Review

# More Night Than Day — Circadian Rhythms in Polymyalgia Rheumatica and Ankylosing Spondylitis

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***ABSTRACT.*** The circadian rhythm of symptoms in patients with chronic inflammatory diseases is well known. Circadian rhythms could be used to identify targets for time-adapted antiinflammatory therapies, which are administered prior to the flare of cytokine synthesis and inflammatory activity. In recent years, the diurnal variations in rheumatoid arthritis have been described precisely for pain, stiffness, and functional disability, as well as the underlying cyclic variations in hormone levels and cytokine concentrations. This review summarizes the current knowledge on circadian rhythms in other rheumatic diseases, focusing on polymyalgia rheumatica and ankylosing spondylitis. (J Rheumatol First Release April 1 2010; doi:10.3899/jrheum.091283)

*Key Indexing Terms:*
CIRCADIAN RHYTHM POLYMYALGIA RHEUMATICA RHEUMATIC DISEASES
GLUCOCORTICOIDS ANKYLOSING SPONDYLITIS DELAYED-ACTION PREPARATIONS

It is well known that symptoms of chronic inflammatory diseases follow typical circadian rhythms. For example, allergic rhinitis and bronchial asthma are both medical conditions that are primarily nocturnal[1,2]. The major symptoms of rheumatic diseases (pain, stiffness, heat, swelling, and other clinical signs of inflammation) also vary with the time of day[3]. Symptoms of rheumatoid arthritis (RA) such as pain and stiffness are typically most prominent during the early morning hours. In the 1970s it became clear that the 24-hour daily cycle is controlled by a central circadian oscillator located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN targets many different neuroendocrine systems, leading to well regulated cell and organ activities in the periphery[4]. In recent years the diurnal variations in RA have been described precisely (Figure 1)[5] for pain, stiffness, and functional disability, as well as the underlying cyclic variations in hormone levels (cortisol, melatonin, and prolactin) and cytokine concentrations [tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6)]. Observation of the typical undulation of clinical symptoms with a maximum in the early morning hours led to the hypothesis that the best time to apply immunosuppressive therapy is during the turning-on phase of a proinflammatory response (not in the turning-off phase; Figure 2)[5,6]. This is experimentally supported by a study in rats in which splenic TNF secretion, induced by lipopolysaccharide, could be inhibited only if the immunosuppressive agent (released sympathetic neurotransmitters) were administered at an early time (i.e., as TNF release was increasing)[7].

Knowledge about circadian rhythms of rheumatic diseases could be used to identify targets for time-adapted antiinflammatory therapies that are administered prior to the flare of cytokine synthesis and inflammatory activity. Indeed, a recent study was able to demonstrate that a newly developed time-release prednisone, which exerts its full effect between 2 and 3 A.M., led to a significant decrease in morning stiffness in patients with RA[8]. Optimal timing of therapy might improve therapeutic benefits and reduce risks of treatments. This therapeutic approach may be applicable to chronic diseases with a circadian pattern of symptoms. First, suitable diseases for such treatment must be identified. This review summarizes current knowledge on circadian rhythms in various rheumatic diseases. We focus on polymyalgia rheumatica (PMR) and ankylosing spondylitis (AS) and present selected findings for other rheumatic diseases.

## MATERIALS AND METHODS

We searched the literature to determine the current evidence for the presence of circadian rhythms in rheumatic diseases other than RA. We looked for papers published up to March 2008 in Medline and/or PubMed

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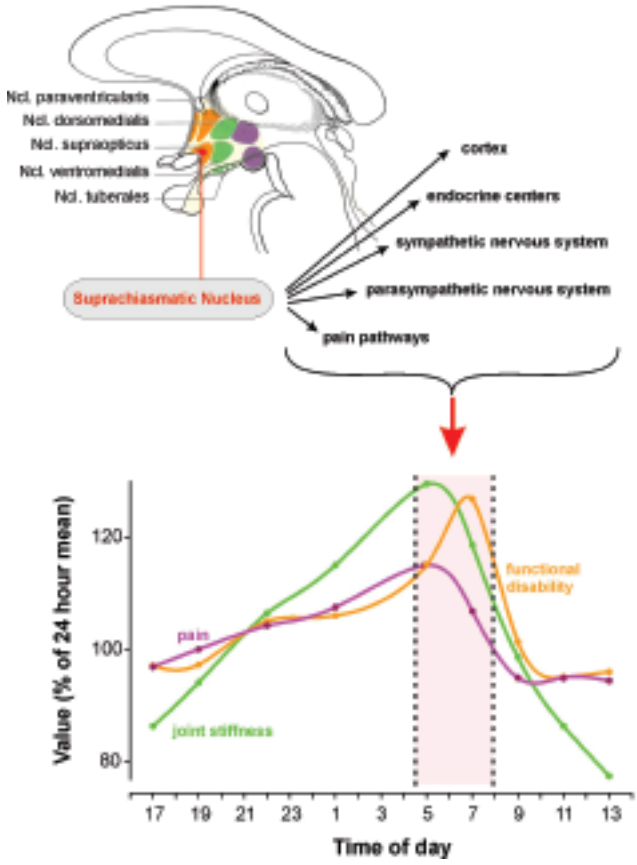


*Figure 1*. Generation of the circadian rhythm and its effect on clinical symptoms in patients with rheumatoid arthritis. The circadian rhythm is generated in the suprachiasmatic nucleus of the hypothalamus. This nucleus has many connections to other centers in the brain. The circadian activity of this particular nucleus is transferred to the immune and another peripheral system leading to typical undulation of clinical symptoms with a maximum in the early morning hours (pink area). Figure modified from Straub RH, *et al*[5], Arthritis Rheum 2007;56:399-408.

(National Center for Biotechnology Information, National Institutes of Health; 1950 to March 2008), as well as in BIOSIS Previews (1969–2004), BIOSIS Previews Archive (1926–1968), Biological Abstracts (1969–2004), Biological Abstracts Archive (1926–1968), and Embase (1989 to November 2007). Only papers in English or German were reviewed. The search strategy included the keywords circadian, rhythm, or variations combined with the keywords polymyalgia rheumatica, giant cell arteritis, vasculitis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), scleroderma, or rheumatic diseases. Brief meeting reports were also acquired and reviewed but not reported in this review. We also screened the journals *Biological Rhythm Research* (1996 to February 2008), *Chronobiology International* (January 1984 to February 2008), and the *Journal of Circadian Rhythms* (January 2003 to February 2008) for available literature on rheumatic and inflammatory diseases. The primary aim was to locate clinical studies that systematically investigated the circadian kinetics of pain, stiffness, functional disability, immunologic measurements, and hormones. Moreover, if no systematic investigations were found, we screened the literature for trials related to certain timepoints. We took into account whether a circadian rhythm is indicated in common disease descriptions as well as diagnosis, classification, or response criteria.

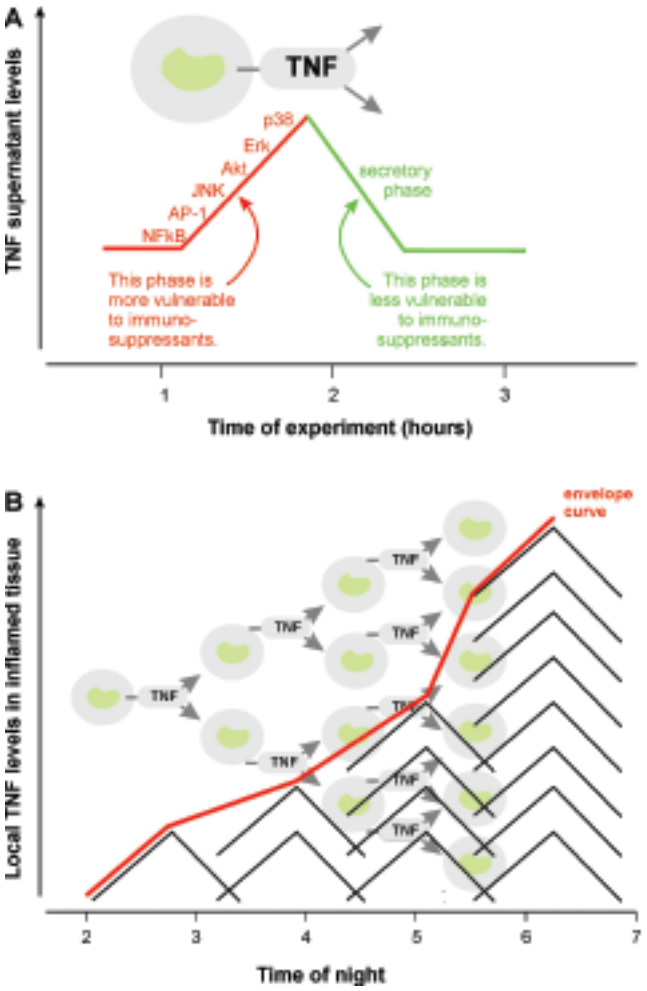


*Figure 2*. Time-dependent effect of immunosuppressants relative to induction of cytokine secretion. A. Release of tumor necrosis factor-α (TNF) from a single cell. TNF is rapidly induced by the activation of signaling factors, which occurs within minutes and can be further modulated through phosphorylation by mitogen-activated protein kinases such as p38, c-Jun N-terminal kinase, extracellular signal-regulated kinase, or by the serine/threonine kinase AKT[6]. This turning-on phase of an inflammatory event is tightly regulated and vulnerable to immunosuppressants. This immunosuppressant influence is less pronounced in the secretory turning-off phase[7]. B. Combined effect of many single cells. Since cytokines such as TNF can stimulate their own release (the TNF promoter itself contains nuclear factor-κB and activator protein 1 binding sites and is subject to positive autoregulation)[6], a cumulative effect leads to a steady increase in TNF from many cells. TNF stimulates interleukin 6 (IL-6), and IL-6 is often the indicator of prior TNF secretion. An increase of tissue TNF and in particular of IL-6 leads to spillover of these cytokines into the circulation (where they can be measured). Thus, we hypothesize that the entire increase of TNF is regulated mainly during the turning-on phase of TNF induction. TNF itself stimulates anti-TNF effects, and these lead to down-regulation of its secretion (e.g., cortisol in the morning and many others).

## RESULTS

*Circadian rhythms in PMR*. PMR is the most common inflammatory rheumatic disease of the elderly and represents a frequent indication for longterm glucocorticoid therapy[9,10]. Symptoms are aching and morning stiffness in the cervical

region as well as in the shoulder and pelvic girdles[11]. Glucocorticoids are the drugs of choice for treating PMR because patients usually respond rapidly to low and medium doses[11]. A circadian rhythm seems to be obvious, as descriptions of the disease emphasize the nighttime and morning symptoms. Barber, who in 1957 proposed the use of the term "polymyalgia rheumatica," wrote: "Sleep was much disturbed by pain and all complained of lassitude and depression. A few patients mentioned some degree of morning stiffness apparently similar to that found in rheumatoid disease"[12]. Also, Hart, *et al* described in a review about pain at night that "in polymyalgia rheumatica, night and morning symptoms are characteristic"[13]. All current diagnostic criteria for PMR include the daytime specific core symptom "morning stiffness with a duration of more than 1 hour"[14-17]. Further, in the "consensus process to identify potential classification criteria for PMR," a panel of experts identified "morning stiffness with a duration of more than 45 minutes" as one of 10 core criteria of PMR[18]. Morning stiffness is one of 5 items of the proposed core set of the European League Against Rheumatism response criteria for PMR[19]. The PMR activity score (PMR-AS) is based on 5 variables including morning stiffness[20].

Thus, nighttime pain and morning stiffness are obviously and generally accepted core symptoms of PMR. To our knowledge, no systematic investigations of the 24-hour variation of pain, morning stiffness, and/or functional disability in PMR have been published. Typical values for pain evaluation on a 0–100 mm visual analog scale in patients with untreated PMR vary between 62 and 74 mm; typical values for morning stiffness duration are between 60 and 120 min, but all measurements refer to only 1 timepoint/period during the day[19,21,22]. At least 1 study worked out that questions in the Health Assessment Questionnaire on morning activities (rising, dressing, grooming, and eating) were more responsive to change by treatment than questions about day activities (walking, hygiene, reach, grip, and activities), presumably reflecting the contribution of early morning stiffness to the patients' disabilities[22].

PMR has been suggested to be a hypothalamic-pituitary-adrenal (HPA) axis-driven disease because of a lack of an adequate HPA axis response[23]. Serum cortisol levels are assumed to be inappropriately low in relation to the proinflammatory status, as illustrated by increased levels of IL-6, for example[5,24-28]. There are also conflicting results supporting the hypothesis that abnormalities in the HPA axis are the consequence of chronic illness rather than a pathogenetic factor[29]. In patients with RA, it has been demonstrated that the circadian rhythm of endogenous cortisol secretion is similar to that of healthy subjects, but serum levels of IL-6 are 10 times higher[5]. The phenomenon has been described as an inadequate cortisol secretion in relation to inflammation. The situation might be similar in PMR, but most of the studies dealing with cytokines and hormones in PMR gathered respective data for only 1 time of day. In these studies the exact time of blood withdrawal was not mentioned[25-27,30,31] or was described only as "in the morning"[32,33], or the venipuncture took place within 1 defined time period in the early or late morning hours, i.e., 8–9 A.M.[34], 8–10 A.M.[35], 9 A.M.–noon[36], or 10 A.M.–noon[24,37]. Figure 3 illustrates the data extracted from the few studies that mention a defined time period[24,34-37]. Interestingly, for TNF-α, the 1 study that found increased levels in comparison to healthy controls referred to earlier morning hours (8–9 A.M.)[34], while the studies that found similar values gathered respective data during the later morning hours (9 A.M.–noon; Figure 3A)[36,37]. IL-6 levels in studies done at earlier morning hours[34] were by trend higher than comparable levels in studies done at later morning hours[24,36,37] (Figure 3B). With regard to cortisol levels, a statistically significant difference between patients and healthy controls was not found in any of the studies involving 1 timepoint, and we could not see a difference between earlier and later morning hours[24,34,35,37] (Figure 3C). These results might indicate a circadian variation of TNF-α and IL-6 secretion in PMR with peak values in the early morning hours, but exact data are still missing.

One of the few kinetics in the literature regarding IL-6 in polymyalgia rheumatica/giant cell arteritis was provided by Roche, *et al*, who showed a 24-hour kinetic of plasma levels of IL-6 following a single oral dose of prednisone (60 mg) in 2 patients with giant cell arteritis, a clinical syndrome closely related to PMR[26]. Roche found that IL-6 concentrations decreased abruptly, but showed a rebound toward pretreatment concentrations before the next dose of prednisone was given 24 hours later, i.e., during the night. When glucocorticoid therapy was withdrawn short-term, the rebound of IL-6 was paralleled by the reappearance of clinical symptoms[26]. This might indicate that a time-adapted glucocorticoid therapy that is administered prior to the flare of cytokine synthesis and inflammatory activity could be more effective than administration in the morning. To our knowledge, more detailed circadian courses of cytokine and hormone secretion in patients with PMR have not yet been thoroughly determined.

*Circadian rhythms in AS*. AS is characterized by inflammatory back pain (IBP) and stiffness. Nonsteroidal antiinflammatory drugs and anti-TNF therapies are used to treat AS, while glucocorticoids are mainly used for local therapy (and only occasionally for systemic pulse therapy), because low-dose systemic therapy is considered to be less effective (although controlled studies are lacking)[38].

One of the first precise clinical descriptions of IBP dates to the report by Hart, *et al*, in 1949[39,40]. Hart wrote, "Waking in the morning stiff and in pain, the patient gradually became more supple during the day, feeling at his best from the afternoon until bedtime. Another woke himself up every two hours throughout the night to exercise his spine as otherwise he suffered unduly in the morning"[39]. In the survey about pain at night, Hart wrote later that "for patients

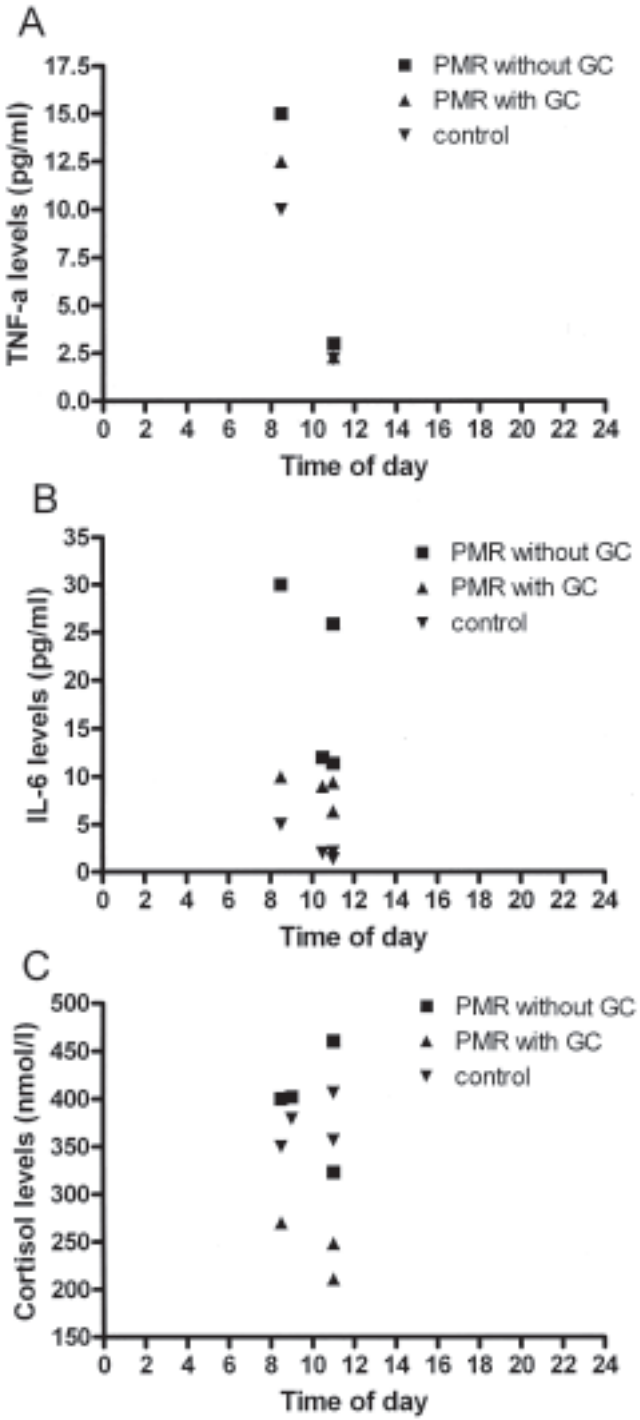


*Figure 3*. "Circadian rhythm" of levels of tumor necrosis factor-α (A)[34,37], interleukin 6 (B)[24,34,36,37], and cortisol (C)[24,34,35,37] in patients with polymyalgia rheumatica (PMR) and healthy controls. Data are shown differentially for healthy controls, for patients with PMR without previous glucocorticoid treatment, and for patients with PMR who have had glucocorticoid treatment.

with AS the night, and early morning in particular, may be the worst time in the 24 hours"[13]. Morning stiffness belongs to the 5 diagnostic criteria of IBP introduced by Calin, *et al*[41]. Two of 4 of the new classification and diagnostic criteria for IBP proposed in 2006 are circadian symptoms: "Morning stiffness of more than 30 minutes duration" and "Awakening because of back pain during the second half of the night only"[40]. The new "Evidence-based recommendations for the management of AS" of the 3E Initiative mention "Back pain at night" and "Morning stiffness" as features of IBP[42]. Two of the 6 questions in the Bath Ankylosing Spondylitis Disease Activity Index refer to the severity of morning stiffness in intensity and duration[43]. In addition, the generally accepted Assessments in Ankylosing Spondylitis response criteria include the symptom "morning stiffness"[44].

Only a few systematic circadian investigations exist in AS. We found 1 larger study that displays a rough plot of the circadian variation of pain and vertebral stiffness in 39 patients, showing for both these measurements a 12-hour rhythm with a peak between 6 and 9 A.M. and a second peak between 6 and 9 P.M.[45]. Another small study of 11 patients depicts a similar graph[46].

There is 1 study that noted the circadian variation of acute-phase response measurements (erythrocyte sedimentation rate, leukocyte count, fibrinogen) and temperature in patients with AS and patients with fever[47]. The informative value is limited because the measurements were done at only 3 times during the day (7 A.M., 3 P.M., and 11 P.M.). The measurements do not seem to be related to pain and stiffness, because at 7 A.M. (when pain and stiffness ought to be high), the lowest values of acute-phase measurements and temperature were recorded. Temperature was highest at 11 P.M. and acute-phase measurements at 3 P.M. The same study found no difference in cortisol levels between patients with AS and controls, with a minimum of cortisol levels at 11 P.M.

Another study investigated the circadian rhythm of bone metabolism measurements and cortisol levels in patients with AS[48], showing a circadian variation of the levels of osteocalcin (peak 4 A.M.), bone-specific alkaline phosphatase (bAP; peak 6 A.M.), and cortisol (peak 6–8 A.M.); there were no significant differences between patients with AS and controls. It is not clear whether this is due to low disease activity. The observation that the peak of osteocalcin and bAP precedes the cortisol peak could be interesting because cortisol appears to have an inhibitory effect on bone resorption in organ culture[49]. In contrast with findings in other inflammatory diseases such as RA and PMR, the present data indicate that there is no apparent abnormality of the HPA axis activity in AS[50,51]. This also might explain to some extent the respective lesser efficacy of glucocorticoids in seronegative spondyloarthropathies, in contrast to the outstanding therapeutic efficacy of glucocorticoids in PMR. Altogether, there is some evidence for circadian rhythms in AS, but the data are not yet appropriate to presume a well regulated relation.

*Circadian rhythms in other rheumatic diseases*. For other rheumatic diseases, such as primary Sjögren's syndrome

(SS), SSc, SLE, polymyositis, or vasculitis, only scattered information is available.

There are studies of the circadian variation of clinical measurements, such as sleep disturbances in SS[52] or fatigue in SS and SLE[53]. Regarding cytokine levels, 1 study found no circadian variation of IL-6 and TNF-α levels in patients with connective tissue diseases, in contrast to patients with RA[54]. There are almost no studies of the circadian pattern of immune cell populations in rheumatic diseases, for example of natural killer cells[55]. Single observations describe circadian variations of other immunologic measurements such as immune complexes or neutrophils in SLE as well as myoglobin levels in polymyositis[56-58]. Some studies try to present evidence for disease-specific alterations of the circadian rhythm, for example of prolactin levels or blood coagulation/fibrinolysis or hemostatic measurements in SSc[59-61].

## DISCUSSION

There are some indications for circadian rhythms in PMR and AS, but the available body of data is not yet sufficient and not comparable to what we know in RA. For other rheumatic diseases, only scattered information is available.

In PMR, symptoms such as pain and stiffness seem to be typically most prominent during the early morning hours. There are indications for a circadian variation of TNF-α and IL-6 secretion with peak values in the early morning hours, but exact data are still missing. Given the known high glucocorticoid sensitivity of PMR, a time-adapted glucocorticoid therapy can be hypothesized to be more effective than the current standard regimen in improving clinical symptoms and therefore to be possibly dose-sparing. But this needs to be investigated in proper studies[23,62].

For AS, pain and stiffness seem to be most prominent during the early morning hours; there might be a second peak in the evening. However, the data are insufficient to speculate about possible advantages of a time-adapted therapy.

It is important to carry out studies quantifying circadian rhythms of clinical measurements, hormones, and cytokines in PMR, AS, and other rheumatic diseases. If a circadian rhythm is present, proper clinical studies need to be conducted to find out whether time-adapted therapies represent a significant treatment option.

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