Obstructive sleep apnoea in relation to rheumatic disease

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Abstract
Sleep problems are common concerns in rheumatology patients and have been independently linked to increased pain perception and fatigue severity. Evidence supports an increased prevalence of primary sleep disorders, including sleep apnoea, in some rheumatic disease populations, particularly RA. Obstructive sleep apnoea is a significant public health concern and contributes to increased cardiovascular morbidity and mortality. Patients with obstructive sleep apnoea have also been found to have elevations in circulating acute-phase markers and pro-inflammatory cytokines. Co-existence of sleep apnoea in rheumatic disease patients may influence the severity of reported symptoms of pain and fatigue, accelerate the risk of cardiovascular events and possibly influence levels of circulating inflammatory markers and mediators. In this article we review the risk factors, prevalence and impact of sleep apnoea from a rheumatological perspective. Additionally, we recommend considering sleep apnoea screening in patients with rheumatic disease and, when appropriate, referral to a specialized sleep disorders clinic.

Key words: sleep, obstructive sleep apnoea, rheumatology, RA.

Introduction
Problems relating to sleep and fatigue are common concerns voiced by rheumatology clinic patients and often co-exist with other clinical features, including depression, pain and increased rheumatic disease activity [1–3]. Sleep difficulties may be viewed in many rheumatology patients as a secondary phenomenon related to their rheumatic disease but impairment of sleep has been independently linked with both increased pain perception and reported fatigue severity [4–6]. Sleep dysfunction has been observed to have a negative impact on quality-of-life measures in RA and OA patients [7].

Sleep abnormalities have been recognized in a number of different rheumatic diseases, including RA, OA, FM, JIA, SS, SLE, scleroderma, SpAs, sarcoidosis and Behçet’s syndrome [8]. Sleep disturbances vary from clinically recognizable distinct sleep disorders to diminished sleep quality, sleep fragmentation and insomnia. Because specific therapeutic interventions are available for primary sleep disorders, identification of such a distinct diagnosis is clinically important. Less well-defined sleep dysfunction and insomnias may also benefit from a review of sleep hygiene and related issues [7, 8].

Among the primary sleep disorders are included the different forms of sleep apnoea. Sleep apnoea may be broadly categorized as either (i) central, which is relatively uncommon, or (ii) obstructive in aetiology. Obstructive sleep apnoea (OSA) is increasingly recognized to be a significant public health issue [9]. Rheumatologists could have the best opportunity to identify such a concurrent disease within their patient populations. The co-existence of sleep apnoea in rheumatic disease patients may influence the severity of patient-reported symptoms of pain and fatigue, as well as potentially impacting on levels of circulating inflammatory markers and mediators [10, 11]. The presence of sleep apnoea as a comorbidity may interfere with the evaluation of rheumatic disease activity and responsiveness to therapy. In this article, we review risk factors for OSA and prevalence data from a rheumatological perspective.

OSA: what is it?
Of the sleep disorders that may affect rheumatic disease patients, OSA is perhaps the most widely recognized.
OSA is a specific sleep disturbance that is characterized by recurring apnoeas (cessation of airflow for 10 s or longer) or hypopnoeas during sleep. Hypopnoeas may be defined as a 30% reduction in airflow for at least 10 s accompanied by a 4% reduction in oxygen saturation; an alternative definition of hypopnoea is a reduction in airflow by 50% for 10 s or more with an associated 3% reduction in oxygen saturation [12]. OSA is defined by the American Academy of Sleep Medicine as repetitive episodes of upper airway obstruction occurring during sleep and usually associated with a reduction in oxygen saturation [13]. When accompanied by excessive daytime somnolence or fatigue, the term OSA syndrome may be used.

Clinical features associated with OSA, particularly in men, include a history of apnoic pauses during sleep as well as frequent and loud snoring [14]. The underlying pathophysiology of OSA involves partial or complete collapse of the posterior oropharynx during sleep. Risk factors for OSA in adults include increasing age, obesity (BMI >30 kg/m²) and larger neck circumference (>43 cm in men), although OSA can occur in individuals with none of these risk factors [14, 15]. Patients at risk for OSA are more susceptible to apnoeas/hypopnoeas when sleeping supine and also during the rapid eye movement stage of sleep (due to more shallow respiration and loss of upper airway muscle tone) [16].

How is sleep apnoea diagnosed?

A diagnosis of sleep apnoea can be indicated by symptomatology and the presence of known risk factors. The gold standard for diagnosis is the overnight polysomnogram (PSG). When a PSG is scored, the total number of apnoeas and hypopnoeas is added and then divided by the recorded total sleep time. This ratio is the apnoea-hypopnoea index (AHI). An AHI of £ 5 events/h of sleep is abnormal and indicative of sleep apnoea. An AHI of £ 5 with symptoms or an AHI of £ 15 is diagnostic of OSA [17]. Symptoms of concern include unintentional sleep episodes during wakefulness; daytime sleepiness; unrefreshing sleep; fatigue; insomnia; waking up breath holding, gasping or choking; or the bed partner describing loud snoring, breathing interruptions or both during the patient’s sleep [18]. Generally the higher the AHI, the more significant the OSA, with an AHI of £ 30 representing severe OSA.

Accessibility and cost of PSG is a concern in many areas and may limit test utilization. Alternative diagnostic tools are available and include type III portable monitoring, which has the merits of being less expensive, more convenient for the patient because it can be performed in their own home and validated for use in the diagnosis of OSA [19].

Screening questionnaires are also available. A commonly used tool is the Berlin Questionnaire, which is a three-part instrument that categorizes respondents into the dichotomous choices of high or low risk for sleep apnoea [20]. The Berlin Questionnaire has been validated by comparison with PSG and, perhaps not surprisingly, has been demonstrated to perform better when the patient’s bed partner completes it than when it is self-completed [21].

The STOP-BANG questionnaire is a simple and rapid screening survey to assess if an individual is at high or low risk for OSA. STOP is an acronym for snoring, tiredness, obstructive apnoeas and blood pressure. BANG helps to ascertain if one is at moderate to severe risk of OSA and includes questions on snoring, tiredness, obstructive apnoeas and blood pressure. STOP-BANG helps to ascertain if one is at moderate to severe risk of OSA and includes questions on snoring, tiredness, obstructive apnoeas and blood pressure. STOP-BANG helps to ascertain if one is at moderate to severe risk of OSA and includes questions on whether the patient is at risk for OSA.

What is the prevalence of sleep apnoea?

The Wisconsin Sleep Cohort Study found an estimated prevalence of 9% of women and 24% of men having sleep apnoea [25]. More recently, in their 2005 Sleep in America poll of 1506 adults, the National Sleep Foundation classified 31% of men and 21% of women to be at high risk for sleep apnoea by using the Berlin Questionnaire [26]. With consistent findings, in 2007 Kapsimalis and Kryger used the Berlin instrument in a survey of 1254 women, reporting 25% of respondents to be at high risk for sleep apnoea [27]. The Sleep Heart Health study found a sleep apnoea prevalence of 17% in their 5237 participants [28].

A combination of both Berlin Questionnaire screening and overnight PSG was used in a recent Norwegian general population study with more than 16 000 participants [29]. Questionnaire screening identified 24.3% of participants to be at high risk for OSA, whereas 16% of a random sample from this population selected for PSG met AHI criteria for OSA.

There has been increasing recognition that OSA in women may differ symptomatically [30, 31]. These differences may contribute to underestimation of OSA in women. As many rheumatological disorders affect a higher proportion of women than men, this concern may be relevant for clinical rheumatologists.

Is sleep apnoea seen in rheumatic disease patients?

Sleep apnoea and risk for sleep apnoea have been observed in rheumatic disease patients. This has been most frequently reported in the RA population. Objective documentation of sleep apnoea by PSG has been noted in several small series. In a 1989 report, Mahowald et al. [32] hypothesized that diurnal fatigue in RA patients may be a
manifestation of measurable disturbances in sleep physiology. Study participants included 16 RA patients with active disease and problems with onset of fatigue within 6h after arising. From the PSG data, it was observed that two male patients met sleep apnoea criteria despite the absence of recognizable OSA symptoms. Lavie et al. [33], in a study of female RA patients with no known sleep disorder who were undergoing PSG assessments as part of an efficacy study for tenoxicam, found one-third (4/12) had significant episodes of sleep apnoea on their PSG recording. It was observed that these patients tended to be older, with a mean age of 66 years, in contrast to the total group mean age of 55.8 years. In a study evaluating objective and subjective sleep disturbances, Hirsch et al. [34] studied 19 RA patients compared with control subjects. It was observed that 2 of the 19 RA patients exhibited slight obstructive sleep hypopnoea on PSG. However, predisposing factors such as TMJ pathology, micrognathia or cervical myelopathy were excluded in the study population. Additionally, the participants were predominantly female and relatively young, with a mean age of 47.6 years. In a recent PSG evaluation of 25 RA patients, 68% had an AH1 of $\geq 5$, consistent with sleep apnoea. Of these 25 patients, 10 were hypersomnolent, with an ESS score of $>10$. In these 10 patients with excess sleepiness, 80% had an AH1 of $\geq 5$; however, 60% of the 15 patients with no sleep complaints also had an abnormal AH1 of $\geq 5$ [35].

Other rheumatic disease groups have also been investigated objectively by PSG. Solak et al. [36] studied PSG recordings in a group of 31 AS patients. In that study, 22.6% of the total population met PSG criteria for OSA. It was observed that the frequency of OSA was 6.3% for those aged $<35$ years and 40% for those aged $\geq 35$ years. Laboni et al. [37] studied PSG recordings in SLE patients with disabling fatigue. Of the 35 patients studied, 26% met criteria for sleep apnoea. May et al. [38] performed PSG studies on newly diagnosed FM patients whose history was suggestive of a co-existing sleep disorder. This selection process resulted in 13 of 25 men and 4 of 92 women being included in the PSG study, of whom 11 (84.6%) men and 2 (50%) women had significant sleep apnoea.

Sleep-disordered breathing has been reported in children with JIA. Although there are both paediatric and adult PSG criteria for OSA, Accardo et al. [39] recently applied both to an adolescent population, with comparable results.

In a larger population, Reading et al. [40] used the Berlin Questionnaire in 164 RA patients and 328 non-RA control subjects. In these study groups, 50% of RA patients and 31% of control subjects were categorized as high risk for sleep apnoea. In a mixed general rheumatology clinic population, again using the Berlin instrument, 35.2% of 423 participants were classified as being at high risk for sleep apnoea [41]. These results indicate a substantial proportion of patients with rheumatic disorders have co-existing sleep apnoea or are at high risk for sleep apnoea, as per these screening tools.

A clinical association of gout with sleep apnoea has also been observed. Abrams [42] has elaborated on pathogenic mechanisms in sleep apnoea that may contribute to hyperuricaemia and gout. With uric acid excretion dependent on renal function, it is interesting that Ahmed et al. [43] have recently reported a link between nocturnal hypoxia in patients undergoing overnight PSG and accelerated renal function loss over the 2-year observation period.

**Why should rheumatic disease patients be at risk for sleep apnoea?**

The concept of increased prevalence of OSA in rheumatic disease patients is consistent with understood pathophysiological principles. Rheumatic disease patient subsets at particular risk for OSA include those with general risk factors such as increasing age, BMI and neck circumference [14]. Also at risk are patients with characteristics specifically related to rheumatic disease sequelae. Such features include mandibular (retrognathia, micrognathia), TMJ or cricoarytenoid joint pathology [44–47]. In such cases, a direct mechanical influence on airway closure is implicated. Redlund-Johnell [46] reported 30 of 400 RA patients as having upper airway obstruction episodes, with a relationship to the extent of arthritic destruction of the TMJs. Earlier reports highlight the role of cricoarytenoid arthritis as a cause of upper airway obstruction [47].

Cervical spine instability related to RA has also been associated with sleep apnoea. Shoda et al. [48], in a series of 29 patients with progressive myelopathy due to occipitocervical pathology, described a prevalence of OSA of 79%. Occipitocervical fusion has been reported by Ataka [49] to potentially improve sleep apnoea in RA patients with upper cervical lesions.

**Is there a relationship between inflammation and sleep?**

Cytokines have been recognized as playing a role in sleep physiological regulation. It has been observed that some ILs, such as IL-1, IL-2, IL-6, IL-8 and IL-18, and TNF-α promote non-rapid eye movement sleep; conversely, IL-4, IL-10, IL-13 and TGF-β have been reported to inhibit non-rapid eye movement sleep [50]. A diurnal rhythm has been observed for IL-1β, IL-6 and TNF-α, with peak levels during sleep periods and troughs during usual wake times [51–53]. This diurnal variation is disturbed in patients with insomnia or sleep deprivation [54]. Increased levels of inflammatory markers such as CRP and pro-inflammatory cytokines have been observed in sleep-deprived normal volunteers and both adults and children with OSA or sleep-disordered breathing [55–58]. The elevation in CRP in the setting of OSA has been observed to be independent of obesity [10, 59].

In one randomized, 16-day, controlled, in-laboratory study of the effect of sleep restriction on 18 healthy volunteers, inflammatory markers and pain scores were measured at baseline and during the study. IL-6 and CRP were
significantly increased after sleep restriction compared with after 8 h of sleep/night. In that study, elevated IL-6 levels were strongly associated with increased pain scores in response to sleep restriction. The authors conclude that insufficient sleep quantity may exacerbate pain through elevations of IL-6 [55].

In another sleep deprivation study, Irwin et al. [60] measured monocyte intracellular pro-inflammatory cytokine gene transcription in healthy volunteers. In this population, monocyte production of IL-6 and TNF-α mRNA was significantly greater after sleep loss. The authors concluded that sleep loss induces a functional alteration of the monocyte pro-inflammatory cytokine response.

The association with TNF-α and sleep disorders has been particularly closely studied. Increased levels of TNF-α have been reported by several investigators in patients with OSA [11, 57, 61, 62]. Higher levels of TNF-α have been associated with more severe obstructive disease and hypoxia [62]. Treatment with continuous positive airway pressure (CPAP) devices has been shown to be associated with a decrease in TNF-α levels in these OSA patients [61]. TNF-α is coded for by a nuclear factor-κB (NF-κB)-dependent gene. Ryan et al. [62] have demonstrated selective activation of NF-κB-dependent inflammatory pathways by intermittent hypoxia, which is characteristic of OSA. Although a relationship between the severity of OSA and TNF-α elevation has been demonstrated, it is unclear if the effect is reciprocal. There has been some evidence of inherent TNF-α variation as a contributing factor in sleep disorders. In patients with the primary sleep disorder narcolepsy, a functional alteration in the TNF-α system has been reported [63]. Increased production of TNF-α has also been reported to be associated with functional gene polymorphism at the promoter region, position −308 [64]. Hypothesizing that OSA may be associated with this genetic polymorphism, Riha et al. [64] studied a UK population of 103 Caucasian patients recruited from a sleep centre. Each participant recruited a sibling for inclusion as a sib-pair. All 206 participants underwent PSG and genotyping. The authors reported that the TNF-α (−308) allele was significantly associated with a diagnosis of OSA, when cases were compared with either established population controls or siblings. Interestingly, the TNF-α (−308)A allele has been identified as a candidate gene in determining anti-TNF-α therapeutic responsiveness in RA [65].

TNF-α is a pro-inflammatory cytokine and a strategic therapeutic target in the treatment of rheumatic diseases. The impact of anti-TNF-α strategies on sleep has also been evaluated in patient groups both with and without concurrent rheumatic disease. Vgontzas et al. [66], in a small study of eight OSA patients, found initiation of the anti-TNF-α therapy etanercept resulted in a marked decrease in sleepiness and an associated decrease in AHI. In RA patients without a known sleep disorder, Zamarron et al. [67] reported the first infliximab infusion to result in improved sleep latency and sleep efficiency by PSG observations. Consistent findings with improved sleep efficiency were observed in a group of 10 RA patients treated with etanercept or adalimumab for a mean of 2 months [68].

In a large rheumatic disease population study, Wolfe and Michaud [69] did not observe any significant differences in sleep scores in RA patients treated with anti-TNF therapies compared with other RA patients. However, in recent clinical trials, subjective sleep assessment outcomes have shown some improvement in RA patients treated with abatacept [70].

In summary, inflammatory cytokine levels have been observed to be elevated in proportion to the severity of OSA. Intermittent hypoxia has been demonstrated to be strongly predictive of activation of NF-κB-dependent inflammatory pathways in OSA. The impact of co-existing OSA on the extent of and response to therapy of inflammatory rheumatic disease is unknown.

Why is OSA important?

People with OSA have been clearly identified to be at greater risk for motor vehicle and work-related accidents [71, 72]. In terms of general well-being, a poorer quality of life is reported by patients with OSA [73]. Furthermore, OSA is an independent risk factor for cardiovascular disease, including hypertension, congestive heart failure, atherosclerotic coronary artery disease and pulmonary hypertension [74, 75]. With the recognized increased prevalence of cardiovascular disease in inflammatory rheumatological disorders [76], concurrent OSA is likely to further contribute to this risk.

How is OSA treated?

The standard therapy for OSA at present is the use of CPAP during sleep. This therapy has been demonstrated to be effective in improving symptoms of OSA and PSG characteristics, including the AHI [77]. Occasionally patients have trouble tolerating CPAP devices, and long-term compliance may be a concern. Other interventions that have been used include controlling body position during sleep, weight reduction programmes and mandibular advancement devices to help thrust the mandible forwards, thereby reducing the likelihood of airway obstruction during sleep [78]. In some countries, a new nasal expiratory positive airway pressure device is available for therapy of OSA [79]. Surgical approaches to OSA are occasionally used but are generally not first-line therapies.

Conclusion

There is evidence that patients with rheumatic disorders may be at increased risk for sleep disorders, particularly OSA. The co-existence of OSA in this population may contribute to increased morbidity and mortality, particularly with reference to cardiovascular events. Sleep abnormalities have also been linked to increased pain and fatigue perception, which are common concerns in rheumatology patients. Untreated OSA with intermittent hypoxia is associated with elevated levels of systemic
inflammatory markers: CRP and pro-inflammatory cytokines. The impact of OSA as a comorbidity on measures of therapeutic response to RA therapies is not established.

It is not expected that rheumatologists would diagnose and treat OSA; however, many symptoms of, or risks for, OSA may be picked up during rheumatological review. A high index of suspicion may facilitate recognition of possible OSA. Utilization of a simple screening questionnaire for OSA or daytime somnolence may be of additional benefit. Referral to a dedicated sleep clinic for further diagnostic assessment and therapy as required would be appropriate. Treatment for co-existing OSA in patients with rheumatic diseases may prove beneficial in terms of future cardiovascular and respiratory morbidity, as well as potentially improving measures of fatigue, pain and inflammatory markers.

**Rheumatology key messages**

- Rheumatic disease patients may be at increased risk for co-existing sleep apnoea.
- Co-existing sleep apnoea may contribute to increased pain and fatigue, as well as increased cardiovascular morbidity/mortality, in rheumatology patients.

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