Chapter 5

Long-term effects of melatonin on quality of life and sleep in hemodialysis patients (Melody study): a randomized controlled trial

Marije Russcher
Birgit C P Koch
J Elsbeth Nagtegaal
Frans J van Ittersum
Pieter C M Pasker-de Jong
E Chris Hagen
Wim Th van Dorp
Bas Gabreëls
Thierry X Wildbergh
Monique M L van der Westerlaken
Carlo A J M Gaillard
Piet M ter Wee

Structured summary

Aim
The disturbed circadian rhythm in hemodialysis patients results in perturbed sleep. Short-term melatonin supplementation has alleviated these sleep problems. Our aim was to investigate the effects of long-term melatonin supplementation on quality of life and sleep.

Methods
In this randomized double-blind placebo-controlled trial hemodialysis patients suffering from subjective sleep problems received melatonin 3 mg/day versus placebo during 12 months. The primary endpoint quality of life parameter ‘vitality’ was measured with Medical Outcomes Study Short Form-36. Secondary outcomes were improvement of three sleep parameters measured by actigraphy and nighttime salivary melatonin concentrations.

Results
Sixty-seven patients were randomised. Forty-two patients completed the trial. With melatonin, no beneficial effect on vitality was seen. Other quality of life parameters showed both advantageous and disadvantageous effects of melatonin. Considering sleep, at 3 months sleep efficiency and actual sleep time had improved with melatonin compared to placebo on hemodialysis days (difference: 7.6%, 95%CI [0.77;14.4] and 49 minutes 95%CI [2.1;95.9] respectively). At 12 months none of the sleep parameters differed significantly from placebo. Melatonin salivary concentrations at 6 months had significantly increased in the melatonin group compared to placebo.

Conclusions
The high drop-out rate limits the strength of our conclusions. However, although a previous study reported beneficial short-term effects of melatonin on sleep in hemodialysis patients, in this long-term study the positive effects disappeared during follow up (6-12 months). Also the quality of life parameter vitality did not improve. Efforts should be made to elucidate the mechanism responsible for the loss of effect with chronic use.
Introduction

Given the increasing prevalence of end-stage renal disease (ESRD) and the associated burden on health status, treatments to improve clinical outcome and quality of life of hemodialysis patients are urgently needed. (1,2) Between 50-80% of hemodialysis patients complain of nighttime sleep disturbances (3) and about 30% of hemodialysis patients report excessive daytime sleepiness (4,5), having a negative influence on these patients’ vitality and general and psychological health. (6,7) Improvement of sleeping patterns is associated with a decrease in inflammatory activity and oxidative stress in hemodialysis patients. (8) Despite the broad array of disabling sleep disorders that are identified in ESRD, including sleep apnea and restless legs, surprisingly little attention is paid to sleep disorders that are caused by dysfunction of the biological clock in these patients. (5,9)

The human’s biological clock is driven by the master pacemaker that resides in the suprachiasmatic nucleus (SCN) in the brain. It coordinates circadian rhythms: fluctuations of bodily functions that recur in a cycle of about 24 hours such as the sleep-wake rhythm. (10) Biological clock disturbances are not only associated with sleep problems. A number of studies point to the interrelationship between dysfunction of the biological clock and the development of kidney disease in animals (11-13) and to the development of diabetes. (14) In humans, disturbances of the biological clock e.g. by working nightshifts is associated with the development of breast cancer (15) and depression. (16)

The pineal hormone melatonin is an important marker of biological clock-time and plays an important role in circadian sleep-wake rhythm. In healthy persons in normal environmental conditions, melatonin secretion shows a clear circadian rhythm with low levels during the day and high levels at night. The increase in melatonin concentration in the evening correlates with an increase in evening sleep propensity and onset of sleep. (17-19) Interestingly melatonin secretion decreases as kidney functions declines (20) and in many daytime hemodialysis patients the nocturnal melatonin surge is even absent. (21) Melatonin not only exerts effects on timing of sleep. Blood pressure, like many physiological processes, shows a 24-hour-rhythm. A ‘non-dipping blood pressure profile’ (22) which often exists in daytime hemodialysis patients (23) is associated with an impaired nocturnal endogenous melatonin secretion. (24)

The alleged association between reduced melatonin secretion and disturbances in sleep and blood pressure regulation in ESRD prompted studies investigating the effect of exogenous melatonin. Previously we reported that short-term administration of exogenous melatonin in hemodialysis patients markedly improved subjective and objective sleep parameters. (21) Based on these beneficial effects on sleep of short-term
use of melatonin and the known influence of sleep problems on quality of life, the present
study was designed to investigate the effects of melatonin administration during 12
months on sleep and quality of life in daytime hemodialysis patients that had subjective
sleep problems according to the Epworth Sleepiness Scale (ESS) and increased sleep
onset latency.

**Methods**

**Study design**
The Melody trial is a randomized double-blind placebo-controlled clinical trial conducted
in 5 large regional hospitals in The Netherlands that provide hemodialysis treatment to
approximately 500 patients. The institutional review boards approved the protocol of the
study (ClinicalTrials.gov: NCT00388661, EudraCT-number 2006-005719-89) and written
informed consent was obtained from all patients. The study was conducted according to
the Declaration of Helsinki. The study design is shown in figure 1.

![Study design diagram](image)

**FIGURE 1. Study design**
The study measurements and the dates of measurement are displayed.
Setting and Participants
Stable hemodialysis patients aged 18 to 85 years with a hemodialysis history of at least 3 months and adequate dialysis efficacy were eligible for inclusion. Patients could participate when they suffered from subjective sleep problems at baseline according to the Epworth Sleepiness Scale (ESS) questionnaire and their mean sleep onset latency measured by means of actigraphy was longer than 15 minutes. The ESS measures subjective daytime sleepiness and has been used in hemodialysis patients before.(7) Table 1 sums up the inclusion and exclusion criteria.

Daytime hemodialysis patients were randomized to receive melatonin 3 mg immediate release tablets (Pharma Nord®, Vejle, Denmark) or placebo tablets (Pharma Nord®, Vejle, Denmark) for 12 months. Study medication was prescribed by the participating physicians of the patients. Random allocation of 68 study medication kits was made in block sizes of 4. Study treatment was started throughout the year shortly after inclusion of the patient. Patients were instructed to take their study medication at 10 PM daily. Dialysate flow, blood flow and type of dialyzer membrane type were chosen according to standard practice of the participating dialysis centres.

TABLE 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Age 18-85 years</td>
<td>Current melatonin use</td>
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<tr>
<td>Stable daytime hemodialysis (&gt; 3 months)</td>
<td>Known hypersensitivity to melatonin</td>
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<tr>
<td>Subjective sleep problems</td>
<td>Severe psychological or neurological disease</td>
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<td>Mean sleep onset latency &gt; 15 minutes</td>
<td>Unstable angina pectoris</td>
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<td>NYHA class IV heart failure</td>
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<td>Pregnancy</td>
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<td>Participation in another clinical trial</td>
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<td>1 month prior to the start of this study</td>
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Outcome measures
Quality of life questionnaire
The primary outcome measure was defined as an improvement of at least 15 points on the vitality score of the Medical Outcomes Study Short Form 36 (MOS SF-36). The Dutch version of this validated quality of life questionnaire was used at baseline, 6 and 12 months to measure physical, functional, mental and social health.(25)
Sleep measurements: actigraphy

Secondary outcome measures were reduction in sleep onset latency and improvement of sleep efficiency and actual sleep time. Sleep parameters were investigated by means of 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.(26) Model Actiwatch-L (Cambridge Neurotechnology Ltd®, Cambridge, United Kingdom) actiwatches validated against polysomnography in the hemodialysis population were used.(27)

The actiwatch was placed on the wrist of the arm without graft or fistula. Patients were asked to record bedtimes and rise times on a registration form. Actiwatch Activity & Sleep Analysis version 5.32 was used to score 1 minute epochs of actigraphic data as sleep or wake.(28) The following parameters were calculated according to standardized methods (29): sleep onset latency (SOL), which is the time period between 'lights off' and sleep onset, sleep efficiency (SE), which is the actual sleep time divided by time in bed and is a well recognized measure of sleep quality and actual sleep time (AST), defined as the total duration of recorded sleep periods. Each episode of actigraphy recordings was carried out during 5 consecutive days and nights (figure 1).

Melatonin rhythm

Melatonin concentrations in saliva were measured at baseline and after 6 months both on the night after daytime hemodialysis and subsequent non-dialysis night at 9 PM, 11 PM, 1 AM, 7 AM and 9 AM (figure 1). Patients collected saliva samples by slowly moving a cotton plug (Salivetten®, Sarstedt Numbrecht, Germany) in their mouth for one minute. They were instructed not to take their study medication on the days of saliva sampling. Five patients in the melatonin group reached melatonin levels > 50 pg/ml at 6 months. Since the authors doubt that these reflect endogenous concentrations considering the low baseline levels and the melatonin levels reached by the other patients in the melatonin group, it could not be excluded that these patients had taken their study medication on the day of saliva sampling despite the instructions. This could not be checked reliably by the investigators, since melatonin concentrations were determined by batch processing, patients had to be asked in retrospect several weeks to months later. The melatonin measurements of these patients were therefore excluded from analysis.

Sampling was performed under semi-constant routine conditions in a dimly lit room (<20 lux) at home.(30) Saliva samples were kept at -18 degrees Celsius until analysis. After centrifugation of the cotton plugs, aliquots of 400 microliter of saliva sample were transferred into assay tubes. Melatonin levels were measured using the commercially available RIA kit
(Bühlmann Laboratories, Schönenbuch, Switzerland) with a detection limit of 0.5 pg/ml.

**Dipping profile of blood pressure**

Patients were asked to wear an ambulatory blood pressure monitor (SpaceLabs® ItéMedical, Tiel, The Netherlands) for 24 hours at baseline and at 12 months. Measurements were taken according to local standards of the participating hospitals. Dipping profile was determined by a decrease in systolic blood pressure of at least 10% during the night compared to daytime systolic blood pressure. (22)

**Echocardiography**

At baseline and at 12 months echocardiography was performed according to a standard protocol. The echocardiogram was evaluated by an experienced cardiologist blinded for allocated treatment. The following standard parameters were assessed to quantify cardiac dimensions: left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular post wall diameter end diastolic (LVPW), left ventricular intraventricular septal end diastolic diameter (LVIVS), left ventricular ejection fraction (LVEF) and left ventricular mass index (LVMI).

**Statistics**

A required sample size of 27 patients per group was calculated based on a clinically relevant difference of 15 points on the MOS-SF36 vitality scale between melatonin and placebo and a standard deviation of 18.9 points based on a previous study (power 0.90, α 0.05). (31) Since a 25% drop-out rate was expected, the final projected sample size was 34 per group.

Mean values and standard deviations of baseline characteristics, quality of life questionnaire and sleep parameters were calculated. For variables that were non-normally distributed, medians and interquartile ranges were determined. Sleep parameters were calculated for hemodialysis days and non-hemodialysis days separately.

An intention to treat analysis of quality of life results and sleep measures was performed. Data were analysed using longitudinal linear regression analysis in SPSS version 19 with the mixed models procedure. This is a sophisticated method suitable for longitudinal data on a time-dependent continuous outcome and several time-dependent and time-independent co-variates and factors. The method takes into account that measurements within individuals are more correlated than measurements between individuals. The validity of this method is not hampered by missing values. In the longitudinal linear
regression analysis the sleep and quality of life parameters studied were analysed as dependent variables using study group (melatonin or placebo), time and their interaction as independent variables. This allows for the effect of the intervention to change over time. The effect estimates and their 95% confidence intervals were taken from the model and marginal means per group per time point were calculated and plotted. Variables that were non-normally distributed were ln-transformed before analysis. Their means and confidence intervals were transformed back and then plotted. These can be interpreted as medians and their 95% confidence intervals.

Drop out rate exceeded the predefined expected drop out rate. We therefore performed a post-hoc sample size calculation on the secondary endpoint sleep onset latency, based on actual study inclusion rate. This calculation was done with a suitable formula for longitudinal data analysis, which takes into account the added information by multiple measurements, while correcting for the higher correlation between multiple measurements in one patient. (32)

**Results**

Sixty-seven daytime hemodialysis patients were included from April 2007 until March 2009, Forty-two patients completed the study. Reasons for loss to follow-up are shown in figure 2.

Clinical characteristics between the melatonin and placebo group at baseline did not differ (table 2). Some baseline values of quality of life and sleep parameters differed between the melatonin and placebo group, therefore we corrected for baseline values in our analyses. Throughout the study no side effects of melatonin were reported.

**Quality of life**

The primary outcome parameter vitality did not improve with melatonin treatment compared to placebo after 12 months (difference: -1.9% 95%CI [-12.6;8.7]). Regarding the other quality of life parameters, physical functioning decreased in the melatonin group compared to placebo after 12 months (difference: -11.4% 95%CI [-21.8;-1.1], whereas general mental health increased in the melatonin group compared to placebo after 12 months (difference: 9.3% 95%CI [-0.1;18.7] p=0.052). Emotional role activities and last year’s health change tended to improve in the melatonin group (difference: 29.8% 95%CI [-1.4;61.0] after 12 months and difference: 14.6% 95%CI [-0.6;29.8] after 6 months respectively). However there was a tendency towards decreased physical role activities in the melatonin group after
Long-term effects of melatonin on quality of life and sleep in hemodialysis

12 months compared to placebo (difference: -22.2% 95%CI [-49.2;4.8]. Other parameters did not significantly improve or worsen with melatonin treatment compared to placebo. In figure 3 the results of all quality of life parameters are shown.

FIGURE 2. Study profile
## TABLE 2. Baseline characteristics

<table>
<thead>
<tr>
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<th>placebo</th>
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</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Number of males (%)</td>
<td>19 (58)</td>
<td>22 (65)</td>
</tr>
<tr>
<td>Age in years, mean (sd)</td>
<td>65.5 (11.7)</td>
<td>64.4 (12.0)</td>
</tr>
<tr>
<td>Kt/V* pro week, incl. residual kidney function, mean (sd)</td>
<td>4.1 (0.6)</td>
<td>4.2 (0.7)</td>
</tr>
<tr>
<td>Body Mass Index (kg m-2), mean (sd)</td>
<td>26.3 (4.4)</td>
<td>25.6 (5.4)</td>
</tr>
<tr>
<td>Dialysis duration pro week in hours, mean (sd)</td>
<td>11.2 (1.2)</td>
<td>11.3 (1.9)</td>
</tr>
<tr>
<td>Dialysis vintage in months, mean (sd)</td>
<td>30.6 (27.3)</td>
<td>28.3 (22.5)</td>
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### 24-h Ambulatory blood pressure

<table>
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<tbody>
<tr>
<td>Systolic, mean (sd)</td>
<td>128 (26)</td>
<td>121 (17)</td>
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<tr>
<td>Diastolic, mean (sd)</td>
<td>71 (15)</td>
<td>69 (10)</td>
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### Sleep

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<th>placebo</th>
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<tbody>
<tr>
<td>Sleep onset latency on hemodialysis days in minutes, median (interquartile difference)</td>
<td>23.5 (24.5)</td>
<td>25.2 (33.1)</td>
</tr>
<tr>
<td>Sleep onset latency on non-hemodialysis days in minutes, median (interquartile difference)</td>
<td>20.3 (30.0)</td>
<td>25.0 (31.0)</td>
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<tr>
<td>Sleep efficiency on hemodialysis days in %, mean (sd)</td>
<td>69.7 (16.5)</td>
<td>69.9 (13.1)</td>
</tr>
<tr>
<td>Sleep efficiency on non-hemodialysis days in %, mean (sd)</td>
<td>66.3 (19.7)</td>
<td>64.9 (18.1)</td>
</tr>
<tr>
<td>Actual sleep time on hemodialysis days in minutes, mean (sd)</td>
<td>342 (128)</td>
<td>363 (80)</td>
</tr>
<tr>
<td>Actual sleep time on non-hemodialysis days in minutes, mean (sd)</td>
<td>318 (129)</td>
<td>323 (82)</td>
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### Quality of life

<table>
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<tbody>
<tr>
<td>Physical functioning in %, mean (sd)</td>
<td>44 (25)</td>
<td>45 (28)</td>
</tr>
<tr>
<td>Social functioning in %, mean (sd)</td>
<td>55 (22)</td>
<td>58 (26)</td>
</tr>
<tr>
<td>Role activities – physical in %, mean (sd)</td>
<td>35 (41)</td>
<td>36 (41)</td>
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<tr>
<td>Role activities – emotional in %, mean (sd)</td>
<td>48 (45)</td>
<td>67 (43)</td>
</tr>
<tr>
<td>General mental health in %, mean (sd)</td>
<td>68 (19)</td>
<td>72 (19)</td>
</tr>
<tr>
<td>Vitality in %, mean (sd)</td>
<td>49 (16)</td>
<td>48 (22)</td>
</tr>
<tr>
<td>Bodily pain in %, mean (sd)</td>
<td>63 (25)</td>
<td>62 (30)</td>
</tr>
<tr>
<td>General health perception in %, mean (sd)</td>
<td>36 (17)</td>
<td>37 (20)</td>
</tr>
<tr>
<td>Last year’s health change in %, mean (sd)</td>
<td>49 (25)</td>
<td>56 (29)</td>
</tr>
</tbody>
</table>

* Kt/V, index of dialysis adequacy, fractional reduction of urea
FIGURE 3. Quality of life
Mean predicted values of MOS-SF results (in %) of quality of life parameters Physical functioning, Social functioning, Role activities – physical, Role activities – emotional, General mental health, Vitality, Bodily pain, General health perception and Last year’s health change. Higher percentages indicate better quality of life. The horizontal axis reflects the time in months. Solid lines represent the melatonin group, dashed lines represent the placebo group. Vertical lines at the measuring point represent 95% confidence intervals.

Actigraphy
In figure 4 the median sleep onset latency, mean sleep efficiency and mean actual sleep time are shown for hemodialysis and non-hemodialysis days separately. There were no significant differences for these parameters between the two groups at baseline. At 3
months, sleep efficiency (difference: 7.6% 95%CI [0.77;14.4] and actual sleep time difference: 49 min, 95%CI [2.1;95.9] had improved with melatonin treatment compared to placebo treatment. These effects were not seen on non-hemodialysis days. At 6, 9 and 12 months, no significant differences in any of the sleep parameters between melatonin treatment and placebo were seen.

**FIGURE 4. Sleep**
Panel A to C: Results of predicted values of median sleep onset latency (A), mean sleep efficiency (B), mean actual sleep time (C) on hemodialysis days. Panel D to F: Results of predicted values of median sleep onset latency (D), mean sleep efficiency (E), mean actual sleep time (F) on non-hemodialysis days. Lower sleep onset latency, higher sleep efficiency and higher actual sleep time indicate better sleep. The horizontal axis reflects the time in months. Solid lines represent the melatonin group, dashed lines represent the placebo group. Vertical lines at the measuring point represent the 95% confidence intervals.

**Melatonin in saliva**
Figure 5 shows mean melatonin concentrations in saliva on a hemodialysis day and on a non-hemodialysis day. At baseline, a clear nocturnal melatonin rise was absent in all patients. After 6 months of melatonin treatment, nocturnal melatonin concentrations had significantly increased in the melatonin group compared to the placebo group at all measured time points as well as exposure to melatonin over the entire night on both hemodialysis and non-hemodialysis days after correction for baseline using general linear
methods. Melatonin concentrations at 6 months in the placebo group did not differ significantly from baseline values.

Melatonin concentrations of patients that were left out of figure 5 are shown in table 3.

![Figure 5](image)

**FIGURE 5.** Mean melatonin concentration measured in saliva on the day of hemodialysis (panel A) and the day without hemodialysis (panel B).
The horizontal axis reflects the time of day in hours and the vertical axis reflects the melatonin concentration in saliva in pg/ml. Lines with open circles represent the baseline measurements of the melatonin group. Lines with open squares represent the baseline measurements of the placebo group. Lines with closed circles represent the measurements after 6 months of melatonin treatment. Lines with closed squares represent the measurements after 6 months of placebo treatment. Vertical lines at the measuring points represent 95% confidence intervals.

**TABLE 3.** Melatonin concentrations in saliva (pg/ml) of patients that were left out of figure 5

<table>
<thead>
<tr>
<th>patient</th>
<th>hemodialysis day</th>
<th>non-hemodialysis day</th>
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<tbody>
<tr>
<td></td>
<td>9 pm</td>
<td>11 pm</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>11.7</td>
</tr>
<tr>
<td>2</td>
<td>4.7</td>
<td>24.8</td>
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<tr>
<td>3</td>
<td>13.5</td>
<td>10.8</td>
</tr>
<tr>
<td>4</td>
<td>6.7</td>
<td>11.9</td>
</tr>
<tr>
<td>5</td>
<td>20.7</td>
<td>16.0</td>
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</table>

**Dipping profile of blood pressure and echocardiography**

Data collection of ambulatory blood pressure measurements was hampered, therefore analysis of blood pressure effects of melatonin could not be performed. Data on blood pressure measurements at both baseline and 12 months were available in only 13 (39%) patients in the melatonin and 14 (41%) patients in the placebo group. In the melatonin group 6 patients exhibited a dipping profile and 7 patients exhibited a non-dipping profile.
at baseline. In the placebo group these were 5 patients and 9 patients respectively. No obvious intra-individual change in dipping status was observed at the end of the study. Although supposedly melatonin has blood pressure lowering effects (24,33), we were not able to show changes in nocturnal blood pressure dipping profile since the number of patients was too small to draw definite conclusions due to drop-out. In addition no changes in cardiac dimensions measured by echocardiography were seen (data not shown).

**Discussion**

This is the first long-term study on the effects of melatonin on quality of life and sleep in hemodialysis patients. In a previous study beneficial short-term effects of melatonin were reported, yet in this study we failed to demonstrate that the melatonin effects persist in the long run. This finding is of particular importance since, although hypnotics are frequently prescribed for longer periods of time, few RCT studies address long term effects and observational studies show that persistent use of hypnotics may be associated with worse outcomes.(34)

Vitality measured as part of the MOS-SF-36 quality of life questionnaire was delineated as the primary outcome parameter of the study. No effect of melatonin on vitality was observed in this study. With regards to the other quality of life parameters we did find a positive long-term effect of melatonin on general mental health and tendencies towards improvement of emotional role activities and last year’s health change, but on the other hand we found a negative long-term effect of melatonin on physical functioning and a tendency towards decreased physical role activities. Therefore we conclude that with the used dosage regimen of melatonin, it has no substantial positive effect on quality of life. Nevertheless the possibility still exists that melatonin may contribute to improvements in quality of life, since in other patient populations improvements of the MOS-SF36 questionnaire were observed after melatonin treatment.(31) Efforts should now be made to elucidate if the melatonin dosage regimen can be optimized, resulting in improvements on quality of life e.g. due to better sleep.

In addition, no clinically relevant long-term improvements on sleep were found in the melatonin group although the previously reported short-term beneficial effects of melatonin on sleep efficiency and actual sleep time were confirmed after 3 months of melatonin use.(21). However, these findings were apparent only on hemodialysis days. Due to the higher than the expected 25% drop-out rate, which we accounted for in
our projected study size it may be questioned whether the lack of a persisting effect of melatonin on sleep was caused by loss of power of the study or was related to true absence of long term melatonin effect on sleep. In order to estimate attained study power a post hoc power calculation was performed. The original power calculation was made on vitality using the standard formula. However since the study consists of a large number of repeated values and the effects of melatonin on sleep were deemed important, a post-hoc sample size calculation suitable for longitudinal data analysis was performed on one of the sleep parameters: sleep latency. Based on the number of follow-up measurements, intra individual correlation coefficient and standard deviation of the actual patient data, 28 patients per group were needed to significantly show a clinically relevant 20 minute difference in sleep onset latency (power 0.80). This number of patients was only present at baseline and at 3 months. Therefore, since there was a substantial decline in number of participants during the study period, a lack of power could be the reason of the absence of a statistically significant difference in sleep parameters at 6 months and later. However, even though group sizes were too small to definitely conclude on the long-term effect of melatonin on sleep, the courses of the sleep parameters over time in figure 4 render it unlikely that long-term positive effects of melatonin would have been identified if group sizes had been larger. Selective loss-to-follow-up could obscure such a positive effect (if those on melatonin who benefited stopped participating). This does not seem likely, given the reasons for drop out in figure 2.

Therefore we question our original hypothesis that melatonin 3 mg administration at 10 PM daily has a long-term positive influence on sleep. A number of possible mechanisms for the decline of effect on sleep exist, including inappropriate melatonin effect or dosing and inadequate time of administration. A possible explanation for the decline in hypnotic effects after 3 months may also be altered melatonin receptor sensitivity or decreased receptor density. Changes in melatonin receptor sensitivity and receptor density have been described before. Indeed, hypnotic effects during three months of therapy have been observed in other placebo controlled studies using more traditional hypnotics such as benzodiazepines as well but generally the time of use of benzodiazepines for insomnia is restricted, because of loss of effect and occurrence of dependency with time of use. Since continued use of benzodiazepines is associated with an increased mortality rate, it is important to find alternative long-term therapies to treat sleep disturbances.

In addition, although melatonin concentrations had risen at night compared to baseline in the melatonin group, the resulting concentration curves were not optimal from a circadian point of view. Melatonin reached maximum levels in the early morning instead of midnight on hemodialysis days. In addition melatonin concentrations in the melatonin group were
higher than in the placebo group at all time points, including the early evening and morning samples, which suggests higher than desirable daytime melatonin levels. This might indicate accumulation of the highly liposoluble melatonin in fatty tissues due to declined clearance and subsequent redistribution from these tissues. It is important to learn more about melatonin accumulation and redistribution from other tissues in hemodialysis patients to be able to explain this different course. One could argue that a prolonged release melatonin formulation instead of an immediate release formulation would have had potential benefits on quality of sleep as described by Lemoine et al. in elderly people suffering from insomnia. However, we question the added value in the hemodialysis population. Due to reduced kidney function and the dialysis treatment 3-4 times a week, the pharmacokinetics of melatonin in hemodialysis patients will probably differ from the insomniacs to a certain extent, resulting in a longer elimination half life. From figure 5 we hypothesize that accumulation within fatty tissue occurs, even with the immediate release formulation that we have used. Here we might look at a physiological slow release mechanism, which in our opinion has unfavourable aspects since the difference between the day and night levels diminishes, which may negatively influence the opening of the so called ‘sleep gate’ during the evening and thus may reduce the therapeutic benefit.

‘With respect to the elevated melatonin levels, the decline in physical functioning that we have found is also interesting. These results are consistent with earlier published data from various animal species in which elevated levels of melatonin were elicited by melatonin administration at several time points to monitor the effect of melatonin on, among others, locomotor activity. Following melatonin administration, the elevated melatonin concentrations resulted in reduced locomotor activity in the observed animals at all time points. Furthermore, the underlying mechanism to the lack of long term response to melatonin may well be related to the state of refractoriness to melatonin found in photoperiodic seasonal breeders. For example sheep is a photoperiodic species, in which reproductive activity is sensitive to a change in day-length. Melatonin serves as an endocrine code for day-length and mimicking a short-day pattern by melatonin infusion can result in reproduction induction. However, the ewes become unresponsive to stimulatory day-length after a few months, although circadian melatonin patterns remain constant during this time. Finally, it should be noted that the cause of prolonged sleep onset latency may be multifactorial in this highly complex patient group. The effect of melatonin in hemodialysis patients needs to be optimized and possibly combined with synergistic treatments that add to reinforcement of the circadian rhythm, such as light therapy, cognitive therapy, other dialysis regimens and daytime exercise.'
Future research should focus on optimization of melatonin use. Pharmacokinetics of melatonin in hemodialysis patients should be clarified. In addition to this other melatonin dosages and dosing strategies (e.g. intermittent use to avoid accumulation) should be investigated. Timing of melatonin administration is also important and should ideally be adjusted to the patient’s dim light melatonin onset (DLMO). The DLMO is the time at which melatonin concentration rises above a certain threshold. This is the best characterisation of the 24-h melatonin rhythm, it corresponds to biological clock time and is strongly associated with the circadian sleep-wake rhythm. Usually DLMO will be observed about 2-3 hours prior to habitual sleep. With a regular western sleep schedule this will be between 8 and 10 PM. Since many hemodialysis patients do not show any DLMO at all, we have chosen to administer melatonin 3 mg tablets at 10 PM. Perhaps for some patients this was not the optimal time of ingestion.

In conclusion, although a previous study endorsed melatonin as a safe and potentially short term drug for sleep improvement in hemodialysis patients, in this study melatonin failed as an effective long term alternative to treat sleep disorders in hemodialysis patient. Efforts should be made to try and find methods to prolong its positive effects on sleep.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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