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10

Sleep and rheumatic diseases

Tobias Boeselt [a, *], Rembert Koczulla [a, b], Christoph Nell [a], Bjoern Beutel [a], Konrad Guenter [a], Werner Cassel [a], Olaf Hildebrandt [a], Ulrich Koehler [a], Johannes Kroenig [a]

[a] *Philipps-University of Marburg/ Institute for Internal Medicine, Department of Pulmonology, Marburg, Hessen, Germany*
[b] *Pulmonology Schoen Clinic Berchtesgadener Land, Teaching Hospital of Philipps-University of Marburg, Germany*

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A B S T R A C T

This review article discusses various forms of sleep disorders associated with musculoskeletal diseases (MD). It presents the pathophysiology and interaction of sleep-related disorders and MD and summarizes clinical symptoms and therapies from a somnological perspective.

Background: A large number of patients suffering from MD report fragmented sleep with poor overall sleep quality. Sleep disorders often lead to increased symptoms such as daytime fatigue, depression, or increased pain intensity. In contrast, the perception of pain worsens the quality of sleep.

Sleep is a complex regulation of hormonal and neuromodulatory influences to maintain regenerative processes and signal processing. Furthermore, interleukins (e.g., IL-6 and TNFα), messenger substances, or inflammatory markers (e.g., CRP) may have a regulatory influence on sleep.

Therapy: Sleep disorders in MD can often be treated with behavioral therapies or drug approaches. Another and very important influence is physical activity. In combination with training, regular physical activity can lead, for instance, to improved sleep quality, endurance performance, and reduced inflammation values. The

* Corresponding author. Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg, Member of the German Center for Lung Research (DZL), 35043 Marburg, Germany.
E-mail addresses: tobias.boeselt@uni-marburg.de, boeseltt@staff.uni-marburg.de (T. Boeselt), rkoczulla@schoen-klinik.de (R. Koczulla), christoph.nell@googlemail.com (C. Nell), beutelb@med.uni-marburg.de (B. Beutel), konrad.guenter@hotmail.de (K. Guenter), cassel@staff.uni-marburg.de (W. Cassel), olaf.hildebrandt@med.uni-marburg.de (O. Hildebrandt), koehleru@staff.uni-marburg.de (U. Koehler), kroenig@med.uni-marburg.de (J. Kroenig).

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change of lifestyle with regard to activity and nutrition is another key concept in the optimal therapy of patients with MD.

Introduction

Humans spend almost a third of their lives sleeping, a state that lies outside of conscious perception. In sleep, humans are vulnerable, because in this state we cannot perceive the environment. For our ancestors, this situation was an enormous danger, because they shared the dark nights with predators. If sleep as such was not vital, it would have long since disappeared from our habits from an evolutionary point of view. Accordingly, sleep research over the last 20 years has identified an increasing number of life functions of sleep that do not only concern pure recovery. Good and restful sleep is important for learning, memory (including forgetting), dementia prophylaxis, mood, psychological stability, and conflict resolution. Of particular importance in rheumatic diseases is the connection between sleep, the function and regulation of the immune system, wound healing, cell repair, and pain (see Fig. 1).

About 70% of patients with rheumatic diseases report disturbed sleep [1], and sleep disorders like Obstructive Sleep Apnea and Restless Legs Syndrome are present in about 20% of these patients [2]. Rheumatic diseases occur with increased cytokine levels, some of which can promote, while others can impair sleep [3]. Sleep deprivation can lead to increased IL-6 and TNFα levels [4]. Pain is the leading clinical symptom of rheumatic diseases, and numerous studies have shown an interaction between pain and sleep. Increased pain is a predictor of disturbed sleep, but impaired sleep is probably an even stronger predictor of increased pain and maintenance of chronic pain [5].

Recognition and management of sleep disorders is therefore a promising and necessary part in the comprehensive management of rheumatic diseases.

Physiology of sleep

Sleep is not a uniform or several-hour process of unconsciousness. Rather, it can be divided into clearly separated, periodically repeating phases. Sleep begins with a transition phase (N1) characterized by rolling eye movements and a deceleration of electrical brain activity. This is followed by stage N2, in which the EEG frequencies slow down further and typical waveform patterns (sleep spindles and K-complexes) occur. Typically, after a 10–30 min sleep phase (N2), there is a change to deep sleep level

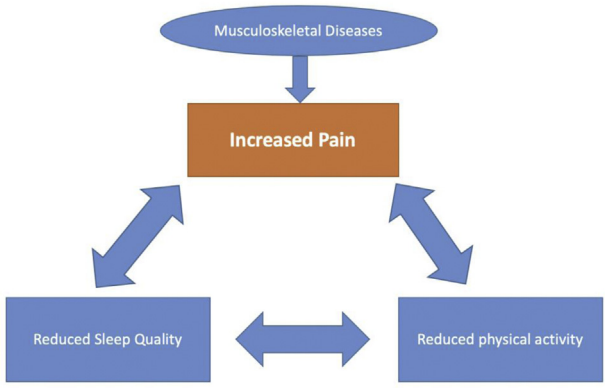

Fig. 1. Relationship between musculoskeletal diseases and pain in connection with physical activity and sleep quality.

N3, which often lasts 20–50 min. Deep sleep is characterized by a highly synchronous and very slow EEG frequency of 0.5–4 Hz and low excitability. After deep sleep, the patient returns to sleep stage N2, followed by REM sleep (Rapid Eye Movement). In this sleep phase, rapid eye movements are registered and episodic dreams are experienced. The first REM phase often lasts only a few minutes. Muscle tone is lowest in REM sleep because the activity of the striped muscles is inhibited by specialized neurons in the subcoeruleus locus (pons) and in the magnocellular nucleus (medulla). Dreamed motor activities produce similar neurological activities as the action itself - but the switch in the brainstem does not perform any movements.

The end of the first REM phase concludes the first sleep cycle after approx. 90 min. Nightly sleep usually consists of 4–6 sleep cycles in 6–8 h. In the following cycles, the deep sleep phases shorten or disappear, while the REM and light sleep phases increase in duration.

Often the subjective feeling regarding sleep quality and sleep time does not coincide. A healthy person wakes up about 25 times per night, which probably was an evolutionary and life-saving cause for our ancestors. If these waking phases are rather short, they will not be remembered. This amnesia is probably due to the memory stabilizing function of sleep. The brain is sorting, structuring and stabilizing the contents of memory during sleep and stores what it has learned during the nightly rest phases.

Sleep regulation

Sleep is regulated homeostatically and via circadian factors. The duration of wakefulness increases sleep pressure (homeostasis, process S), which is counteracted by alerting circadian factors (e.g., orexine levels). Even though sleep pressure rises over the course of the daily activity phase, it is usually difficult to fall asleep in the early evening because circadian alerting factors reach their peak during that time [6]. Once this so-called process Z wanes the alerting factors, sleep pressure can manifest itself and healthy subjects fall asleep easily. Our understanding of the circadian factors modulating sleep has been changed dramatically by recent findings, which can explain age-related changes of sleep and offers insight into potential detrimental effects of our current lifestyles on sleep.

The most important single factor for the circadian regulation of sleep and wakefulness is light. In 1998, it was first described [7] that a subset (about 1–3%) of the retinal ganglion cells located on the light-facing side of the retina do not just relay visual information from rods and cones to the visual cortex, but are light-sensitive and do not project into the visual cortex. Instead the nerve fibers that emanate from these cells branch off at the junction of the optic nerves and connect into the suprachiasmatic nucleus (SCN) [8].

The SCN regulates, among other things, the secretion of the hormone melatonin in the pineal gland. In healthy people, melatonin is secreted almost exclusively at night. The melatonin release is determined by two factors: relative darkness for about 90 min and a circadian rhythm generator, which is located in the SCN and clocked at approximately 24 h. The combination of these two signals usually increases the melatonin secretion from about 9 p.m. [9].

Melatonin receptors in the SCN constantly sense melatonin levels in the blood. About 1–2 h after the onset of melatonin secretion, it reaches its steepest increase. In turn, this is detected in the SCN and processed as a clock signal for the 24-h rhythm generator [10]. Although in healthy people the body clock usually runs slightly slower than 24 h, it will be synchronized to a 24-h day, even in light-deprived conditions.

Under normal conditions, this feedback ensures a stable 24-h rhythm, but also allows adjustment of the internal clock, e.g., after an intercontinental flight [11].

Consequently, the light-synchronized release of melatonin constitutes an important sleep-regulating factor. Unfortunately, the nocturnal melatonin levels decrease already in early adolescence, because the pineal gland is prone to calcification. In young adults, by as much as 15% of the tissue of the pineal gland may already be calcified. By the age of 50 years, this may already be as much as 30% [12]. Furthermore, melatonin production may also be affected via the tryptophan-melatonin-serotonin metabolism and by the amount of daylight exposure: Less daylight exposure can result in lower levels of serotonin and melatonin [13].

Sleep in musculoskeletal disease

Between 54 and 80% of patients with rheumatoid arthritis report poor sleep, frequent waking, early waking, daytime sleepiness and/or fatigue [2,14–16]. Polysomnographic studies show a relatively normal sleep architecture, yet often more frequent nocturnal awakenings, longer waking hours, and a partly reduced sleep efficiency [17], especially in phases of increased disease activity [18]. Accordingly, disease activity and perceived sleep problems have a clear positive correlation [19]. Interestingly, the proportion of slow wave sleep in RA is higher than in controls [17,20]. This is believed to reflect the increased need for restorative sleep in patients with RA.

Sleep-related comorbidities occur more frequently in patients with rheumatic diseases. Restless Legs Syndrome is significantly more common with a prevalence of up to 30% in RA patients [21]. The symptoms have to be separated from the underlying disease; affected persons complain especially in the evening and at night under resting conditions about an increasing urge to move. Sleep disorders can occur. Periodic limb movements, detected by polysomnography, can be indicative. These movements can lead to wake-up reactions and thus a disturbance of the sleep structure [22].

Sleep apnea syndrome is one of the most common sleep-related respiratory diseases. If it occurs in up to 7% of the general population, the figures are probably significantly higher for patients with rheumatic diseases. However, figures are only available for studies with a small number of cases where OSAS was found in up to 44% of patients [23]. Registry data from Taiwan report a 1.7-fold increased risk for RA patients to develop OSAS [24]. In particular, skeletal changes in the area of the neck or rheumatic affection of the temporomandibular joint and affections of the brain stem can lead to an obstruction of the upper respiratory tract [25,26].

While altered sleep patterns of RA have been extensively studied, the pathophysiology of disturbed sleep is not well understood.

Sleep is a construct of complex interactions between the endocrine system [8], the central nervous system [27], and the immune system [28]. Any of these systems could cause insomnia in RA patients. Previous studies have shown that changes in inflammatory load in patients have a significant impact on sleep quality [28]. Cytokines such as interleukin (IL) −6, IL-1β, or tumor necrosis factor (TNF) have been shown to be important factors of sleep quality [28–30].

Patients with rheumatic disease show an increase in proinflammatory cytokine activity, and sleep deprivation leads to an excessive increase in pain compared to reactions in healthy controls [31]. Similarly, sleep disorders lead to an increase in circulating levels of IL-6 and TNF and an increase in transcriptional expression of IL-6 and TNF [32,33]. Furthermore, the shortening of sleep from 8 to 6 h leads to an increase in the monocytic production of IL-6 and TNF stimulated by lipopolysaccharide (LPS) [32,34]. Monocytes account for about 5% of circulating leukocytes and essentially contribute to proinflammatory cytokine production in peripheral blood. LPS acts by stimulating the toll-like receptor (TLR)-4. In turn, increases in TLR-4 stimulated production of IL-6 and TNF correlate with symptoms of fatigue [35,36]; increased TNF levels are also associated with fatigue and daytime sleepiness in patients with chronic fatigue syndrome, insomnia, or obstructive sleep apnea [37].

Today, we have evidence for the relationship between TNF and sleep disorders: Anti-TNF therapy has a positive effect on sleep efficiency and significantly reduces sleep disruption [38]. Likewise, anti-IL-6 therapy with, e.g., Tocilizumab, improves the subjectively reported sleep quality [39]. Similarly, the inhibition of T-cell co-stimulation of the immune system with abatacept showed a reduction in subjective sleep disorders [40].

In addition to the immune system, hormones of the hypothalamic-pituitary-adrenaline axis (HPA) could be involved in the sleep disorders of RA patients. Activation of the Corticotropin Releasing Hormone (HPA) axis has been shown to cause sleep disturbances in healthy volunteers and in those with major depression and appears to have a direct impact on sleep quality [41]. The major influence on the change of sleep patterns seems to be the HPA axis hormones: Corticotropin-releasing hormone (CRH) and cortisol [42]. The fact that the HPA axis may be disturbed in patients with RA has been extensively researched and published [43].

The circadian rhythm is subject to a variety of mediators, including serum cortisol. In patients with RA, this rhythm may be disturbed due to severe inflammation [44], whereas lower inflammatory activities seem to have no effect on circadian rhythm [45]. The discovery of the relationship between HPA

hormones and inflammatory events opens up completely new dimensions for future research and possibly therapies [46]. Further studies between serum cortisol and cytokines will shed more light on the regulatory mechanism of hormone-immune interaction. Similar to a neural network, changes in one system also affect other systems. This interaction was recently demonstrated in a computer-based simulation of the circadian rhythm in RA patients [47].

In addition to the loss of function, pain determines the clinical picture of musculoskeletal diseases. In the past, numerous studies have shown a reciprocal relationship between sleep quality and pain, whereby impaired sleep appears to be a stronger predictor of increased pain perception and the maintenance of chronic pain than vice versa [5]. The causes are not fully understood.

Treatment of sleep disorders in patients with rheumatic diseases

Sleep disorders are independent risk factors for impaired quality of life, depression, and suicidality in healthy people, and should therefore be treated. This is especially true for patients with rheumatic diseases, as sleep disorders are common (s. above), furthermore, impaired sleep can cause increased sensitivity to pain (s. above). A successful treatment of poor sleep may potentially also treat pain.

Treatment of the underlying disease and its symptoms

The priority is an optimal treatment of the underlying disease in accordance with the rheumatologic treatment recommendations. The effect of musculoskeletal diseases on sleep can be reduced by adequate pain treatment and limitation of inflammation. Hence, these possibilities will not be further discussed. The best possible symptom control should be achieved by a guideline-oriented therapy. In particular, pain control should be achieved.

Concomitant sleep disorders

In patients with rheumatic diseases, respiratory disorders of sleep (obstructive or central apnea) or movement disorders (RLS) occur with above-average frequency. These patients should be identified. An adequate anamnesis regarding sleep difficulties, snoring, nocturnal breathing pauses, daytime tiredness, and dry mouth is necessary. There are validated questionnaires for self-evaluation of the patient. If sleep disorders are suspected, a polysomnography should be performed. In addition, screening should be carried out for accompanying depression. These diseases require therapy independent of the underlying disease.

Chronic comorbid insomnia

In general, the diagnosis of insomnia includes one or more of the following disorders:

- difficulty in initiating sleep;
- difficulty in maintaining sleep; or
- waking up too early.

Insomnia is classified into an acute (less than 30 days) and a chronic form (>30 days or > 6 months; depending on different references). (NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults 2005).

In most cases of acute insomnia, a certain cause such as a current stress factor can be identified [48]. Historically, in case of chronic disease, a primary and secondary insomnia was postulated. In the secondary form, another condition (=main diagnosis) was meant to be the reason for insomnia. According to this classification, secondary insomnia would disappear if the main diagnosis was successfully treated. However, there are no data supporting this thesis, and daily clinical practice rather contradicts this assumption [49,50]. For this reason, a division into organic and non-organic insomnia is recommended.

We must take into account that often there is only a limited understanding about insomnia caused by the underlying disease. A conclusion on the direction of causality is not always possible or an interrelationship seems comprehensible.

Prevalence studies have estimated that up to 90% of insomnia cases are comorbid with other conditions [51,52]. On the other hand, chronic comorbid insomnia is common in rheumatic diseases (Table 1).

Therapy of insomnia

It is well known that good and enough sleep is important. If, for various reasons, sleep disturbances occur, it can lead to changes in behaviour. This includes, for example, the increased use of caffeine, taking naps at noon to compensate for the actual or perceived sleep deficit and leads to patients increasingly having to deal with their sleep. The raising demand to sleep triggers a self-reinforcing process of insomnia. This vicious circle is difficult to break without direct intervention [50].

Although an adequate therapy of the underlying disease is provided – the symptoms are controlled as best as possible and accompanying respiratory disorders or movement disorders have been excluded – sleep disorders can still occur. The following concepts are therapeutic approaches to improve the subjective and objective well-being of patients. Essentially, they can be divided in pharmacological and cognitive behavioral concepts.

If patients have very strong nocturnal pain due to an acute inflammatory rheumatic disease, they have an increased risk of nonrecovering sleep and of not feeling sleepy. This psychophysiological component plays a very important role in the maintenance and generalization of sleep disorders associated with rheumatic diseases.

Cognitive behavioral treatment of insomnia (CBTi) provides various nondrug therapeutic strategies. This mainly includes sleep education, sleep hygiene, stimulus control, sleep restriction, relaxation training, and cognitive therapy.

Sleep education and cognitive therapy

In treatment, the most important aim is to break down the acute focus on sleep. This is achievable through cognitive-behavioral treatment, which has been proven to be an effective treatment [50]. This applies in particular to organic insomnia [53].

Sleep education is an essential prerequisite for cognitive behavioral therapy, as misjudgments about day and night deficits or one's own ideas about sleep often lead to counterproductive behaviour.

Information about physiology of sleep is a first step toward counteracting the sleep pressure experienced by many patients and makes it easier to deal with nocturnal wakefulness, and a relaxed attitude toward sleep is required for good sleep.

Table 1
The rheumatic diseases with the percentage of insomnia-related poor sleep quality [1].

Rheumatic disease	Insomnia-related bad quality of sleep
Rheumatoid arthritis	up to 70%
Fibromyalgia	75%
Systemic lupus erythematosus	60%
Ankylosing spondylitis	54%
Sarcoidosis	–
Systemic Scleroderma	+
Behçet's disease	up to 25%
Osteoarthritis	up to 81%
Psoriatic arthritis	+
Juvenile arthritis	+
Sjögren syndrome	75%

Benzodiazepines and Z-substances

The most commonly used hypnotics at present are benzodiazepine agonists (Z drugs) [54]. Their main advantage is their strong sleep-promoting effect, which makes them the drug of choice in critical situations. Their prolonged use and effect is viewed with some concern. A very critical side effect is the overall increased risk of falling in rheumatic diseases [55]. Benzodiazepines and Z-substances also have a considerable addictive potential, impair memory formation during sleep, and increase the risk of dementia [56].

Sleep-inducing antidepressants

Some antidepressants have a sleep-inducing effect. Due to the close connection between rheumatoid arthritis (RA) and depression, the psychotropic effects are often desirable. However, there is evidence that antidepressants have limited efficacy in patients with RA, especially in patients with elevated IL-6 levels [57]. Non-depressive patients who take sedative antidepressants only to improve sleep often report unpleasant side effects such as morning fatigue and emotional apathy.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized from serotonin in the pineal gland and is subject to a light-sensitive circadian rhythm. It conveys information about darkness in the body and thus influences circadian rhythm and seasonality. Against this background, melatonin is not a sleep hormone. Melatonin receptors (MT1 and MT2) distributed throughout the body have been identified. Circadian effects are found in many functions of the body. These include sleep, temperature regulation, blood pressure, immune response, cell regulation and many more [13].

There is a correlation between melatonin suppression and the enhancement of alertness by light exposure at night. There is evidence that melatonin possesses sleep-inducing effects.

Exogenously added melatonin could demonstrate in studies that it shortens sleep latency and improves sleep quality [58]. The patients experience improved sleep, a better recovery the next morning, and they rate mood and quality of life more positively [59,60].

Melatonin intake does not lead to a reduction in the body's own melatonin production, and no habituation or dependence effects were observed [59]. Melatonin is not considered a medication in the United States, and it is only approved for the treatment of insomnia in Germany for a limited period of time.

Melatonin acts as an immune regulator, which includes proinflammatory and pro-oxidant effects as well as antioxidant and anti-inflammatory effects [61]. For rheumatoid arthritis as an inflammatory autoimmune disease, there are findings that show higher nocturnal melatonin levels in patients than in healthy controls [62]. Melatonin is present in the synovial fluid of RA patients, and synovial macrophages have a melatonin-specific binding site [63]. Whether the elevated melatonin levels in patients with RA are the result of increased production of this hormone or the result of a different melatonin metabolism is still unclear. To date, there are no large randomized studies on melatonin substitution in patients with musculoskeletal diseases; however, studies on critical ill patients have not shown any serious side effects [64].

Excursus: Rheumatoid arthritis - a disorder of the circadian rhythm?The results of the gene expression of clock genes in patients with RA compared to non-inflammatory osteoarthritis show significant differences in RA, leading to the hypothesis that RA could be part of a circadian clock disease [65]. Circadian dysfunction may cause synovial membranes to be generally at rest during the activity phase and unable to rest and repair at night. This circadian misalignment could also contribute to morning stiffness, fatigue, and altered circadian cytokine production in RA patients with much higher and phase-shifted TNF and IL-6 peaks. TNF and IL-6 are present at the beginning of the activity phase and show a temporal association with pain, stiffness, and functional disability [66].

It is conceivable that improving the circadian rhythm by optimizing photonic timers may have the potential to prevent or positively influence the development of rheumatoid arthritis [66]. This behavioral intervention seems to be a promising field for future research.

In addition to the altered gene expression of clock genes, epidemiological studies also point to a circadian component in joint pain and rheumatic symptoms. In nocturnally active people, our modern lifestyle with artificial light in the evening or at night shifts the circadian rhythm further back, so that a backward shifted TNF and IL-6 peak could also be causally involved here.

In contrast to RA, the administration of melatonin in fibromyalgia seems unproblematic or even advisable, because the disease process and pain figures were positively influenced by melatonin treatment [62].

Rheumatism, physical activity and training

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints [67]. This may result in these people being less physically active than their healthier peers [68].

Physical activity

A special area of research has investigated the effects of physical activity and exercise on sleep in the general population. The results generally indicate a positive impact on sleep. It remains to be shown how large the effects are and to what extent other variables such as age, type, and duration of workout can alter the effects [69].

Current guidelines recommend physical activity and exercise as a key component in the treatment of rheumatoid arthritis. Less evidence, however, exists with regard to the effects of physical activity and exercise on sleep quality as well as sleep disorders in patients with RA.

Sleep is an important aspect in maintaining the body's circadian rhythm. In general, it has been found that less than 5 h of sleep a night is associated with higher incidence of cardiovascular problems, diabetes, obesity, and anxiety [70,71]. Poor sleep is a common problem in people with rheumatoid arthritis. In addition to mental and physical health, this also has an impact on the quality of life of these patients.

It is known that physical activity can improve mental health [72], which can also be an additional factor in improving sleep quality [73]. Physical training is one of the most important part of non-pharmacological therapy for poor sleep. In a 2013 Cochrane Review [74] on exercise and fatigue, it was found that sleep quality has never been studied in this context. Therefore, exercise-related changes in sleep quality should be assessed to improve our understanding of its potential for long-term changes of general health in RA patients.

Restful sleep plays an important role in the maintenance of health. Disturbed or unrestful sleep is associated with serious consequences such as an increased risk of morbidity and ultimately mortality [17].

Importantly, poor sleep (due to pain) in RA may contribute to increased pain and fatigue [75], or may contribute to depression and inflammation [34,76,77]. Therefore, treating poor sleep quality may be important to promote health and well-being of patients with RA.

Thus far, few studies have dealt with the treatment of sleep deprivation in patients with RA. In contrast, there are studies investigating medical (eszopiclone, zopiclone, valerian) or biological therapies with respect to sleep quality in patients with rheumatic diseases (tocilizumab, infliximab, anti-tumor necrosis factor α, abatacept) [78–80].

Cross-sectional studies have shown that physical inactivity increases the likelihood of having poor sleep [81]. Furthermore, it has been shown that, regardless of age and gender [82], the maximum aerobic efficiency is lower in patients with poor sleep quality than in those without sleep problems.

In a small study by McKenna et al. (2018), patients with inflammatory arthritis who underwent a walking-based training intervention were compared with a control group. A total number of 8 patients completed walking sessions two to three times a week for 8 weeks. The study was feasible, safe and achievable for all study participants. The participants in the training group showed a significant improvement in sleep duration and sleep quality compared to the control group. The side effects were mostly minor [83].

The American College of Sports Medicine (ACSM) divides training for people with chronic illness into cardiovascular, resistance training, flexibility exercises and neuro-motor exercises. Overall, the number of studies dealing with this specific question is still very small, so that no explicit

recommendations can be made. Nevertheless, it can be assumed that the existing training therapies and lifestyle changes in physical activity are likely to have a very positive effect on sleep.

It should be noted that the terms training and physical activity are different. The term training is defined as a planned action with physical workout over a defined period of time. Physical activity, on the other hand, is defined by everyday activities such as shopping or household tasks.

Exercise training

Which training is recommended for which patient? The basis for recommending activity and sports is a sufficient physical condition of the patient. Depending on the biological age and co morbidities, a patient can show a higher biological age. Many patients with chronic inflammatory diseases suffer not only from joint and muscle pain, but also have an increased risk of fractures due to generalized osteoporosis [84]. As a result of this pain, many patients avoid physical activity and simply rest. This leads to muscle waste and to rapid exhaustion. This vicious cycle intensifies with prolonged inactivity and increases the risk of cardiovascular diseases and diabetes mellitus. Furthermore, these patients have an increased cardiovascular mortality due to reduced oxygen uptake capacity [85]. Recent data show that 68% of patients with rheumatic diseases are inactive.

The culprit of inactivity is not only the pain and exhaustion, but also the fear of the harmful effect of sport on their illness [85]. For this reason, it makes sense to ask the patient about his personal sport preferences. In addition to the medical history, a joint status should be performed. Is it a monoarthritis of the shoulder or advanced polyarthritis? The information is important for further methodological training recommendations. As already mentioned, diagnostics for estimating fracture risk are recommended for patients with severe osteoporosis. The bone can be strengthened and stimulated to new growth by tensile and compressive loads. Suitable for this purpose are, e.g. special osteoporosis exercises or guided classic weight-bearing exercises.

The goal should be to build or maintain muscle mass and increase cardiopulmonary performance.

For example, in patients with rheumatoid arthritis, individualized strength and endurance training improved not only performance but also the cardiac risk profile (LDL, blood pressure), and reduced obesity [86,87]. Furthermore, the study by Cooney et al. (2011) showed a long-term, anti-inflammatory effect of training on the patient.

Through general physical training, it was possible to relieve the classic symptoms such as fatigue, morning stiffness, and pain significantly. In this context, it should be mentioned that neither patients nor doctors could ever prove a progression of the underlying disease through training [86]. There are, of course, so-called “red flags” of which patients should be mindful. During acute attacks of inflammation, the patient should not rest as previously recommended, but continue to perform moderate exercise until the acute attack is treated.

As already mentioned, the physical activity reflects our everyday life. In addition to training, it is a second important pillar in patients’ therapy. We can see various positive effects by consequently climbing stairs, cycling, or going for a walk. In general, the WHO recommends a daily step count of 10,000 steps, although this guideline cannot be applied to every clientele. The recommendation for a patient with chronic disease is 5000–7500 steps per day [88].

Recent studies, however, show positive effects of high-intensity training in rheumatoid patients with DMARD therapy [18,89,90]. In a Dutch study, a group of patients exercising a high load circuit training were compared to a control group receiving normal physiotherapy. In the training group, there was less joint damage to small joints of the foot and hand, less pain, lower cortisone demand, and a better overall aerobic performance compared to the control group [89]. These findings do not suggest that all patients should do high intensity training.

A study by Durcan et al. (2014) clearly showed that a training program led to a significant improvement in sleep quality and fatigue. This once again highlights the importance of fatigue as an outcome measure in RA and gives another reason to prescribe exercise in this population [91].

Summary

Regular physical training has been shown to improve cardiovascular performance and reduce pain. The American College of Sports Medicine (ACSM) divides training for people with chronic illness into cardiovascular, resistance training, flexibility exercises, and neuro-motor exercises [92].

Conflicts of interest

None of the authors have a conflict of interest in this paper.

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Practice points

- About 70% of patients with rheumatic diseases report disturbed sleep and sleep disorders.
- Patients with rheumatic disease show an increase in proinflammatory cytokine activity, and sleep deprivation leads to an excessive increase in pain.
- A successful treatment of poor sleep may potentially also treat pain.
- Activity and exercise have a very positive effect on the course of rheumatoid arthritis and also have a positive influence on the quality of sleep

Research agenda

- More studies are needed to understand the relationships of chronic inflammation at the molecular level.
- In addition, more intensive educational work is required in order to achieve the greatest possible compliance and to show patients the risk factors for a worsening of rheumatoid arthritis.

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