

Circadian sleep–wake rhythm disturbances in end-stage renal disease

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Abstract | End-stage renal disease (ESRD) is an increasing health problem worldwide. Given the increasing prevalence of this disease, the high cost of hemodialysis treatment and the burden of hemodialysis on a patient's life, more research on improving the clinical outcomes and the quality of life of hemodialysis-treated patients is warranted. Sleep disturbances are much more prevalent in the dialysis population than in the general population. Several studies investigating the effect and importance of sleep problems on quality of life in dialysis patients revealed that sleep disturbances have a major influence on the vitality and general health of these patients. Sleep disturbances in this patient group are caused both by the pathology of the renal disease and by the dialysis treatment itself. This Review focuses on circadian sleep–wake rhythm disturbances in individuals with ESRD. The possible external and internal influences on sleep–wake rhythmicity in patients with ESRD, such as the effect of dialysis, medications, melatonin and biochemical parameters, are presented. In addition, possible approaches for strengthening the synchronization of the circadian sleep–wake rhythm, such as nocturnal hemodialysis, exogenous melatonin, dialyzate temperature, exogenous erythropoietin, use of bright light and exercise during dialysis treatment, are explored. Further research in this area is warranted, and a greater awareness of sleep problems is needed to improve the quality of life of patients with ESRD.

Koch, B. C. P. *et al.* *Nat. Rev. Nephrol.* 5, 407–416 (2009); published online 26 May 2009; doi:10.1038/nrneph.2009.88

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the normal physiology of sleep.
- 2 List ways in which patients with end-stage renal disease (ESRD) may be at particular risk for sleep disturbances.
- 3 Identify how exogenous melatonin and nocturnal hemodialysis may improve sleep disturbances among patients with ESRD.
- 4 Specify other potential treatments for sleep disturbances among patients with ESRD.

Competing interests

The authors, the Journal Editor C. Harman and the CME questions author C. P. Vega declare no competing interests.

Introduction

Sleep disturbances are much more prevalent in the dialysis population than in the general population.¹ Several studies on the effect and importance of sleep problems on quality of life in patients on dialysis revealed that sleep disturbances have a major influence on the vitality and general health of these patients.² Sleep disturbances in patients on dialysis might be caused by both the pathology of the renal disease and the dialysis treatment itself.³ Although sleep disorders found in this population can be complex—for example, sleep apnea and restless legs syndrome and periodic limb movement disorder can cause sleep problems in patients on dialysis—this Review will focus on disturbances in the circadian sleep–wake rhythm. Focusing on these disturbances is a novel field of interest in this patient group, but such disturbances can have a prominent role in the development of sleep disorders, and, therefore, in impairment of quality of life, in patients with end-stage renal disease (ESRD).

An overview of the circadian sleep–wake rhythm, the scope of the problem regarding sleep disturbances in this population, the possible external and internal influences on sleep–wake rhythmicity in patients with ESRD and also possible approaches for strengthening the synchronization of the circadian sleep–wake rhythm will be explored.

Circadian rhythms

Circadian rhythms are fluctuations of nearly all bodily functions that recur on a cycle of about 24 h. In mammals, the circadian system is composed of many individual tissue-specific cellular clocks whose phases

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Key points

- Sleep disturbances are much more prevalent in patients with end-stage renal disease (ESRD) than in the general population
- Several studies on the impact and importance of sleep problems on quality of life in patients on dialysis revealed that sleep disturbances have a major effect on the vitality and general health of these patients
- Sleep disturbances in patients on dialysis might be caused by the pathology of the renal disease as well as by the dialysis treatment itself
- External and internal factors that might be associated with disrupted sleep–wake rhythmicity in patients with ESRD include dialysis, medications, melatonin rhythm and biochemical parameters
- Approaches that might be useful in treating disturbances in the circadian sleep–wake rhythm in patients with ESRD include nocturnal dialysis, exogenous melatonin, lowering dialyzate temperature, exogenous erythropoietin, bright light and intradialytic exercise

are synchronized by the master circadian pacemaker residing in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus of the brain (Figure 1). These tissue-specific clocks are located throughout the body and can also function independently of the SCN.^{4,5} Light that impinges on photoreceptors in the retina causes signals to travel along the optic nerve to the SCN. Signals from the SCN travel to several regions of the brain and periphery.

This Review will focus on the circadian sleep–wake cycle, which is regulated by the SCN. This circadian cycle can be described by periods of low and high sleep propensity (that is, the urge to fall asleep) each day.⁶ The sleep–wake cycle can be influenced by a number of factors (Figure 2). A circadian core body temperature cycle is well documented.⁷ Sleep propensity is closely linked with core body temperature. In humans, sleep is typically initiated in the falling limb of the temperature circadian rhythm.⁷

Circadian rhythm sleep disorders are primarily caused by alterations in the circadian time-keeping system or by a misalignment between the endogenous circadian rhythm and the external factors that affect the timing or duration of sleep. The diagnostic criteria for circadian rhythm sleep disorders and subtypes of these disorders are similar to the criteria published in the 2nd edition of the International Classification of Sleep Disorders (ICSD-2).⁸ In clinical practice, the most commonly encountered primary circadian rhythm sleep disorders are delayed sleep phase type (DSPT) and advanced sleep phase type (ASPT) disorders. These disorders are characterized by sleep onset and wake-up times that are delayed (in DSPT) or advanced (in ASPT) by 3 or more hours relative to the desired or socially acceptable sleep and wake times. Nonentrained, or free-running, sleep–wake type is a disorder that occurs predominantly in blind individuals and is characterized by a steady daily drift of the major sleep period as the sleep–wake cycle is usually longer than 24 h. When the nonentrained circadian clock is out of phase with the timing of conventional sleep and wake times, affected individuals suffer from insomnia and excessive daytime sleepiness.⁹

Definitions of sleep

Two main states of sleep have been defined: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Both types are present in nearly all mammals and these states are as distinct from each other as each is from wakefulness. During REM sleep, the electroencephalogram (EEG) is desynchronized, muscles are atonic (lacking normal muscular tone or strength) and dreaming is typical. During NREM sleep, cortical EEG shows a synchronous pattern and this sleep state is associated with low muscle tone and minimal mental activity.¹⁰

NREM sleep is conventionally subdivided into four stages, 1, 2, 3 and 4. Under normal circumstances, sleep begins with NREM stage 1 sleep and advances through progressively deeper sleep—NREM stages 2, 3 and 4—before the first episode of REM sleep occurs approximately 80–100 minutes after sleep onset. On EEG, stages 3 and 4 NREM sleep are characterized by increasing amounts of high-voltage, slow-wave activity.¹⁰ NREM sleep and REM sleep alternate through the night in a cyclical fashion.¹⁰

Several parameters are used to measure sleep patterns in normal sleep. Sleep parameters can be measured objectively through use of polysomnography or actigraphy, and subjectively through use of sleep logs or sleep questionnaires. Subjective sleep measurements can be correlated against objective measurements. Sleep onset latency is the length of time between going to bed and sleep onset. Total sleep time is the duration of recorded sleep. Awake time is the total duration of intermittent wakefulness within the sleep period.¹⁰ Sleep efficiency is the total sleep time divided by the time in bed and is a well recognized measure of sleep quality.¹¹ The fragmentation index is an index of restlessness of the sleep and is calculated in a number of different ways.^{12–14}

Melatonin and the sleep–wake rhythm

The neurochemical agent melatonin, which is produced mainly by the pineal gland, plays a key role in the regulation of the circadian sleep–wake rhythm.¹⁵ The production pathway for the synthesis of melatonin from tryptophan is schematically presented (Figure 3). Activity of a rate-limiting enzyme in melatonin synthesis—5-hydroxytryptamine *N*-acetyltransferase (NAT)—is regulated by the adrenergic activation of the pineal cells. The light–dark cycle is the main *zeitgeber* (time cue) of the regulating system of melatonin secretion. The photic information is transmitted to the SCN via retino-hypothalamic fibers. The subsequent signal from the SCN travels onwards through the cervical sympathetic ganglia and ultimately influences melatonin production in the pineal gland.^{15,16} During the day, the presence of light inhibits melatonin secretion by the pineal gland (Figure 4).¹⁷

In physiological conditions, melatonin is only secreted during the night, with higher maximum levels of the hormone occurring in the serum of young adults than in older subjects.^{18–20} The timing of onset of the circadian melatonin rhythm is best quantified by the onset of the

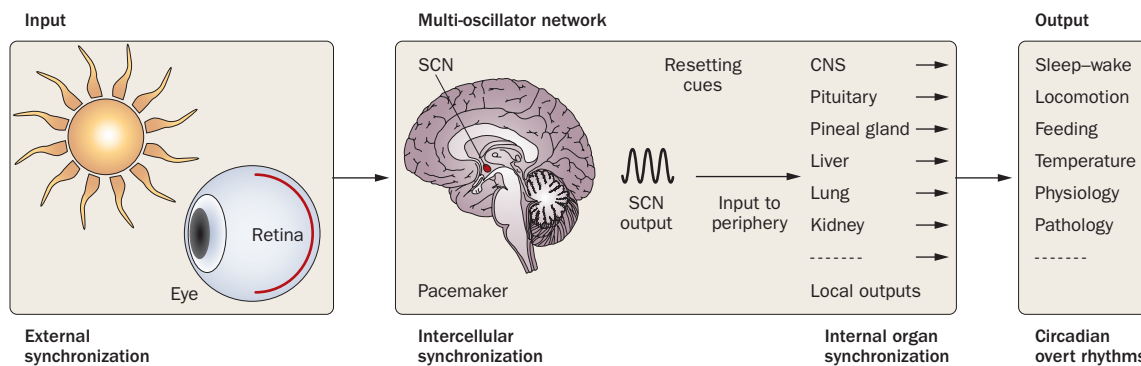


Figure 1 | The human circadian clock. The circadian clock can be described as having three components: the inputs, the 24 h clock and the outputs. The mammalian circadian clock is organized in a hierarchy of multiple oscillators, in which the SCN is the central pacemaker at the top of the hierarchy. The SCN is synchronized by the external 24 h cycle and in turn coordinates the physiological outputs. The multi-oscillator network is synchronized through multiple lines of communication. For the SCN, light represents the primary input. Peripheral oscillators are reset by timing cues from the SCN (that is, SCN outputs), which regulate local circadian physiology (local outputs). Intercellular synchronization within the SCN is very important for the robust operation of the entire body clock. Abbreviations: CNS, central nervous system; SCN, suprachiasmatic nucleus. Adapted, with permission, from Nature Publishing Group © Liu, A. C., Lewis, W. G. & Kay, S. A. *Nat. Chem. Biol.* 3, 630–639 (2007).⁹⁹

evening rise in plasma melatonin, the dim light melatonin onset (DLMO).²¹ The DLMO can be calculated as the first interpolated point above 10 pg/ml in serum after which the melatonin concentration continues to rise.²² The increase in melatonin levels that occurs in the evening correlates with the onset of self-reported evening sleepiness²³ and with the increase in the evening sleep propensity.²⁴ The salivary concentration of DLMO is proposed to be 4 pg/ml in patients with DSPT.²⁵

The SCN initiates synthesis of melatonin by the pineal gland. Melatonin influences the SCN by a feedback mechanism. In healthy humans, the nocturnal decline in core body temperature is inversely related to the rise in melatonin level.²⁶

Melatonin receptors have been detected in several organs, including the kidney. In addition to its effects on the circadian sleep–wake rhythm, melatonin has been suggested to influence the cardiovascular system, the immune system and the endocrine system.^{27,28}

Sleep disturbances in renal disease

Studies have suggested that between 30% and 80% of individuals with ESRD report subjective sleep-related problems.^{29–32} A population study of daytime hemodialysis patients showed that 60% of these patients experienced subjective sleep problems.³³ Information on circadian rhythm sleep disorders, such as DSPT, is not available in patients with ESRD.

Patients on daytime hemodialysis and patients with chronic kidney disease (CKD) have reduced total sleep time and reduced sleep efficiency in comparison with healthy subjects.³⁴ Patients on hemodialysis have less REM sleep, a higher brief arousal index, a higher respiratory disturbance index, less total sleep time, increased wake-time after sleep onset, lower sleep efficiency, a higher periodic limb movement index and longer sleep

onset latencies in comparison to patients with CKD.³⁴ These findings suggest that the sleep problems experienced by patients with CKD and those experienced by individuals on hemodialysis might have different etiologies. Functional and psychological factors might have a greater role in patients with CKD, and intrinsic sleep disruption (for example, arousal, apnea and limb movements) secondary to the effects of intermittent daytime hemodialysis might have a more important role in individuals on hemodialysis.³⁴ Furthermore, low serum albumin and psychological stress have been associated with insomnia in individuals with CKD.³⁵ Population-specific sleep-promoting interventions might be needed.

Little data comparing the prevalence of sleep disorders in patients on daytime hemodialysis and those on peritoneal dialysis (PD) exist. One study reported that sleep disturbances are more common in hemodialysis patients than in PD patients.³⁶ However, other studies found that the type of dialysis and dialysis adequacy did not affect the prevalence of sleep disorders.³⁷ One study showed that patients on automated peritoneal dialysis (APD) were more likely to experience sleep problems than patients on continuous ambulatory peritoneal dialysis (CAPD).³⁸ Another study showed that changing from CAPD to APD resulted in an alleviation of sleep apnea, possibly owing to more vigorous clearance of fluid with APD.³⁹ Actigraphy or polysomnography studies have rarely been performed in patients on PD and more such studies are needed. It may be hypothesized that the different dialysis techniques (that is, the short, but intense urea reduction in conventional daytime hemodialysis and the slow, but constant urea reduction in PD) might have an important role in the differences in the prevalence of sleep problems in these populations. The influence of urea on melatonin and sleep–wake rhythm will be discussed.

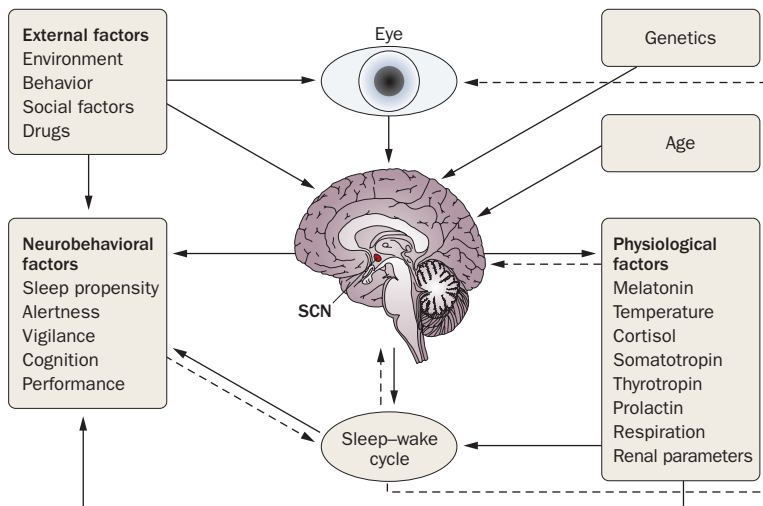


Figure 2 | Factors influencing the sleep–wake cycle. The signals between the extrinsic factors and the SCN and the signals between the SCN and the sleep–wake rhythm, the physiological variables and the neurobehavioral variables are indicated by solid arrows. The feedback influences of the variables on this pathway are indicated by dashed arrows.¹⁰⁰ Abbreviation: SCN, suprachiasmatic nucleus.

Factors causing sleep disturbances in ESRD

In patients with ESRD, the circadian sleep–wake rhythm can be disrupted by both internal factors (for example, biochemical parameters and melatonin) and external factors (for example, dialysis and medications).

The effects of dialysis

Daytime hemodialysis can increase daytime sleep propensity, which can lead to delayed sleep onset and decreased night time sleep. Several possible causes for these sleep disturbances exist.

Firstly, mononuclear cells produce interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) as a result of complement activation, interaction with the dialyzer, and/or exposure to bacterial cell wall fragments (muramyl peptides).^{40–42} IL-1 is involved in both fever production and sleep induction.⁴⁰ Fever and chills commonly occur during or after dialysis in the presence of endotoxin-contaminated dialyate. However, a slight increase in body temperature has also been observed in patients undergoing hemodialysis with uncontaminated dialyate.⁴² IL-1, IL-6 or TNF produced by peripheral blood mononuclear cells in the bloodstream are thought to be recognized as a pyrogenic signal by specific centers within the central nervous system (CNS). Such signals induce the synthesis of prostaglandins that represent the central mediators of the coordinated response, which leads to a rise in core body temperature.^{3,40–42}

Body temperature can also rise as a result of heat load from the dialysis bath. Because of the known association between body cooling and sleep onset,^{43,44} hemodialysis-associated elevations in body temperature might activate cooling mechanisms that enhance daytime sleep propensity, particularly during the post-hemodialysis period. Chronic, episodic elevations in body temperature in

association with hemodialysis might therefore alter the sleep propensity rhythm.⁴⁵

In addition, dialysis can induce imbalances of brain and serum osmolarity, resulting in shifts of water from the blood to the brain. This condition, known as disequilibrium syndrome, is associated with a paradoxical acidosis in the cerebral spinal fluid that results from the slow movement of bicarbonate across the blood–brain barrier. Disequilibrium syndrome causes cerebral edema, which can lead to depression of the CNS. This depression causes a decrease in alertness and arousal.^{46,47} The depression of the CNS in dialysis patients can lead to daytime sleepiness and can, therefore, result in an impaired sleep–wake rhythm.⁴⁸

Also, the hemodialysis procedure is a significant physical and psychological stressor. The stress response triggered by emotional arousal can lead to reactions such as anxiety, depression and increased daytime sleepiness.^{49,50}

Finally, hemodialysis may also affect the sleep–wake cycle by altering exposure to *zeitgebers* that help set or entrain the circadian system. The time of day that treatment is given can affect an individual’s wake-up time, time for physical activity, meal times, light exposure, social activities³ and even survival.⁵¹

The effects of medication

Several drugs that are commonly prescribed to patients on dialysis can have adverse effects on sleep such as insomnia and sedation.⁵² This Review focuses only on medications with potentially sleep-disturbing effects that are prescribed more often to ESRD patients than to individuals of the same age and gender in the general population.⁵³ Among the antihypertensive drugs, β -adrenergic-receptor antagonists (β -blockers) have been associated with tiredness, insomnia, nightmares and vivid dreams, depression, mental confusion and psychomotor impairment.⁵² One study found that 60% of hemodialysis patients used β -blockers whereas only 12% of the general population of the same age and gender used these drugs.⁵³ Both age of the patient and the dose given can affect the severity of adverse effects, which may diminish with time on the medication. Older patients are more sensitive to medication, as a result of altered absorption and metabolism of drugs in older age.⁵⁴ In general, sleep disturbances seem to be more common with lipophilic β -blockers (for example, metoprolol) than with hydrophilic β -blockers (for example, atenolol). However, even atenolol, the most hydrophilic β -blocker available, has been shown to increase total wake time at night.⁵⁵ β -blockers have also been associated with depression of nocturnal melatonin production.⁵⁶

Benzodiazepines can be used for their sleep-inducing effects. These drugs increase total sleep time, reduce sleep latency, and suppress REM and slow-wave sleep.⁵⁷ Benzodiazepines also decrease nocturnal melatonin production.⁵⁸ Research in a group of hemodialysis patients disclosed that Dutch patients on hemodialysis were

twice as likely to be prescribed benzodiazepines compared with the general Dutch population of the same age and gender.⁵³ Benzodiazepines have been shown to have minimal efficacy in the general older population with sleep problems⁵⁹ and in hemodialysis patients.³³

The effects of melatonin

Studies in patients with chronic renal failure, patients on daytime hemodialysis and animal models of chronic renal failure have shown that the nocturnal surge in melatonin above DLMO is absent in chronic renal failure.^{60–64} The melatonin rhythm was more likely to be abolished in patients on hemodialysis than in patients with chronic renal insufficiency who were not on hemodialysis, suggesting an influence of hemodialysis on the rhythm.⁶² Decreased melatonin levels are associated with more-severe sleep disturbances in hemodialysis patients.⁶⁵ Melatonin levels during the daytime in patients with renal disease are conflicting as both increased and decreased melatonin levels have been reported in daytime hemodialysis patients.^{61–64}

A number of mechanisms could explain the disturbance of the circadian melatonin rhythm in patients with renal disease. As mentioned above, daytime dialysis can result in daytime sleepiness and nocturnal insomnia.^{1,3} The resulting disturbed sleep–wake rhythm could lead to the absence of the trigger to start melatonin production at night.³ The decline in melatonin levels in patients with renal insufficiency has been reported to be the result of an impairment in β -adrenoreceptor-mediated responsiveness.^{62,66} The adrenergic system plays an important role in the synthesis of NAT,^{58,66} a key enzyme in melatonin biosynthesis (Figure 3). Nocturnal levels of NAT activity are decreased in rats rendered uremic by partial nephrectomy.⁶⁷ In addition, sleep apnea is common in patients with ESRD. During the daytime, melatonin levels have been reported to be much higher in the general apnea patient population without ESRD than in healthy controls, but the nocturnal melatonin surge was absent in the patients with apnea.⁶⁸

Although our study found that patients on APD experienced fewer sleep problems than patients on hemodialysis, melatonin rhythm was absent in both patient groups, suggesting that nocturnal melatonin production might have a different role in patients on APD than in patients on hemodialysis.¹³

The effects of biochemical parameters

Blood urea nitrogen level is significantly higher in patients on conventional hemodialysis with pathological daytime sleepiness than in 'alert' patients.^{69,70} In addition, sleep onset latency is negatively correlated with blood urea nitrogen level.⁷⁰ These findings indicate that excessive daytime sleepiness in patients with ESRD might be related to uremia.^{69,70} Furthermore, in plasma from uremic patients the number of β_1 - and β_2 -adrenoreceptors is significantly decreased, compared with normal values.⁷¹ Such impairment in adrenergic

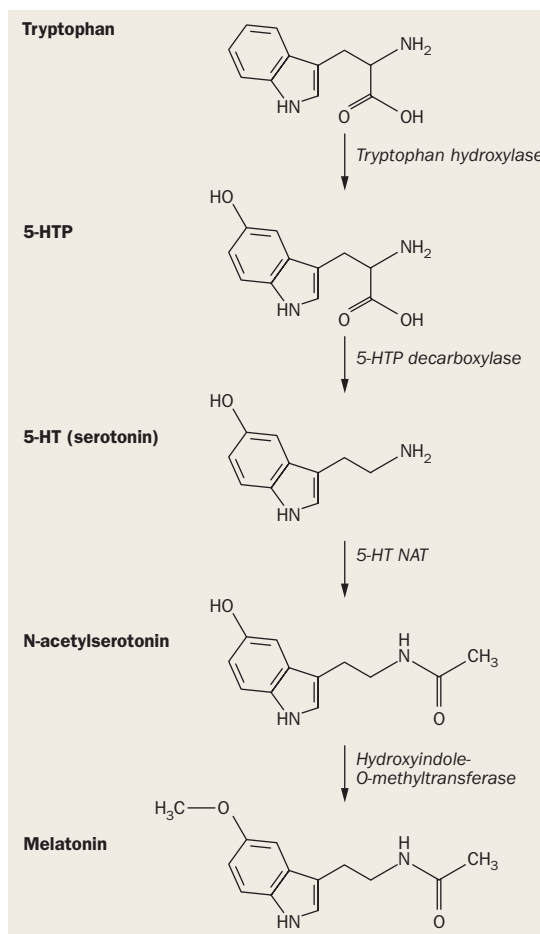


Figure 3 | Synthesis of melatonin from tryptophan. 5-HT NAT and hydroxyindole-O-methyltransferase are the rate-limiting enzymes in melatonin synthesis. Abbreviations: 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; NAT, N-acetyltransferase.

function is associated with the decline in melatonin levels in patients with renal insufficiency.⁶³

The results of earlier studies in patients on hemodialysis investigating other possible associations between biochemical parameters and sleep disturbances show conflicting results. One study showed serum phosphate levels to correlate inversely with sleep disturbances,⁷² but another study showed that only urea showed a significant relationship with sleep disturbances.²⁹ Other researchers found no correlations at all between biochemical markers and sleep disturbances.³⁰ In one study investigating sleep disturbances among 694 patients on hemodialysis, plasma creatinine and urea levels were surprisingly higher in the control group (without insomnia) than in the insomnia group.³¹ This finding was probably a result of an increased protein intake and a greater percentage of male individuals in the control group.³¹ A study of 883 patients on maintenance dialysis found that advanced age, excessive alcohol intake, cigarette smoking, polyneuropathy and a dialysis shift in the morning were independent risk factors for sleep disturbances.³² Laboratory

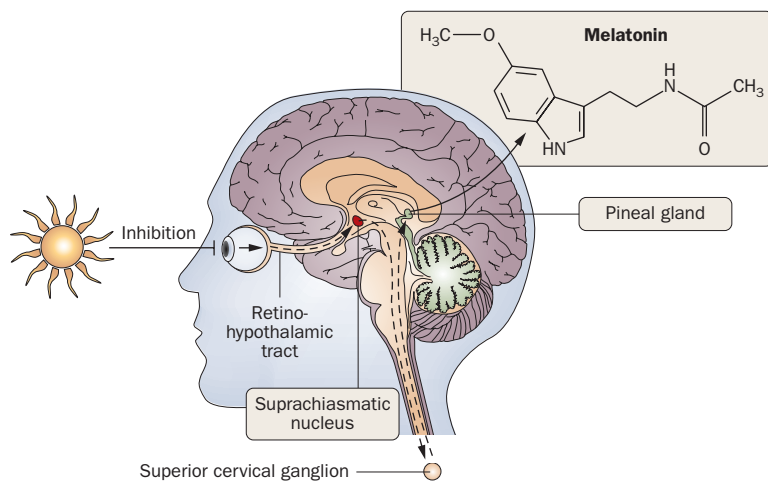


Figure 4 | The mechanism through which light inhibits melatonin secretion by the pineal gland involving the neural pathway originating in the retina and passing through the suprachiasmatic nucleus in the brain, to reach pinealocytes via adrenergic nerves and adrenergic receptors, and subsequently to the periphery. During darkness, the circadian system 'free runs', resulting in increased melatonin concentrations. The dotted lines represent the signal pathway. Adapted with permission, from Polish Physiological Society © Konturek, S. J., Konturek, P. C., Brzozowski, T. & Bubenik, G. A. *J. Physiol. Pharmacol.* **58** (Suppl. 6), 23–52 (2007).¹⁷

data were not, however, reported in that study.³² Our study, published in 2008, found that increased levels of phosphate and urea correlated independently with impaired sleep efficiency. Hemoglobin levels between 100 g/l and 120 g/l were associated with improved sleep efficiency.³³ We found no other relationships between laboratory, clinical or demographic parameters and sleep efficiency. Erythropoietin deficiency seems to have a role in the dysregulation of melatonin metabolism in chronic renal failure.⁶⁰ However, the precise role of erythropoietin in melatonin metabolism in renal failure, the existence of its circadian rhythm^{73–76} and its relationship with melatonin need further investigation.

Resynchronizing the sleep–wake rhythm

Various approaches have the potential to resynchronize a disrupted circadian sleep–wake rhythm, including nocturnal dialysis, lowering of dialyzate temperature, administration of exogenous melatonin, administration of exogenous erythropoietin, bright light and intradialytic exercise. Studies of these approaches in ESRD, although limited, have been successful in strengthening the circadian sleep–wake rhythm in this population.

Nocturnal hemodialysis

Several studies have investigated the effect of changing from conventional hemodialysis to nocturnal home hemodialysis. The prevalence of sleep apnea declined in patients switching from conventional hemodialysis to nocturnal home hemodialysis, but improvements in sleep efficiency, periodic limb movement disorder and sleep fragmentation were not seen.^{77,78} Another study

showed that conversion to nocturnal home hemodialysis resulted in a decrease in daytime sleepiness and an improvement in sleep onset latency, partly owing to improved control of uremia.⁷⁰ With respect to strengthening the sleep–wake rhythm, nocturnal hemodialysis has some advantages. Although anxiety, restricted positions and alarms might have adverse effects on sleep during nocturnal dialysis, the sleep-promoting effects of dialysis described earlier coincide with the appropriate and conventional time of day. Therefore, a switch to nocturnal dialysis could restore the normal temporal relationship between the sleep period and the other circadian rhythms, and would likely result in an improved quality of both sleep and daytime functioning. The increased dialysis time of nocturnal hemodialysis leads to improved clearance of toxins, which might enhance the improvements in sleep and daytime functioning further. In addition, it is hypothesized that if the normal synchronization between sleep–wake behavior and the circadian system is restored, the endogenous melatonin concentration will exhibit its normal nocturnal surge. To the best of our knowledge, only one study investigating the melatonin rhythm in nocturnal dialysis has been published, and found no difference between melatonin rhythm on dialysis nights and non-dialysis nights.⁶⁵ Data on the difference in melatonin rhythm between patients on daytime hemodialysis and those on nocturnal hemodialysis are limited, but a recent study demonstrated that objective and subjective sleep parameters improved and a partial recovery of the melatonin rhythm was found when patients switched from conventional daytime hemodialysis thrice weekly to nocturnal in-center hemodialysis 4 nights per week for 6 months.⁷⁹

Exogenous melatonin

One potential solution to circadian desynchronization problems is a chronobiotic, a drug that phase shifts circadian rhythms in the desired direction—resynchronizing the rhythm—and acts as a *zeitgeber* to maintain this stable phase. Exogenous melatonin could presumably fulfill this role.⁵⁸ In studies of individuals without renal disease in whom normal melatonin rhythm was disturbed, administration of exogenous melatonin resulted in synchronization of the melatonin rhythm and an improved sleep rhythm.^{80,81} Subjective sleep quality improved and patients felt more refreshed after a night of sleep.^{80,81} Research on the effect of exogenous melatonin supplementation in patients on dialysis is limited. Exogenous melatonin has also been shown to have a beneficial effect on symptoms of insomnia in medically ill patients recently admitted to hospital with diseases including cardiovascular disease, diabetes, pulmonary disease and liver disease.⁸² Again, the study included no patients with renal disease and only subjective measurements of sleep evaluation were used.

In individuals with an inappropriately timed endogenous melatonin rhythm, exogenous melatonin can produce a phase advance or a phase delay in the melatonin

rhythm, thereby resynchronizing the rhythm.⁸³ In individuals with an abolished melatonin rhythm and an absence of the nocturnal melatonin surge, however, exogenous melatonin might have another role. Exogenous melatonin bypasses NAT, a key enzyme in melatonin synthesis, which might result in a temporal recovery of the enzymatic activity.⁸¹ Therefore, after a period of exogenous melatonin administration, the endogenous enzymatic activity of NAT might be resensitized, enabling the synthesis and release of endogenous melatonin to be triggered at night.⁸¹ A randomized, controlled, crossover study in 20 daytime hemodialysis patients found a decrease in sleep onset latency, relief of sleep fragmentation and a restored melatonin rhythm after administration of 3 mg melatonin at 2200 h every night.⁸⁴

Lowering dialyrate temperature

Patients on hemodialysis, who are typically hypothermic,⁸⁵ often obtain a net heat load during a dialysis treatment session. This net heat load activates the cooling process in the body, which is associated with the onset of sleep propensity.⁴⁸ Subsequent daytime napping therefore increases, which can result in a disturbed sleep–wake rhythm.⁴⁹ One study showed that decreasing dialyrate temperature resulted in improved nocturnal sleep, by decreasing sympathetic activation and maintaining the normally elevated nocturnal skin temperature until later into the morning.⁸⁶ The time of sleep onset was earlier with cool dialyrate (35 °C) than with warm dialyrate (37 °C), and trends were seen towards longer total sleep and shorter latencies to REM sleep. The heat load was significantly lower with cool dialyrate than with warm dialyrate during and after dialysis.

Exogenous erythropoietin

A study in rats with chronic renal failure showed that administration of erythropoietin resulted in the normalization of the defective melatonin rhythm.⁶⁰ Amelioration of melatonin metabolism with erythropoietin administration in rats with chronic renal failure appears to be consistent with the demonstrated beneficial effects of this therapy on various other neuroendocrinological disorders of uremia.⁸⁷ Erythropoietin therapy has been shown to restore thyroid-stimulating hormone response to thyroid-releasing hormone, to improve follicle-stimulating hormone response to gonadotropin-releasing hormone and to normalize the basal levels of growth hormone and prolactin in patients with ESRD.⁸⁷

The available data do not allow any conclusions as to the mechanism(s) by which erythropoietin replacement improves the dysregulation of melatonin metabolism in chronic renal failure. Further studies are required to determine whether the effect of erythropoietin therapy is mediated by correction of anemia or represents a direct action of the hormone on melatonin production.⁶⁰

Exogenous melatonin has been shown to prevent oxidative stress induced by iron and erythropoietin administration in patients on chronic hemodialysis.⁸⁸

A study in patients on hemodialysis showed that normalization of hematocrit level with recombinant human erythropoietin therapy resulted in improvements in periodic limb movement disorder, improvements in sleep quality and less daytime sleepiness, probably owing to an increased sense of well-being and improved cognitive functioning.⁸⁹

Furthermore, a study investigating anemia correction in patients with congestive heart failure and anemia found that improvements in hemoglobin level (following treatment with erythropoietin and intravenous iron) correlated significantly with the improvements in minimal oxygen saturation seen during sleep and with decreases in daytime sleepiness.⁹⁰ Anemia correction with erythropoietin treatment was also associated with a reduction in sleep-related breathing disorders in this patient group.

Exercise during hemodialysis

As daytime napping during hemodialysis treatment has been associated with disrupted night-time sleep,⁶⁹ exercise during hemodialysis treatment might have a beneficial effect on the sleep–wake rhythm. Indeed, improvements in physical functioning and health-related quality of life were seen after the initiation of exercise training in patients on hemodialysis.⁹¹ In addition, transcutaneous electrical muscle stimulation and passive cycling movements have been shown to have beneficial effects on blood pressure and urea and phosphate removal during hemodialysis.⁹²

Symptoms of restless legs syndrome have also been shown to be attenuated when hemodialysis patients participate in intradialytic aerobic exercise training.⁹³ No studies investigating the association between exercise and the sleep–wake rhythm in patients with ESRD have yet been published, but studies in other groups have shown that physical exercise is associated with improved sleep, as measured by actigraphy.⁹⁴

Use of bright light

The circadian system is highly sensitive to environmental light and might not function optimally in the absence of its synchronizing effect. Use of bright light ($\pm 1,000$ lux) has been shown to ameliorate sleep disturbances in the elderly population.⁹⁵ With advancing age, the circadian clock may initiate sleep-promoting mechanisms at an earlier time of day (phase advance) and the amplitude of the circadian variation in sleep propensity is lower. Bright light can influence circadian factors, and timed exposure to bright light can be used to alleviate insomnia in older individuals.^{96,97} Not all research on bright light in older individuals with insomnia have shown positive results, however.⁹⁸

Bright light has not yet been studied in patients with ESRD, but it might be an interesting new field of research given that ESRD patients show a desynchronization of the circadian sleep–wake rhythm as do older individuals with insomnia.

Conclusions

An overview of the external and internal factors involved in the sleep–wake rhythm of patients with ESRD has been presented. These factors can lead to disruption of the circadian sleep–wake rhythm and sleep disturbances in this patient population. Several approaches for resynchronization of the biological clock in patients on hemodialysis have been discussed. Possible causes of sleep disturbances, which are highly prevalent in the ESRD population, have been described. Although different approaches to decrease such disturbances are outlined, data are limited. Further research is warranted, and

a greater awareness of the problem is needed to improve the quality of life of patients with ESRD.

Review criteria

The PubMed database was searched using the following terms: “end-stage renal disease”, “circadian rhythm”, “hemodialysis”, “melatonin” and “biological clock”. The bibliographies of retrieved articles were searched for relevant references. We focused on English-language articles published in the past 25 years.

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Acknowledgments

The authors would like to thank the Dutch Kidney Foundation for supporting our work and Inzicht Graphic Design, Arnhem, The Netherlands, for their assistance with the figures. Charles P Vega, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the MedscapeCME-accredited continuing medical education activity associated with this article.