Obstructive sleep apnea, hypoxia and inflammatory arthritis: how may they be linked?

"It may be hypothesized that in conjunction with obesity, chronic or severe intermittent hypoxia may further amplify inflammation or refractory disease [in a patient with RA]."

Obstructive sleep apnea (OSA) is an increasingly prevalent health concern. It has been reported to affect between 3 and 17% of the general population, with a clear gender disparity in favor of higher rates in men [1]. Recent studies demonstrate much higher incidence rates thought in part to be secondary to increasing obesity in western populations as well as increased sensitivity of polysomnogram recording [2].

OSA is characterized by nocturnal snoring and apneic pauses or hypopneas. These apneic pauses are defined as a drop of at least 90% of airflow for 10 s or more and hypopnea defined as a drop in airflow of 30% or more for 10 s or more. Both apneas and hypopneas are associated with oxygen desaturations of 3% or greater and/or arousals [2]. Overnight polysomnography is considered the diagnostic gold standard for OSA.

When left untreated, OSA may result in pathological sequela related to chronic intermittent nocturnal hypoxia. Such hypoxia-related physiologic stress has been recognized to have vascular implications and in more severe cases, sequela including pulmonary hypertension, subsequent cardiac dysfunction, dysrhythmias and renal impairment [3,4].

Increased prevalence of OSA or OSA risk in patients with inflammatory arthritis has been reported by a number of investigators. Reading *et al.* reported that 50% of 164 rheumatoid arthritis (RA) patients at Mayo Clinic were categorized to be at high risk for OSA utilizing the Berlin questionnaire [5]. Similar findings in a Canadian RA cohort were reported with 39% of 145 RA patients categorized as high risk for OSA utilizing the Berlin Questionnaire [6]. Subsequent studies of 25 Canadian RA patients found 78% of those categorized at high risk of OSA to have abnormal polysomnography consistent with OSA, additionally, 63% of those categorized to be at low risk of OSA with this instrument also met polysomnographic criteria for OSA [7]. With respect to other rheumatologic disorders, increased proportions of patients with ankylosing spondylitis (40% of those over age 35) or with Sjögren's syndrome (68% of study population) have been recognized through polysomnography to meet criteria for OSA [8,9]. Rheumatic disease patients categorized at high risk for OSA also tend to have poor sleep quality, increased fatigue and pain, and poorer quality of life [10].

The interplay between sleep, hypoxia and inflammation is complex. It is recognized that cytokines, as intercellular signaling proteins are involved in normal sleep regulation processes. Differential effects from different cytokines have been observed. For example, proinflammatory cytokines IL-1, IL-6 and TNF-α among others have been reported to promote nonrapid eye movement sleep, whereas IL-4, IL-10 and IL-13, again among others, have been reported to inhibit nonrapid eye movement sleep [11]. A balanced effect presumably facilitates a normal restorative sleep pattern.

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For the inflammatory cytokines TNF-α, and IL-6, which have been more closely studied, diurnal variations have been observed with peaks during sleep and lower levels during usual wake times [11]. Those with sleep pattern disorders such as insomnia have been reported to have a shift or imbalance in this usual physiologic variation [12]. Deliberate sleep deprivation has further been observed to be associated with increased IL-6 levels in humans [13]. These findings suggest that cytokines involved in sleep regulation may be influenced by behavioral changes or other factors.

In the case of OSA patients, multiple investigators have reported an increase in the levels of circulating TNF-α [14]. More severe obstructive diseases and hypoxia have been associated with higher measured levels of TNF-α in this population [14]. Improving the hypoxia and obstruction through use of continuous positive airway pressure devices has been correspondingly associated with decrease in TNF-α levels [14]. TNF-α is coded for by a NF-κB-dependent gene. Selective activation of such NF-κB-dependent inflammatory pathways through intermittent hypoxia has been demonstrated [14]. Such hypoxia-related increase in inflammatory cytokines is not confined to OSA patients. These reports are similar to the finding of increased IL-6 levels in people newly exposed to high altitudes [15]. Such evidence supports the premise that systemic hypoxic stress may trigger an increase in circulating inflammatory cytokine levels.

Hypoxia-stimulated increase in inflammatory markers has been identified to be at least in part mediated through the hypoxia-inducible factor (HIF) system. HIF is made up of a constitutively expressed HIF-1β subunit and an oxygen-regulated HIF-α subunit. In hypoxic conditions, HIF-α isoforms are stabilized, and can form a heterodimer with HIF-1β leading to activation of proinflammatory cytokines, and influence on other cellular processes including angiogenesis and vasomotor control [16].

Conversely, inherent TNF-α variation may be a contributing factor in the development of sleep pathology. Increased TNF-α production has been reported to be associated with functional gene polymorphism at the promotor region, position -308 [17]. This TNF-α (-308) allele has been described as significantly associated with a diagnosis of OSA compared with population controls [17]. Anti-TNF-α biologic strategies have been reported to have some efficacy in treatment of OSA patients (without concurrent rheumatic disease) and also on some polysomnographic sleep parameters in RA patients [18,19]. A lower incidence of OSA in ankylosing spondylitis patients on anti-TNF-α therapies has been observed [20]. These observations imply excess TNF-α production or alteration in TNF-α

functional responses may directly influence development of sleep disorders. These clinically based observations suggest the potential for an amplification loop in respect to OSA development, subsequent intermittent hypoxia and increased inflammatory cytokine production.

Many of the rheumatology-related OSA reports have been based on the RA patient population. Considerations for why RA patients may be susceptible to development of OSA have yielded a number of potentially contributing factors, including from a structural perspective, involvement of temporomandibular or cricoarytenoid joints, presence of retro or micrognathia and also cervical spine abnormalities [21]. From a humoral perspective, RA is itself characterized by an increase in proinflammatory cytokines such as TNF-α, to the extent that this forms the basis for targeted biologic therapies. In a sufficiently predisposed individual, it could be hypothesized that this increase in TNF levels may increase susceptibility to OSA.

Obesity is another common link. Increased BMI and larger neck circumference has been long recognized as associated with increased risk for developing OSA [22]. Obesity more recently has been linked with increased risk for both developing RA and also having poorer disease control or biologic therapeutic effectiveness [23,24]. There has been speculation about the role of the active adipose tissue in promoting inflammatory processes directly [25]. Associations have been observed between obesity and increased production of inflammatory adipokines including IL-6 and TNF-α [25]. In susceptible individuals, it is possible that increased circulating proinflammatory mediators from excess adipose tissue may play a role in promoting development of OSA and/or RA.

In the rheumatoid synovial microenvironment, both inflammation and hypoxia are present. NF-κB-activated inflammatory responses manifested in part through production of TNF-α are evident as well as activated HIF-α, which is involved in the hypoxic response within the synovium [16]. The NF-κB and HIF systems have been demonstrated to have some commonality in terms of target genes and stimuli. The full nature of the interactions between these two systems is incompletely understood, although there is some evidence for role duality with both promoting and repressing effects [16]. Further studies elucidating the interactions and interdependence between the various components of these two systems are ongoing.

It is not clear what impact systemic intermittent hypoxia may have on the synovial microenvironment. It does appear that intermittent systemic hypoxia associated with OSA may be implicated in microcirculatory dysfunction and reactivity in other tissues

however, is it not clear whether the synovium may be also susceptible to such physiologic stress [4,26]. In support of the concept for intermittent systemic hypoxia playing a role in promotion of inflammatory processes within local nonairway-related tissue environments, increased gene expression in the skin for both TNF-α induced proteins and HIF-α has been reported in OSA patients with severe intermittent hypoxia compared with OSA patients with milder disease [26]. It is intriguing to consider whether the synovium may demonstrate similar findings. To further speculate, it would be most interesting to determine whether intermittent hypoxia in a patient with RA would be associated with a measurable proinflammatory upregulation systemically or within the synovium microenvironment and whether this would translate to a measurable impact on disease activity and therapeutic responsiveness. It may be hypothesized that in conjunction with obesity, chronic or severe intermittent hypoxia may further amplify inflammation or refractory disease in this setting.

There is suggestive evidence for a complex and intertwined relationship between obesity, obstructive sleep apnea with intermittent hypoxia, and inflammation. When coexisting in a patient with RA or other inflammatory arthritis, there may be potential for promotion of inflammatory disease activity and decreased therapeutic responsiveness.

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