hand osteoarthritis (OA) [69]. Assuming that these findings are generalized to the overall population that has hand OA, there are important implications for scheduling activities of daily living, for measurements in clinical trials, and possibly for the time at which antirheumatic drugs are given [2,62–64,66].

Summary

Altered functioning of the HPA axis and of the pineal gland seem to be important factors in the perpetuation and clinical circadian symptoms of RA [50]. The clinical symptoms of RA show a circadian variation; joint stiffness and pain are more prominent in the early morning. Consistently, human proinflammatory Th1 type cytokine production exhibits a diurnal rhythmicity with peak levels during the night and early morning, at a time when plasma cortisol is lowest and mLT is highest.

An inappropriately decreased secretion of cortisol is a typical feature of the inflammatory disease in patients who have RA. Conversely, the nocturnal rhythm of mLT in patients who have RA shows an earlier peak level and a longer duration in the early morning compared with normal subjects. An imbalance between the anti-inflammatory effects of cortisol and the proinflammatory effects of mLT during the night seems evident in patients who have RA. This imbalance might play an important pathogenetic role in RA and may drive the circadian rhythm of the clinical symptoms (ie, morning stiffness and pain).

The modulation of clinical symptoms in RA, including anti-inflammatory efficacy, that is exerted by low-dosage corticosteroid ‘‘replacement’’ therapy seems to support the importance of counterregulatory mechanisms. Inhibitors of mLT synthesis or mLT antagonists might be considered in the future as having possible therapeutic value, at least in severe cases of RA.

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