

The effects of melatonin on sleep–wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study)

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Disturbances of sleep–wake rhythm are frequently reported in daytime haemodialysis patients.
- The melatonin rhythm, which plays an important role in synchronization of the sleep–wake rhythm, is disturbed in this patient group.
- In other patient groups with disturbed melatonin rhythm, use of exogenous melatonin resulted in an improvement of sleep quality and melatonin rhythm.

WHAT THIS STUDY ADDS

- This is the first study on the effects of exogenous melatonin on sleep–wake rhythm in haemodialysis patients.
- Due to exogenous melatonin, sleep parameters such as sleep fragmentation, sleep onset latency and subjective sleep quality improved.
- Nocturnal melatonin rise was recovered.

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AIM

The aim of this study was to investigate the effects of exogenous melatonin on sleep–wake rhythm in haemodialysis patients.

METHODS

The study design is a randomized, double-blind, placebo-controlled, cross-over study of 3 × 6 weeks melatonin 3 mg at 22.00 h every night. Haemodialysis patients were asked to fill out a sleep questionnaire and to wear an actometer to record their sleep problems objectively. Furthermore, melatonin concentrations in saliva were sampled the night after daytime haemodialysis and the consecutive night. Actometers, the sleep questionnaire and melatonin concentrations were repeated during the study.

RESULTS

In total, 20 patients (six female, median age 71 years) completed the investigation. On nights after daytime dialysis, objective sleep onset latency decreased significantly from a median of 44.5 (placebo) to a median of 15.5 min with melatonin ($P < 0.01$). Sleep efficiency increased from 67.3 to 73.1% with melatonin ($P < 0.05$). Actual sleep time increased from 376 min (placebo) to 388 min with melatonin ($P < 0.01$), and sleep fragmentation decreased from 4.5 to 3.1 ($P < 0.01$). Furthermore, subjective sleep parameters improved also. Patients reported less time needed to fall asleep ($P < 0.05$) and fewer wake periods ($P < 0.05$) on the nights with and without daytime dialysis and an increase in sleep time on the night of daytime dialysis ($P < 0.05$). Furthermore, the nocturnal melatonin rise was recovered.

CONCLUSION

Treatment with melatonin resulted in an improvement of subjective and objective sleep parameters, as well as a recovered nocturnal melatonin rhythm.

Introduction

End-stage renal disease (ESRD) is associated with an increased prevalence of sleep disturbances, which have a major influence on quality of life and morbidity [1, 2]. Approximately 50–80% of patients with ESRD complain about disturbances of the sleep–wake rhythm [1]. In this patient group circadian rhythmicity, defining periods of low and high sleep propensity [3], can be negatively affected due to pathology of ESRD [1] and the dialysis process, causing daytime sleepiness and nocturnal insomnia [4]. The pineal hormone melatonin plays an important role in the synchronization of circadian sleep–wake rhythm. In normal conditions, melatonin is secreted only during the night [5]. The onset of the evening rise in endogenous melatonin is called the dim light melatonin onset (DLMO) and can be calculated as the first interpolated point above 4 pg ml^{-1} in saliva after which the endogenous melatonin concentration continues to rise [6]. This increase in endogenous melatonin level in the evening correlates in normal circumstances with the onset of self-reported evening sleepiness [7] or with the increase in evening sleep propensity [8]. An absence of the nocturnal rise in melatonin concentration in daytime haemodialysis patients has been described earlier [9, 10]. Exogenous melatonin resulted in improved sleep–wake rhythm in other patient groups with disturbed melatonin rhythm [11]. Studies on exogenous melatonin and sleep–wake rhythm of haemodialysis patients have not been described before.

The aims of this study were to investigate the effects of exogenous melatonin on sleep–wake rhythm, focused on sleep quality and feeling rested during daytime, and melatonin rhythm in haemodialysis patients.

Methods

The study design was a randomized, double-blind, placebo-controlled, cross-over study (Figure 1). The Medical-Ethical Committee approved the protocol of the study (ClinicalTrials.gov: NCT00404456), and informed consent was obtained from all patients. Patients between 18 and 85 years and on stable haemodialysis (>3 months on haemodialysis with adequate dialysis efficacy) were included. Patients were excluded in case of prior use of melatonin, use of hypnotics that could not be stopped during the study, and severe psychological or neurological disease. In the first 6 weeks melatonin 3-mg tablets (Pharmanord®, Vejle, Denmark) or placebo tablets (Pharmanord®) were taken at 22.00 h every night. In the second period of 6 weeks placebo and melatonin tablets were reversed. All patients received melatonin 3-mg tablets for the last 6 weeks. There was no wash-out procedure included since melatonin has a short half-life, and Dahlitz *et al.* [12] have shown that the advancing effect of melato-

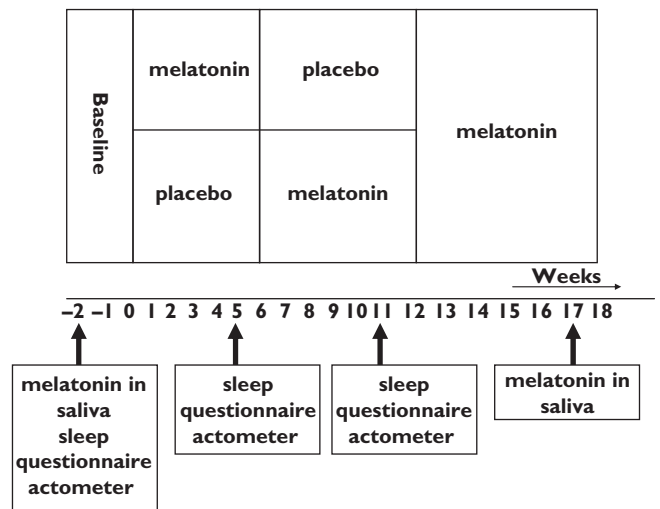


Figure 1

The design of this study. The study measurements and the date of measurement are displayed

nin on the sleep–wake rhythm disappeared within 2 days after stopping the administration. As we performed measurements after 5 weeks in a study period, the carry-over effect will be negligible.

If the patients had a regime of Monday–Wednesday–Friday haemodialysis, all measurements during the study were started on a Monday. If patients had a regime of Tuesday–Thursday–Saturday haemodialysis, all measurements during the study were started on a Tuesday. At baseline, daytime haemodialysis patients were asked to fill out a sleep questionnaire and to wear an actometer for seven consecutive days. In addition, melatonin concentrations in saliva were measured the night after daytime haemodialysis and the consecutive night. When the median sleep onset latency, measured by means of the actometer, was >15 min and melatonin concentration was $<4 \text{ pg ml}^{-1}$ in saliva during the night (inclusion criteria), patients could be included in the study.

During treatment, vascular access was achieved by two needle placements in fistulas or grafts or by internal jugular catheter. Dialysate flow was kept at 300 ml min^{-1} , blood flow was set at $200\text{--}300 \text{ ml min}^{-1}$. High flux polysulfone 1.3/1.8 m^2 dialysers were used (F60/F80; Fresenius Medical Care, Lexington, MA, USA). Information on medication that interfered with melatonin rhythm (such as β -blockers) [5] was collected.

Actigraphy

Actigraphy is an established sleep-monitoring method that records wrist movements and automatically discriminates rest–activity patterns interpreted in terms of sleep and wake periods [13]. Model Actiwatch-L (Cambridge Neurotechnology Ltd®, Cambridge, UK) actometers that

were used have been validated against polysomnography in the haemodialysis population [14]. The actometer is placed on the wrist of the arm without graft or fistula. Patients were asked to write down the times of going to bed (beginning of bedtime) and getting up (end of bedtime) on a registration form, provided with the actometer. On the basis of dedicated software (Actiwatch Activity & Sleep Analysis version 5.32), 1-min epochs of actigraphic data were scored as sleep or wake in the main study [15]. The following parameters were calculated, according to standardized methods [16]: actual sleep time, defined as the duration of actually recorded sleep; actual awake time, the total duration of intermittent wake periods, i.e. the portion of wakefulness within the bed period; sleep efficiency, the actual sleep time divided by time in bed, a well-recognized measure of sleep quality; and sleep onset latency, the difference between in-bed time and sleep onset. Furthermore, fragmentation index (FI) was calculated as an indicator for restlessness of the sleep. FI is the total number of wake bouts (defined as a wake period by the algorithm of the software) divided by the total sleep time in hours. The automatic FI, provided by the software of the actometer, was not used, as the calculation of the parameter of FI is more transparent when using wake bouts and sleep time (analogous to apnoea index calculation in polysomnography) instead of the percentage of 1 min of moving and immobility (in the automatic FI calculation). Actigraphy was carried out at baseline and after 5 and 11 weeks, for seven consecutive days (Figure 1).

Melatonin rhythm

Melatonin concentrations in saliva were measured the night after daytime haemodialysis and the subsequent night without daytime haemodialysis at 21.00, 23.00, 01.00, 07.00 and 09.00 h at baseline and after 17 weeks (Figure 1). To measure endogenous melatonin, exogenous melatonin was not administered during days of sampling of melatonin in saliva. Patients were asked to slowly move a cotton plug (Salivetten®, Sarstedt Numbrecht, Germany) in their mouth for 1 min. Melatonin levels were measured by the commercially available radioimmunoassay kit (Bühlmann Laboratories, Allschwil, Switzerland). Sampling was performed under semiconstant routine conditions at home on all sampling days. Patients followed a protocol and stayed in a dimly lit room (from the 18.00 until 08.00 h the intensity of the ambient light can be estimated as <20 lx [11]). Saliva samples were kept at -18 °C until analysed; then they were centrifuged (1000 g, 2 min). Aliquots of 400 µl of saliva sample were added directly in assay tubes. The detection limit was 0.5 pg ml⁻¹.

Sleep questionnaire: daytime function and subjective sleep experience

Sleep-wake characteristics were derived from the validated Dutch sleep disorders questionnaire [17]. Patients

were asked to keep a log of their sleep-wake schedule for seven consecutive days at baseline and after 5 and 11 weeks (Figure 1). This description included a record of their estimated sleep time, daytime function, sleep onset latency, wake periods during the night, feeling rested during daytime and subjective sleep quality.

Analysis

Median values and interquartile differences of the sleep questionnaire and actigraphy on dialysis days and nondialysis days were calculated during the double-blind cross-over period. The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 14 was employed for all statistical analysis. All parameters were tested by Wilcoxon signed ranks test (two-tailed) to find significant differences ($P < 0.05$) between melatonin and placebo treatment. Plots were made of melatonin concentrations before and after treatment. The melatonin concentrations were analysed by means of paired comparison per measuring point by Wilcoxon signed ranks test analysis.

Results

At baseline 24 patients were included in the study. From this group, two patients died, one terminated his dialysis in our hospital and one was excluded due to noncompliance. Twenty patients (14 male, six female) completed the 18-week investigation period. The general characteristics of the patients, shown in Table 1, were similar to the main characteristics of the general Dutch dialysis population [18]. In the study group nine patients used a β-blocker. No dose changes in β-blockers were made during the study period. During the investigation period no significant side-effects of melatonin were reported.

Actigraphy

As shown in Table 2a, the median sleep onset latency on the night after dialysis significantly reduced after melatonin treatment. Patients needed a median of 44.5 min to fall

Table 1

General characteristics of the patient group, displayed as median and interquartile difference

Parameters	Median (Interquartile difference)
Age (years)	71 (14.3)
Kt/V pro week*	3.9 (0.8)
Kt/V pro week incl. residual kidney function*	4.3 (0.9)
Body mass index (kg m ⁻²)	24.5 (4.7)
Dialysis duration (months)	19 (20)
Dialysis duration per week (h)	10.5 (3)

*Kt/V, index of dialysis adequacy, fractional reduction of urea [35].

Table 2

Results of the actometer on (a) night after daytime dialysis (displayed as median and interquartile difference) after 5 or 11 weeks (depending on the placebo-melatonin period) and (b) the following night without daytime dialysis (displayed as median and interquartile difference)

Parameters	Normal values	Median (interquartile difference) Placebo	Median (interquartile difference) Melatonin
(a)			
Sleep onset latency (min)	<15	44.5 (43.3)**	15.5 (27.8)**
Sleep efficiency (%)	>85	67.3 (30.7)**	73.1 (27.5)**
Actual awake time (%)	<10	20.0 (28.6)	19.4 (13.6)
Actual sleep Time (min)	>350	376.7 (118.6)**	387.5 (155.6)**
Fragmentation index	†	4.5 (1.1)**	3.1 (0.7)**
(b)			
Sleep onset latency (min)	<15	36.0 (31.9)*	28.5 (22.6)*
Sleep efficiency (%)	>85	65.0 (22.1)*	69.2 (30.6)*
Actual awake time (%)	<10	24.8 (14.2)	28.2 (23.7)
Actual sleep time (min)	>350	351.0 (119.7)	386.8 (169.7)
Fragmentation index	†	3.9 (1.3)	3.0 (1.2)

* $P < 0.10$; ** $P < 0.05$. †Normal values not known yet.

asleep with placebo treatment, which reduced to a median of 15.5 min ($P = 0.002$) after melatonin treatment. The 95% confidence interval (mean \pm 2 SD) with placebo was 50 ± 78 min and 33.6 ± 66 min with melatonin.

Sleep efficiency increased from 67.3% (placebo) to 73.1% with melatonin ($P = 0.01$). Actual sleep time increased from 377 min (placebo) to 388 min with melatonin ($P = 0.003$), and sleep fragmentation decreased from 4.5 to 3.1 ($P = 0.007$).

Furthermore, on nights without daytime dialysis, sleep onset latency decreased from 36 min (placebo) to 29 min with melatonin ($P = 0.09$), and sleep efficiency increased from 65% (placebo) to 69.2% with melatonin ($P = 0.08$), as shown in Table 2b. An example of actogram of a patient at baseline is shown in Figure 2.

Melatonin in saliva

In Figure 3 mean melatonin concentrations in saliva before treatment and after melatonin treatment are displayed. Before treatment the nocturnal melatonin rise was absent, its concentration not rising above 1 pg ml^{-1} . After treatment the average melatonin concentration increased well above the DLMO set point of 4 pg ml^{-1} in saliva at night. At all measuring points, endogenous melatonin concentration was significantly increased after treatment in comparison with before treatment ($P < 0.05$).

No differences in melatonin rhythm between patients on β -blockers and patients without β -blockers were observed during the whole study period ($P > 0.1$).

Sleep questionnaires: daytime function and subjective sleep experience

As shown in Table 3a,b, patients reported less time needed to fall asleep on the nights of daytime dialysis ($P = 0.003$)

Table 3

Results of filled-out sleep questionnaire: (a) day of dialysis and (b) day without dialysis

Parameters	Median (interquartile difference) Placebo	Median (interquartile difference) Melatonin
(a)		
Daytime napping (min)	30.0 (48.8)	0 (37.5)
Sleep onset latency (min)	45.0 (90.0)**	15.0 (12.5)**
Wake periods (min)	30.0 (25.0)**	25.0 (22.5)**
Sleep time (min)	345.0 (180.0)**	480 (120.0)**
(b)		
Daytime napping (min)	12.5 (30)	22.5 (35)
Sleep onset latency (min)	40.0 (100)**	15.0 (21.2)**
Wake periods (min)	30.0 (2.5)**	30.0 (17.5)**
Sleep time (min)	420.0 (180.0)	435 (86.3)

** $P < 0.05$.

and the nights without daytime dialysis ($P = 0.04$), when using melatonin instead of placebo. Furthermore, an increase in sleep time was seen on nights after daytime dialysis ($P = 0.01$) with melatonin. Wake periods during the nights were significantly fewer on nights after dialysis ($P = 0.03$) and nights without daytime dialysis ($P = 0.03$). Furthermore, a trend in improvement in sleep quality was found on nights after daytime dialysis ($P = 0.1$). The perception of feeling rested in the morning and feeling rested during the day did not differ significantly between melatonin and placebo administration.

Discussion

Treatment with melatonin resulted in a significant improvement of sleep quality as regards objective sleep onset latency, sleep time, sleep efficiency and sleep fragmentation. Sleep onset latency normalized. In addition to objective measurements, subjective sleep parameters improved also. Patients reported in their sleep questionnaires less time needed to fall asleep, an increase in sleep time, fewer wake periods and an improvement in sleep quality. Furthermore, the normal nocturnal melatonin rise was recovered after treatment.

In our study a decrease in objective sleep fragmentation was found after treatment with melatonin. Fragmentation of sleep reduces the restorative power of sleep [19]. Sleep disruption has been shown to result in performance impairments and subjective sleepiness [19]. In addition, impairment of immune function and worsening cardiovascular risk profiles have been reported [20–23].

Furthermore, a reduction in objective sleep onset latency, as measured by actigraphy, was displayed after treatment. Sleep onset latency is considered to be an

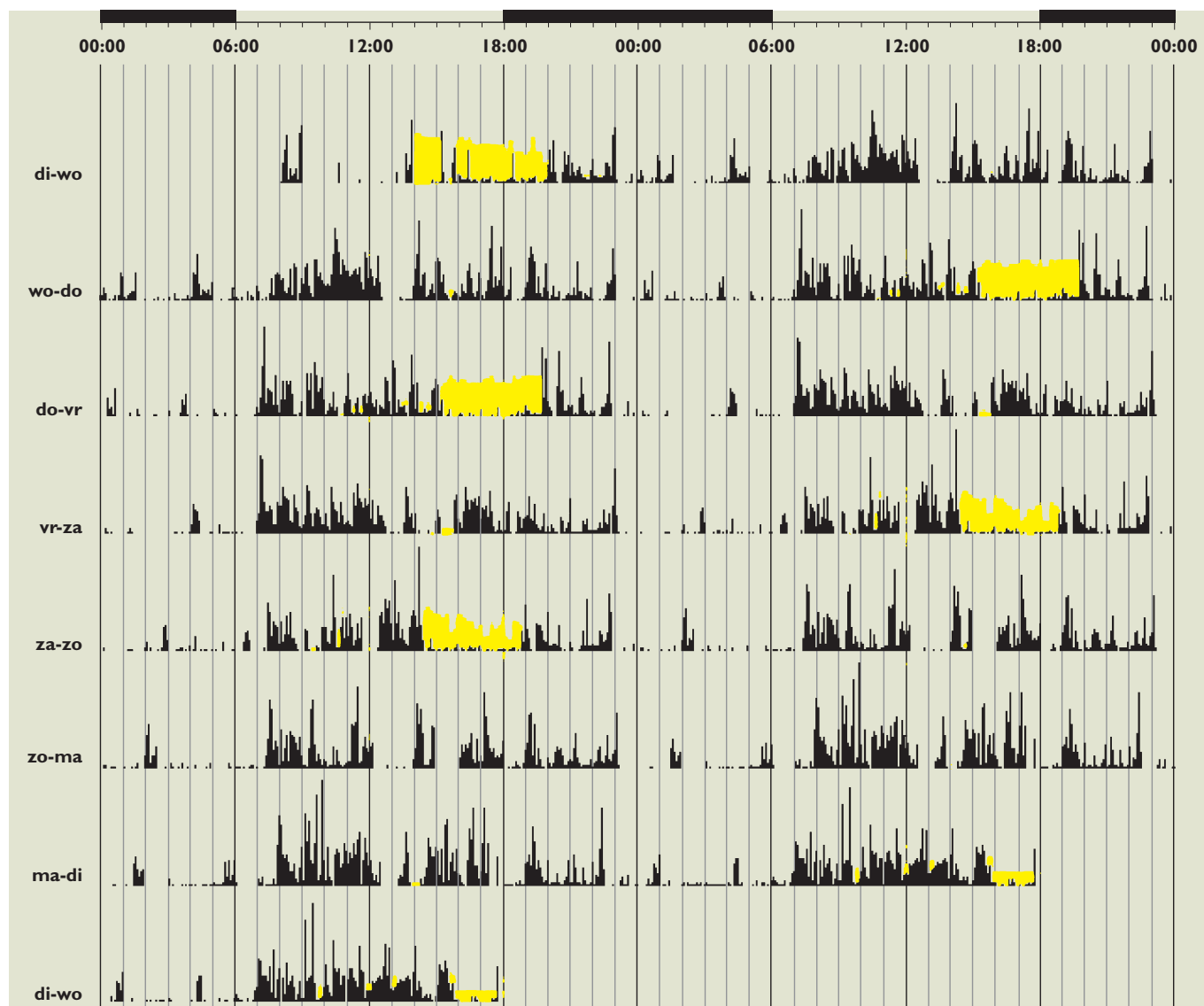


Figure 2

Displays a week's actogram of a patient, at baseline. The graph shows the movements of the wrist during night and day. All days are double plotted, as on all lines two consequent 24-h periods are shown. The black lines reflect the movement of the wrist. The yellow areas represent the light input on the actiwatch of the patient. This patient dialysed on Tuesday, Thursday and Saturday afternoon. As can be seen, there are often low light conditions during the day. Daytime napping does occur based on the absence of wrist movements, which can indicate sleep

important parameter when diagnosing sleep disorders such as insomnia [24, 25], and sleep onset latency and fragmentation of sleep are important parameters in the subjective sleep experience of a patient [26, 27]. Thus, it can be expected that subjective sleep parameters improved as well. Indeed, patients reported, above all, shorter sleep onset latency, prolonged sleep time and fewer wake periods.

After treatment with melatonin, the normal melatonin evening rise was recovered. This increase in melatonin levels correlates in normal circumstances with the onset of self-reported evening sleepiness [7] or with the increase in evening sleep propensity [8]. Administration of melatonin

has led to a reduction of sleep latency in healthy volunteers [28] and in patients with delayed sleep phase syndrome [11]. In the present study in haemodialysis patients the same effect was observed.

The results of baseline measurements from the present study confirm previous observations of an absence of nocturnal melatonin rise in patients suffering from ESRD [9, 10]. This apparent disturbance of the circadian melatonin rhythm may be explained by several mechanisms. Dialysis and its sleep-inducing effect result in a disturbance of sleep hygiene due to daytime sleepiness and nocturnal insomnia [1, 4]. Lack of sleep hygiene can lead to a disturbance of sleep-wake rhythm. This disturbance of circadian

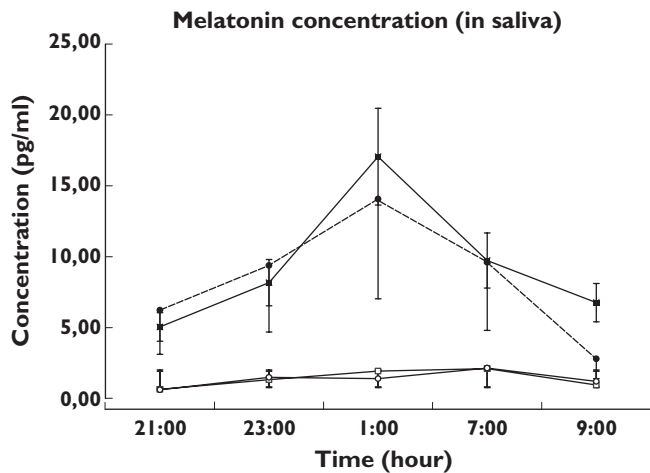


Figure 3

Displays the mean melatonin concentration measured in saliva on the day of dialysis and the consecutive day. The horizontal axis reflects the time of day in hours and the vertical axis reflects the melatonin concentration in saliva in pg ml^{-1} . Lines with open bullets represent the measurements before treatment. Lines with closed bullets represent the measures after treatment. Vertical lines at the measuring points represent the standard deviation error bars. Before treatment: night following dialysis (—○—); Before treatment: night after non-dialysis day (—○—); After treatment: night following dialysis (—●—); After treatment: night after non-dialysis day (—●—)

rhythm is expressed in the absence of a normal onset of melatonin production by the pineal gland [4]. Second, β -blockers, frequently used in haemodialysis patients [29], have been shown to depress nocturnal melatonin production [5]. In our group, nine of 20 patients used a β -blocker (three hydrophilic, six lipophilic β -blockers). However, no difference in melatonin concentration between patients with and patients without a β -blocker was found during the whole study period.

Furthermore, the decline in melatonin levels can also be related to the impairment in β -adrenoreceptor-mediated responsiveness in renal insufficiency [9, 30, 31]. The adrenergic system plays an important role in the synthesis of serotonin N-acetyltransferase (NAT), the key enzyme in melatonin biosynthesis. Suppression of NAT has been observed in rats rendered uraemic by partial nephrectomy [31]. Exogenous melatonin bypasses the enzyme NAT and therefore may allow recuperation of the enzymatic activity of NAT. On this view, the administration of exogenous melatonin constitutes a masking factor that selectively affects the onset of the melatonin curve [28]. Consequently, after a period of melatonin administration, this enzymatic activity may have been sensitized [28]. This would facilitate the triggering of the synthesis and release of endogenous melatonin that was observed in this study (Figure 3).

The melatonin curve was significantly lower on the following night without daytime dialysis. Possibly, sensitized enzyme activity of NAT dropped after 2 days without exogenous melatonin, as this was not administered during days

of saliva sampling. This could further explain the less improved sleep parameters on the second night in comparison with the significantly improved sleep parameters on the first night.

Previous research of our group has investigated the effects on melatonin rhythm when shifting from daytime to nocturnal in-hospital haemodialysis [32, 33]. With respect to sleep-wake rhythm, nocturnal dialysis has advantages. The sleep-promoting effects of dialysis coincide with the appropriate and conventional time of sleeping. Among these proposed sleep-promoting effects of haemodialysis are the elevated production of interleukin (IL)-1 during dialysis leading to sleep induction and the induction of imbalances of brain and serum osmolarity (disequilibrium syndrome), which is associated with depression of alertness and arousal [4]. Furthermore, haemodialysis causes an elevation in body temperature (partly accounted by IL-1). This increase in body temperature triggers cooling processes. Because of the known association between sleep onset and body cooling, haemodialysis-associated elevations in body temperature may activate cooling processes and thus increase sleepiness [4].

In this way, the shift to nocturnal dialysis could restore the normal temporal relationship between the sleep period and the other rhythms of the circadian system, which resulted in an improved quality of both sleep and daytime functioning [32, 33]. These improvements could be enhanced by the better clearance of toxins due to longer dialysis. Furthermore, it is hypothesized that if the normal synchronization between sleep-wake behaviour and the circadian system is restored, the endogenous melatonin concentration will be characterized by its normal nocturnal rise. Nocturnal melatonin rise was indeed recovered [32, 33]. Nocturnal in-hospital dialysis can be performed for only 10 patients at a time in our hospital. Therefore, we started this study to correct melatonin rhythm by means of administration of exogenous melatonin instead of nocturnal dialysis. Additionally, the frequent and ineffective prescription of conventional hypnotics in this population was an additional motivation to start this exogenous melatonin study [34]. The results from the present study on daytime dialysis patients, with positive effects on sleep-wake rhythm and endogenous melatonin concentrations caused by exogenous melatonin, are very promising. The sleep parameters and melatonin rhythm improved even more in the present exogenous melatonin study than in the nocturnal dialysis study [34]. However, this study had a relatively small sample size and a short investigation period, like other studies published on exogenous melatonin [11]. Due to the positive results of the present study, the so-called MELODY study (MELatOnin anD quality of life in dialysis patients) was recently initiated. This is a larger, long-term (1 year), multicentre, placebo-controlled study on the effects of exogenous melatonin on sleep, quality of life, circadian blood pressure

and left ventricular function. Outcomes of this study may confirm the benefits of exogenous melatonin in haemodialysis patients.

Competing interests

None to declare.

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