The Effects of Kidney Transplantation on Sleep, Melatonin, Circadian Rhythm and Quality of Life in Kidney Transplant Recipients and Living Donors

Marije Russcher^a J. Elsbeth Nagtegaal^a S. Azam Nurmohamed^b
 Birgit C.P. Koch^c Monique M.L. van der Westerlaken^a Eus J.W. van Someren^{d,e}
 Stephan J.L. Bakker^f Pieter M. ter Wee^b Carlo A.J.M. Gaillard^f

^aDepartment of Hospital Pharmacy, Meander Medical Center, Amersfoort, ^bDepartment of Nephrology and ICar-VU, VU University Medical Center, Amsterdam, ^cDepartment of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, ^dDepartment of Sleep and Cognition, Netherlands Institute for Neuroscience, Amsterdam, ^eDepartments of Integrative Neurophysiology and Medical Psychology, VU University and Medical Center, Amsterdam, and ^fDepartment of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Key Words

Circadian rhythm · Kidney transplantation · Melatonin · Quality of life · Sleep

Abstract

Background: Sleep disturbance is an important medical problem in patients with end-stage renal disease. It might be related to the disruption of the body's circadian clock since nocturnal levels of its key biomarker melatonin are markedly reduced. We aimed at investigating whether a change in renal function due to kidney transplantation or donation would modify sleep, melatonin levels, circadian rhythmicity, and quality of life in kidney transplant recipients (KTR) and living donors (LD). **Methods:** In KTR, we assessed saliva melatonin concentrations, sleep quality and daytime sleepiness prior to and at 2 weeks and 3 months after transplantation. In LD, we assessed these parameters prior to and at 3 months after donation. We additionally assessed 24-hour core body temperature (cBT), 24-hour blood pressure profile, and quality of life (QoL) prior to and 3 months after transplantation.

Abbreviations used in this article

APD	automated peritoneal dialysis
AUC	area under the curve
CAPD	continuous ambulatory peritoneal dialysis
cBT	core body temperature
CKD	chronic kidney disease
CRICKT	Circadian Rhythm In Kidney Transplantation
DLMO	dim light melatonin onset
eGFR	estimated glomerular filtration rate
ES	effect size
ESRD	end-stage renal disease
ESS	Epworth Sleepiness Scale
KTR	kidney transplant recipient
LD	living donor
NTR	Netherlands Trial Registry
QoL	quality of life
RRT	renal replacement therapy
SE	sleep efficiency
SOL	sleep onset latency
TST	total sleep time
Tx	transplantation
WASO	wake time after sleep onset

Results: Twenty-three KTR and 23 LD completed the study. Regarding sleep, the amount of nighttime awake minutes tended to be reduced in recipients after transplantation ($p = 0.05$). Nocturnal melatonin concentrations did not change with transplantation or donation. Blood pressure dipping profile and the two circadian markers dim-light melatonin onset and time of core body temperature minimum did not change. Nevertheless, KTR reported that daytime sleepiness and QoL had improved. **Conclusion:** Objectively nocturnal sleep quality marginally improved after transplantation. Subjectively patients reported improved QoL and daytime sleepiness scores. Changes in renal function were not associated with modified melatonin secretion or circadian rhythmicity.

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Introduction

Disturbed sleep is highly prevalent in patients with end-stage renal disease (ESRD) and is an important determinant of low quality of life [1–5]. In addition to its effect on psychological well-being, short sleep duration is also associated with increased physical morbidity and mortality [6]. It has been suggested that sleep disturbances represent a risk factor for decline of renal function by promoting hypertension, type 2 diabetes mellitus, and obesity in patients with CKD [7].

Melatonin plays an important role in the sleep wake rhythm, especially in the timing of sleep. This pineal hormone is an important clock-hand of the circadian clock [8]. Its secretion shows a clear circadian rhythm with low levels during the day and high levels at night. It provides a nighttime signal to the body. Its increase in the evening correlates with sleep propensity and onset of sleep [9–11]. In ESRD not only do sleep disturbances frequently occur, but nocturnal melatonin levels are also reduced [12–15]. Even though sleep disturbances in renal patients are well recognized clinically, little attention is paid to their possible linkage with lowered melatonin levels or perturbed functioning of the circadian clock. A combination of sleep deprivation with circadian disruption even raises the chances on developing additional morbidity [16].

Regarding circadian rhythmicity, in kidney transplant recipients (KTR) mainly 24 h blood pressure profiles have been studied. An inadequate fall in nocturnal blood pressure [17] persists after renal transplantation [18, 19]. This ‘non-dipping’ profile is associated with impaired nocturnal endogenous melatonin secretion at least in hypertensive patients [20]. However, information on melatonin

rhythm around kidney transplantation is lacking. In a pilot study, we observed an increase in melatonin concentrations after kidney transplantation in 4 out of 7 transplant recipients [21].

In contrast to transplant recipients, living kidney donors experience an abrupt loss of GFR directly after unilateral nephrectomy. The effects of this sudden decline in renal function on sleep and melatonin concentrations are unknown. A gradual decrease in renal function is associated with reduced nocturnal melatonin levels [14]. We questioned whether a sudden decrease in renal function would also lead to reduced melatonin levels. For kidney donors, again, only the circadian rhythm of blood pressure has been studied. Goto et al. found that with unilateral nephrectomy circadian rhythm of blood pressure was disturbed as a function of GFR loss [22].

In the present study, we aimed to expand on our pilot study and investigate whether changes in renal function occurring in KTR and living donors (LD) would subsequently alter melatonin concentrations and sleep quality in conjunction. Since sleep quality is an important determinant of well-being in patients with ESRD, we also measured changes in the quality of life. An additional investigation of the functioning of the circadian clock was done by measuring circadian rhythms of core body temperature and 24-hour blood pressure before and after renal transplantation and donation.

Patients and Methods

The Circadian Rhythm In Kidney Transplantation (CRIKT) study is a prospective observational longitudinal study conducted at the VU University Medical Centre (VUmc), the Netherlands from April 2011 to October 2013. The institutional review board approved the protocol of the study (NTR2974) and written informed consent was obtained from all participants prior to their inclusion in the study. The study was conducted according to the Declaration of Helsinki.

Setting and Participants

Kidney transplant recipients and donors, all from the living donation program, aged 18–85 years were eligible for inclusion. Participants were excluded in case of hypnotic or melatonin use, severe psychological or neurological disease, blindness, NYHA class IV heart failure, documented sleep apnea and alcohol or drug abuse.

Outcome Measures

Melatonin Rhythm

Melatonin concentrations in saliva were measured at baseline, approximately 1 month before transplantation (KTR and LD), 2 weeks after transplantation (KTR only), and 3 months after transplantation (KTR and LD). Saliva was sampled at 19:00, 21:00,

23:00, 01:00 and 07:00. Saliva samples were collected and melatonin concentrations were determined as described before [23]. Values below the detection limit of 0.5 pg/ml were set at 0 pg/ml for further calculation.

Sleep Measurement

Sleep parameters were investigated with actigraphy. This established sleep-monitoring method records wrist movements and automatically discriminates rest-activity patterns interpreted in terms of sleep and wake periods [24]. Model Actiwatch 2 (Respironics Inc., Murrysville, Pa., USA) was used. Participants recorded bedtimes and rise times on a registration form. Respironics Actiware version 5.59 was used to score 1 min epochs of actigraphic data as sleep or wake. The following parameters were calculated by the software: sleep onset latency (SOL), which is the time period between 'lights off' and sleep onset, sleep efficiency (SE), which is the sleep time divided by time in bed and is a well-recognized measure of sleep quality, total sleep time (TST), defined as the total duration of sleep periods and wake after sleep onset (WASO), defined as the amount of nighttime awake minutes after sleep onset and before final awakening. Each episode of actigraphy recordings was carried out during 4 consecutive days and nights. Participants performed 3 measurements: at baseline, 2 weeks (KTR only), and 3 months after transplantation.

Daytime Sleepiness

Daytime sleepiness was scored with the Epworth Sleepiness Scale (ESS) questionnaire at baseline (KTR and LD), 2 weeks after transplantation (KTR only), and 3 months after transplantation (KTR and LD). It has been used in ESRD patients previously [5]. A score >9 indicates elevated daytime sleepiness.

Quality of Life Questionnaire

Quality of life scores were measured with the Dutch version of the Medical Outcomes Study Short Form 36 (MOS SF-36) at baseline and 3 months after transplantation. This validated questionnaire measures physical, functional, mental, and social health [25].

Ambulatory Blood Pressure

Participants wore an ambulatory blood pressure monitor (SpaceLabs® model 90207 ItēMedical, Tiel, The Netherlands) for 24 h at baseline and 3 months after transplantation. Measurements were taken every 15 min between 8:00 and 23:00 and every 30 min between 23:00 and 8:00. Subjects were allowed to follow their normal daily routine. They were instructed to remain motionless for each blood pressure reading. Dipping status was defined as a decrease in the mean systolic blood pressure of at least 10% at night compared to daytime [26]. Dipping profile was calculated from the mean systolic values of fixed clock time periods ranging from 10:00 to 20:00 (day) and from 0:00 to 6:00 (night).

Core Body Temperature

Core body temperature was measured at baseline and 3 months after transplantation with a Jonah capsule® (Respironics, Bend, Oreg., USA). This ingestible disposable capsule contains a temperature sensor that telemetrically transmits information to a monitor, which has to stay <0.5 m from the ingested capsule. Transmissions begin ~1 min after activation and are repeated approximately every minute thereafter. As only intestinal position-

ing of the capsule provides valid data, the first 2 h of data collection were deleted [27]. In addition, all temperatures below 35°C and above 40°C were discarded, since they were believed to be caused by external factors such as hot or cold drinks.

Statistical Analysis and Parameter Estimates

Based on our previous pilot data, the primary outcome measure was defined as a mean increase in nocturnal melatonin concentrations of 8.0 pg/ml after kidney transplantation. A sample size of 27 patients per group was needed based on a power of 0.90, α of 0.05, and assumed standard deviation of 9.0 pg/ml [21].

Mean values and standard deviations of patient characteristics, melatonin concentrations, actigraphy, ESS, quality of life, and blood pressure were calculated. Sleep onset latency was non-normally distributed; therefore, median [interquartile range] results are reported. Melatonin concentrations and blood pressures were plotted. The area under the melatonin curve (AUC) was calculated from 19:00 to 7:00 after linear interpolation between two consecutive data points.

Differences in mean melatonin concentrations, melatonin AUC, actigraphy, ESS, and quality-of-life scores between pre- and post-transplantation were calculated with paired samples *t* test for recipients and donors separately. In a post-hoc analysis on open versus laparoscopic nephrectomy, quality-of-life results were also compared with paired samples *t* test. To estimate the clinical relevance of changes in quality-of-life scores, effect sizes (ES) were calculated. Effect sizes are used to relate the magnitude of the effects on the various parameters to their clinical meaningfulness. It expresses the change in the mean in terms of variation in the population. Accepted guidelines for the magnitude of the effect size, ES = 0.20, ES = 0.50, and ES = 0.80, indicate small, moderate, and large effects respectively [28].

Dim light melatonin onset (DLMO) (a circadian phase marker) was defined as the time that the salivary melatonin concentrations hit the threshold of 2.5 pg/ml in the ascending limb of the curve with linear interpolation between the point immediately below and above the threshold [29].

Temperature curves were fitted with a linearly detrended two-harmonic (24 + 12 h) cosine function. The clock time of the minimum of the fitted curve was used as indicator of the phase of the 24-hour rhythm in core body temperature [30, 31]. Correlations between time of body temperature minimum and DLMO as well as between renal function and melatonin, sleep and quality-of-life parameters were calculated with the Spearman's rank correlation coefficient. Data analysis was done using IBM SPSS 19 (Chicago, Ill., USA).

Results

Twenty-eight recipients and 29 donors were included between April 2011 and July 2013. Twenty-three recipients and 23 donors completed the study. The study profile, including reasons for loss to follow-up is summarized in figure 1. Clinical characteristics are listed in table 1.

Fig. 1. Study profile.

Melatonin Rhythm

Figures 2a and c show salivary melatonin concentrations before and after transplantation and donation. Within both donors and recipients, none of the mean melatonin concentrations differed significantly between pre- and post-Tx except for donors post-Tx mean melatonin concentration at 11 p.m. was higher than the mean pre-transplantation concentration: 5.6 ± 4.3 versus 4.1 ± 3.1 pg/ml, respectively, $p = 0.04$. Mean melatonin AUCs pre- and post-surgery did not differ significantly for either KTR or LD. Mean melatonin AUCs for KTR were 44.6 ± 34.1 and 49.2 ± 46.1 pg·h/ml at baseline and 3 months after transplantation respectively, $p = 0.44$. Mean melatonin AUCs for LD were 58.9 ± 34.4 and 72.7 ± 43.9 pg·h/ml at baseline and 3 months after transplantation respectively, $p = 0.06$. Intra-individual concentration time curves of melatonin before and after transplantation were visually examined. Neither concentrations at any of the time points nor areas under the curve (AUC) differed pre- versus post-Tx on an individual level [data not

shown]. No significant correlations were found between renal function pre-Tx or post-Tx with melatonin concentrations at 19:00, 21:00, 23:00, 01:00, 07:00 or melatonin AUC for both KTRs and LDs. In addition, no significant correlations between change in renal function and change in melatonin AUC for both KTRs and LDs were found.

Actigraphy and Daytime Sleepiness

The results of the actigraphy measurements and ESS scores are summarized in table 2. Pre-Tx, significant correlations between renal function and sleep efficiency ($r = 0.513$, $p = 0.015$) and WASO ($r = -0.455$, $p = 0.033$) were found. Renal function pre-Tx tended to be correlated with sleep onset latency ($r = -0.380$, $p = 0.081$). After transplantation, mean WASO in KTR tended to be reduced from 79.1 to 64.7 min, $p = 0.051$, at 3 months after transplantation. Sleep onset latency (SOL), total sleep time (TST), and sleep efficiency (SE) did not change significantly after transplantation. For LD, none of the four sleep parameters changed significantly with donation. No significant correlations be-

Table 1. Characteristics of donors and recipients

	Donors	Recipients
Male/female	17/12	18/10
Age, years	54.9±13.3	51.0±13.0
Body mass index, kg/m ²	24.9±3.1	25.0±4.13
RRT before transplantation		
Daytime hemodialysis	n.a.	7
Nocturnal hemodialysis	n.a.	1
CAPD	n.a.	1
APD	n.a.	1
No RRT	n.a.	18
Type of nephrectomy		
Laparoscopic	14	n.a.
Open	13	n.a.
Creatinine, µmol/l		
Baseline	72.7±14.7	499.1±193.7
2 weeks post-Tx		130.6±41.7
3 months post-Tx	110.6±22.5	120.7±28.4
eGFR ^a , ml/min/1.73 m ²		
Baseline	93.9±16.0	10.9±3.2 ^b
2 weeks post-Tx		54.1±17.1
3 months post-Tx	60.5±15.8	56.3±11.8
Smoking	6	3
Diabetes mellitus at baseline	0	2
β-blocker usage	1	15
Alcohol		
None	5	9
<1 unit/day	8	13
1–3 units/day	14	5
>3 units/day	2	1

Data are expressed as mean ± SD or number of patients where appropriate.

n.a. = Not applicable; RRT = renal replacement therapy; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; eGFR = estimated glomerular filtration rate.

^a Calculated by the CKD-EPI formula, <http://mdrd.com>, accessed on December 10th 2013.

^b Calculated for no RRT recipients only.

tween change in renal function and changes in sleep parameters or ESS scores were found for both KTRs and LDs.

Daytime sleepiness scores for KTRs were within the normal range both before and after transplantation, but had significantly decreased at 3 months after transplantation compared to baseline. For LD, daytime sleepiness scores had not changed significantly after donation.

Quality of Life

Initial quality-of-life scores and changes in scores and effect sizes are shown in tables 3a and b. No significant correlations between renal function pre-Tx and quality

of life pre-Tx were found for KTRs. For LDs, renal function pre-Tx tended to correlate with general health perception ($r = 0.439$, $p = 0.053$). For KTR, there was a significant increase in social functioning, role activities-physical, vitality, general health perception and last year's health change between baseline and 3 months post transplantation. For LD, there was a significant worsening of social functioning, role activities-physical, role activities-emotional, vitality, and pain scores 3 months after donation. Using accepted guidelines for the magnitude of the effect sizes [28], for KTR there was a large positive impact of transplantation on health change, general health perception and vitality, a substantial impact on social functioning, physical role activities and physical functioning, and a small positive effect on emotional role activities. Within this short time-frame of the study, donors experienced a negative effect on emotional and physical role activities, social functioning, pain, vitality, and physical functioning.

We found no significant correlations between the change in renal function and changes in quality-of-life scores for both KTRs and LDs, except that the change in renal function for KTRs was correlated to a change in physical role-activities ($r = 0.426$, $p = 0.043$).

The post-hoc analysis on open versus laparoscopic nephrectomy showed that with both types of surgeries, donors experienced significant worsening of physical role activities. Donors who underwent open nephrectomy experienced significant worsening of emotional role activities and pain compared to baseline. Donors who underwent laparoscopic nephrectomy experienced significant worsening of vitality compared to baseline.

Ambulatory Blood Pressure

The mean blood pressure values before and after transplantation are shown in figures 2b and d. At baseline, 6 of the 19 recipients (32%) had a dipping pattern. After transplantation, 3 of the dipping patients had switched to a non-dipping profile and 3 of the non-dipping patients had switched to a dipping profile. Of the 22 donors, 14 persons (64%) had a dipping profile at baseline. After transplantation, 5 of the dipping donors had switched to a non-dipping profile and 4 of the non-dipping donors had switched to a dipping profile.

Circadian Parameters: Core Body Temperature and DLMO

In table 4, the mean values of the circadian phase markers – clock time of the core body temperature (cBT), minimum and dim light melatonin onset (DLMO) – are

Fig. 2. Melatonin and ambulatory blood pressure results of kidney transplant recipients (upper panels) and donors (lower panels). **a, c:** Mean $\pm$ SD melatonin concentrations in saliva. The horizontal axis reflects the time of day in hours and the vertical axis reflects the melatonin concentration in saliva in pg/ml. The solid line represents baseline values, the dashed line represents measurements

2 weeks after transplantation, the dotted line represents measurements 3 months after transplantation. **b, d:** Mean $\pm$ SD ambulatory blood pressure measurements. Solid lines represent baseline values, dotted lines represent values 3 months after transplantation (Tx). Black lines and grey lines indicate systolic and diastolic values respectively. * $p < 0.05$.

listed. For KTR, the results for both cBT and DLMO were not significantly different before and after transplantation. There was no significant correlation between time of temperature minimum and DLMO within the recipients both before and after transplantation ($r = 0.27$, $p = 0.37$ and $r = 0.07$, $p = 0.86$, respectively). Also for LD, the results for both cBT and DLMO were not significantly different before and after transplantation. However, before donation, there was a significant correlation between time of temperature minimum and DLMO within the donors. After donation, this correlation within the donors had disappeared (coefficient = 0.61, $p = 0.017$ and $r = 0.11$, $p = 0.73$, respectively).

Discussion

As expected, in renal patients prior to transplantation, we found a significant relationship between renal function and sleep quality. However, sleep quality did not improve after transplantation, with the exception of the number of nighttime awake minutes. In contrast to our hypothesis, after renal transplantation, melatonin concentrations did not improve in KTR, despite marked improvement in the renal function. Mean AUC nor melatonin concentrations changed significantly. In addition, individual melatonin concentration profiles remained remarkably stable throughout the study period. Post transplantation, we did

Table 2. Actigraphy and daytime sleepiness results for recipients (n = 22) and donors (n = 21)

	SOL, min	p value*	TST h	p value*	SE, %	p value*	WASO, min	p value ^a	ESS score	p value*
Normal values	<15		>5.8		>85		unknown		<9	
Recipients										
Baseline	11.0 (5.69–19.69)	–	6.5±1.0	–	77.8±12.2	–	79.1±38.8	–	7.7±3.9	–
2 weeks after Tx	9.75 (4.31–16.94)	0.25	6.6±1.1	0.68	79.4±9.2	0.64	68.5±35.8	0.19	7.0±4.8	0.43
3 months after Tx	13.0 (7.19–32.1)	0.76	6.6±0.85	0.50	79.2±9.9	0.58	64.7±26.4	0.05	4.7±3.8	0.001
Donors										
Baseline	13.0 (6.38–21.5)	–	6.7±0.83	–	83.5±4.7	–	50.7±19.3	–	5.2±3.2	–
3 months after Tx	10.25 (5.38–15.25)	0.52	6.8±0.82	0.49	83.1±5.6	0.64	51.2±21.9	0.92	5.5±3.2	0.54

Data for SOL are expressed as median (interquartile range), data for TST, SE and WASO are expressed as mean ± SD.

SOL = Sleep onset latency (in min); TST = total sleep time (in h); SE = sleep efficiency (in %); WASO = wake after sleep onset (in min), ESS = Epworth Sleepiness Scale.

* p values calculated versus baseline.

not find significant relationships between (changes in) renal function and (changes in) sleep, melatonin, or quality of life for either KTRs or LDs. However, recipients subjectively experienced less daytime sleepiness as well as major improvements of quality of life after transplantation.

We hypothesized that an increase in renal function would restore melatonin synthesis based on the earlier finding that a decrease in renal function was related to lower nocturnal melatonin concentrations [14] and pilot data showed increased melatonin concentrations in 4 out of 7 transplant recipients [21]. The main ensuing question is why improvement of renal function did not result in increased melatonin levels in this study.

First, our earlier work assessed the effects of a gradual, long-term change in renal function, whereas here melatonin levels were measured relatively shortly after an acute increase in renal function. Apparently, melatonin secretion is not related to improvement of renal function in the short term. Therefore, not glomerular filtration per se, but other long-term, renal function-related mechanisms may be the connection between kidney disease and disturbed melatonin synthesis. At this point, we can only speculate as to the nature of the underlying mechanisms. It has been suggested that the degree of pineal calcification (and therefore the size of remaining uncalcified pineal gland volume) indicates the intra-individual capability to produce melatonin [32]. Indeed, the decrease in melatonin secretion with age is predominantly due to increasing pineal calcification [33]. Although it is unknown

whether CKD is associated with calcification of the pineal gland, at least vascular calcification composes a well-known complication of end-stage renal disease [34].

Second, in this study we found better nocturnal melatonin concentration profiles for KTR at baseline than expected and also sleep was not as disturbed as expected. As a result, we observed only a small, non-significant difference in mean melatonin concentrations and AUCs between donors and recipients, whereas we had expected much lower melatonin concentrations in KTR than in LD based on our earlier findings in hemodialysis patients [15] and recent findings [unpublished data]. In our study, the timing of saliva sampling may have played a role since the nocturnal melatonin peak is expected to occur between 2:00 and 4:00. We did not take samples at these times not wanting to create discomfort to the patients. Possibly, the melatonin peak differences between donors and acceptors would have been larger if nightly samples had been collected between 2 and 4 a.m. [12, 13, 15, 23, 35].

Why did the KTR have relatively high melatonin levels? This could not be explained by a lower rate of β -blocker usage. Beta-blockers are known to suppress melatonin synthesis. Fifty-four percent of the recipients used β -blockers. This is equal to the reported 56% of a previously studied representative hemodialysis population in the Netherlands [36].

Taken together, we submit that our failure to observe improvements of melatonin secretion and the marginal improvement in sleep in KTR is related to the relatively

Table 3. Quality-of-life results**a** In donors and recipients before and 3 months after kidney transplantation

	Donors (n = 23)			Recipients (n = 23)		
	initial ^a	change ^b	ES ^c	initial ^a	change ^b	ES ^c
Physical functioning	95.0±7.9	-6.2±17.1	-0.78	78.2±19.3	6.4±16.8	0.33
Social functioning	94.6±9.1	-11.7±23.4*	-1.28	70.1±25.5	16.3±22.4**	0.64
Role activities – physical	95.7±12.3	-37.5±44.8**	-3.05	40.8±44.3	24.4±55.9*	0.55
Role activities – emotional	98.5±7.1	-23.5±39.4*	-3.31	81.2±36.0	10.1±39.5	0.28
General mental health	83.1±8.2	-2.1±11.8	-0.26	79.1±14.8	2.1±15.5	0.14
Vitality	80.5±12.6	-10.8±15.8**	-0.85	55.9±19.0	18.3±20.3**	0.96
Bodily pain	92.2±13.0	-12.1±20.7*	-0.93	88.6±20.0	0.0±16.4	0.00
General health perception	82.7±13.7	0.2±14.6	0.02	50.0±17.9	14.8±19.1**	0.83
Last year's health change	57.6±14.0	-8.7±23.4	-0.62	28.3±28.5	66.3±33.4**	2.33

b In donors before and 3 months after kidney donation for open versus laparoscopic nephrectomy

	Open (n = 11)			Laparoscopic (n = 12)		
	initial ^a	change ^b	ES ^c	initial ^a	change ^b	ES ^c
Physical functioning	98.6±2.3	-11.4±21.5	-4.78	91.4±9.8	-1.0±9.7	-0.10
Social functioning	92.0±10.1	-11.9±27.4	-1.18	96.9±7.8	-11.5±20.3	-1.47
Role activities – physical	97.7±7.5	-42.0±49.5*	-5.58	93.8±15.5	-33.3±41.7*	-2.15
Role activities – emotional	97.0±10.0	-31.8±46.2*	-3.17	100.0±0.0	-15.1±31.1	#
General mental health	82.9±8.0	-3.3±9.8	-0.41	83.3±8.7	-1.0±13.8	-0.12
Vitality	79.3±13.6	-9.3±15.2	-0.68	81.7±12.1	-12.1±16.8*	-1.00
Bodily pain	95.7±10.5	-19.8±23.8*	-1.89	89.3±14.6	-5.6±16.0	-0.38
General health perception	82.3±13.3	-0.9±18.7	-0.07	83.2±14.7	1.4±9.8	0.09
Last year's health change	56.8±16.2	-13.6±25.9	-0.84	58.3±12.3	-4.2±20.9	-0.34

^a Initial mean MOS-SF36 score ± SD, using scale of 0 (worst health) to 100 (best health). ^b Mean change MOS-SF36 score ± SD. ^c ES is defined as effect size calculated as mean change score per group divided by the standard deviation of the initial mean score in that group. A positive effect size denotes improvement, a negative effect size denotes worsening. # Could not be calculated. * p < 0.05, ** p < 0.005.

Table 4. Circadian parameters: core body temperature and DLMO

	Recipients				Donors			
	n	baseline	3 months after transplantation	p value	n	baseline	3 months after transplantation	p value
Time of cBT, h	12	2:42±2:08	1:44±2:59	0.31	13	1:51±4:55	3:52±3:34	0.24
DLMO, h	11	22:18±1:05	21:44±1:15	0.24	16	22:21±1:15	22:03±1:24	0.28

Data are expressed as mean ± SD. DLMO = Dim light melatonin onset; cBT = core body temperature.

short time span after transplantation that was allowed for the final assessment. In addition, these transplant recipients probably were in relatively good condition prior to transplantation as compared to previously studied hemodialysis patients because 57% of our analyzed transplantations were performed preemptively. Indeed, hemodialysis treatment has been identified as one of the predictors of poor pre-transplantation sleep quality [37].

Quality of life improved with the recipients 3 months after renal transplantation, as expected. Obviously, it is not possible to conclude that this is related to an improvement in circadian rhythmicity of melatonin, sleep, or blood pressure since we did not find any changes in these parameters.

As could be expected, kidney donation had short-term negative influences on the quality of life. Previously, several small prospective studies have already shown decreases in SF-36 scores shortly after donation [38]. These are likely to be temporary changes since larger, long-term retrospective studies on quality-of-life changes of kidney donors reported scores to be equal to or better than non-donor controls [39, 40]. The larger negative effect sizes with open versus laparoscopic nephrectomy, possibly point to a more favorable quality-of-life course with laparoscopic nephrectomy.

In conclusion, we did not find an improvement of nighttime melatonin secretion, blood pressure dipping, DLMO and body temperature correlation, sleep onset, total sleep time, and sleep efficiency with kidney transplantation. The number of nighttime wake minutes after initial sleep onset improved after transplantation. However, subjective judgments of quality of life improved just as the as daytime sleepiness scores. It should be noted that daytime sleepiness scores were already within the reference range before transplantation. These subjective improvements could not be related to a better function of circadian rhythmicity. Future research should focus on *the long-term* effects of kidney transplantation on melatonin and sleep in larger groups of transplant recipients with a longer history of renal disease.

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