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The role of melatonin treatment in chronic kidney disease

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1. ABSTRACT

The pineal hormone melatonin plays a major role in circadian sleep-wake rhythm. Patients with Chronic Kidney Disease (CKD), especially those who are on hemodialysis, frequently suffer from sleep disturbances. In this review an overview is given of the classification of stages of chronic kidney disease, followed by a presentation of the circadian rhythm disorders in renal disease involving sleep disturbances in relation to melatonin deficiency. The therapeutic benefit of melatonin treatment in sleep disorders related to chronic kidney disease including the controlled trials solving this topic, is described. Furthermore, the beneficial effect of melatonin on blood pressure alterations in CKD states and the protection of melatonin in oxidative stress and inflammation in renal disorders are explored. Finally a hypothetic model is described for the relation between circadian rhythm disorders and CKD.

2. INTRODUCTION

Sleep disturbances are associated with an altered sleep-wake cycle (1). Sleep disturbances are more prevalent in patients with Chronic Kidney Disease (CKD) (2) and in the hemodialysis population in particular, than in the general population (3,4). Several studies on the influence of sleep problems on quality of life in patients on dialysis revealed that sleep disturbances have a major negative effect on the vitality and general health of these patients (5). Sleep disturbances in patients on hemodialysis are caused both by renal disease and by the hemodialysis treatment itself (6).

Melatonin plays a key role in the regulation of the circadian sleep-wake rhythm (7). This endogenous hormone is produced by the pineal gland during the hours of darkness. To study circadian rhythms, melatonin can be sampled and analysed by established methods like Radio-immunoassays (RIA) (8) and GasChromatograpy-Mass

Spectrometry (GC-MS) (9). The body fluids in which melatonin concentrations are studied most frequently, are blood and saliva. The serum concentration is 2,5 times higher than in saliva (8). Studies that are presented in this review show that melatonin curves in patients with CKD differ from melatonin curves in healthy people.

Melatonin may be administered as a drug for its pharmacological properties on the reduction of the sleep onset latency or for its chronobiotic properties to shift the biological clock time. An overview of the effects of melatonin treatment in CKD patients with circadian sleep–wake rhythm disorders will be described in this review.

3. DEFINITIONS OF RENAL DISEASE

Chronic Kidney Disease (CKD) is defined according to the presence of markers of kidney damage in combination with the level of kidney function (10,11,12). Five stages of CKD are specified, although cut-off levels between stages are arbitrary. In stage 1 CKD albuminuria is accompanied by normal or only mildly diminished renal function, whereas stage 5 CKD is a severe illness and requires some form of renal replacement therapy (dialysis or renal transplantation). CKD may cause progressive loss of renal function over a period of months or years through the five stages. When CKD proceeds to stage 4-5, metabolic acidosis, abnormal serum levels of potassium, calcium and phosphate and anemia can occur. Koch *et al* showed that decreased sleep efficiency is frequently reported in stage 5 CKD and that in patients with hemoglobin levels lower than 10 g/dl or patients with elevated phosphate and urea levels subjective sleep efficiency is affected negatively (13). Long-term complications of CKD are cardiovascular disease (which is the primary cause of death in this population) and bone disease.

In stage 5 of CKD renal replacement therapy is required to clear the blood from toxic solutes and remove excess fluid. Dialysis can be performed by means of hemodialysis and peritoneal dialysis. In hemodialysis, the patient's blood is pumped through the blood compartment of a dialyzer, exposing it to a semipermeable membrane. The cleaned blood is then returned back to the patient. Hemodialysis treatments are typically given in a dialysis centre three times per week during 3-5 hours (conventional daytime hemodialysis). However, different dialysis regimens have been introduced: nocturnal dialysis (slow dialysis during 8 hours for 4-6 nights per week at home or in-centre) or short daily dialysis (5-6 times per week for 2 hours).

In peritoneal dialysis (PD), a sterile solution containing minerals and glucose is run through a tube into the peritoneal cavity, where the peritoneal membrane acts as a semipermeable membrane. The dialysate is left there for a period of time to absorb waste products. Subsequently it is drained out through the tube and discarded. This cycle or "exchange" can be repeated manually 4-5 times during the day, which is called continuous daytime peritoneal dialysis (CAPD) or can be performed overnight with an automated system (APD). Peritoneal dialysis is less efficient than conventional daytime hemodialysis, but because it is carried out each day and for a longer period of time the net effect in terms of removal of waste products and of salt and water are similar to hemodialysis.

4. CIRCADIAN RHYTHM DISORDERS IN CKD

In recent years the importance of circadian rhythm disorders in CKD has become evident. Disorders of the circadian rhythm might result in sleep disturbances (14), but may disrupt several renal rhythms like urinary excretion of water and all major electrolytes as well. The circadian regulation and role of the biological clock in these renal rhythms has been well recognized. Disturbance of the renal circadian rhythm is increasingly recognized as a risk factor for hypertension, polyuria, and other diseases and may contribute to renal fibrosis (15).

4.1. Sleep disturbances in CKD

In patients with renal disease, circadian rhythms can be disrupted by both internal factors (e.g. biochemical parameters and melatonin) and external factors (e.g. dialysis and medications). This may lead to sleep disturbances, as is presented in (Figure 1).

Between 30% and 80% of individuals with end stage renal disease report disturbed sleep, caused primarily by a delayed sleep onset or by frequent awakening, restless legs syndrome (RLS) and generalized restlessness (4,16,17,18). A population study of daytime hemodialysis patients showed that 60% of these patients experienced subjective sleep problems (13).

Patients on daytime hemodialysis and patients with CKD both have reduced total sleep time and reduced sleep efficiency in comparison with healthy subjects (2). Patients on hemodialysis have less rapid eye movement sleep, a higher brief arousal index, a higher respiratory disturbance index, less total sleep time, increased wake-time after sleep onset, lower sleep efficiency, a higher periodic limb movement index and longer sleep onset latencies in comparison to patients with CKD (2). These findings suggest that the sleep problems experienced by patients with CKD and those experienced by individuals on hemodialysis might have different etiologies. Functional and psychological factors might have a greater role in patients with CKD, and intrinsic sleep disruption (e.g. arousal, apnea and limb movements) secondary to the effects of intermittent daytime hemodialysis may play a more important role in individuals on hemodialysis (2).

4.1.1. Effects of dialysis on the sleep/wake rhythm

Although little data comparing the prevalence of sleep disorders in patients on daytime hemodialysis and on PD exist, it may be hypothesized that the different dialysis techniques (the short, but intensive urea reduction in conventional daytime hemodialysis in comparison to the slow, but constant urea reduction in PD patients) may have a role in the reported differences of the prevalence of sleep problems in these populations.

The effects of different hemodialysis techniques are ambiguous when comparing the different studies. For

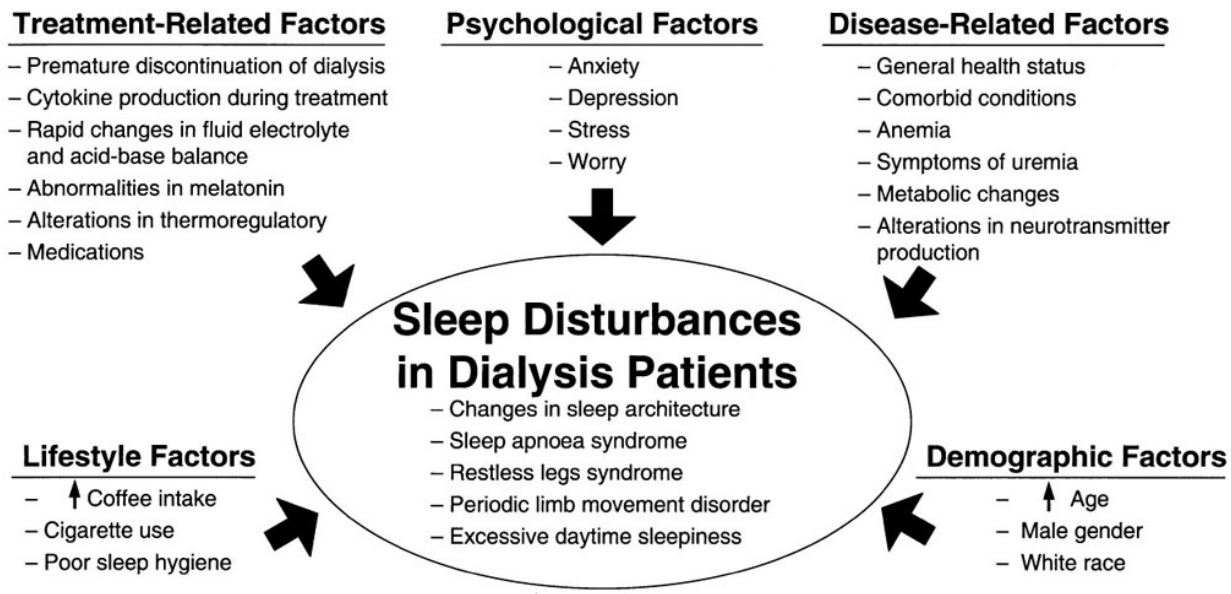

Figure 1. Overview of possible mechanisms of desynchronization of sleep-wake rhythm, leading to sleep disturbances in CKD. Reproduced with permission from (3).

example Theofilou reported more sleep disturbances in hemodialysis patients than in PD patients (19), while Holley *et al.* have found that the type of dialysis and dialysis adequacy did not affect the prevalence of sleep disorders (20) and Bro *et al.* showed that changing from CAPD to APD resulted in an alleviation of sleep apnea, possibly owing to more vigorous nocturnal clearance of fluid with APD (21). Our research group also studied sleep-wake rhythm in different dialysis groups: conventional daytime hemodialysis, nocturnal in-hospital-dialysis and APD. Although most sleep parameters were impaired in all 3 groups, conventional daytime hemodialysis patients experienced worst sleep quality (22).

Since daytime hemodialysis can increase daytime sleep propensity, this may lead to delayed sleep onset and decreased night time sleep. Several possible causes for the sleep promoting effects of hemodialysis exist.

Dialysis can induce imbalances of brain and serum osmolarity, resulting in shifts of water from the blood to the brain. This condition, known as disequilibrium syndrome, is associated with a paradoxical acidosis in the cerebral spinal fluid that results from the slow movement of bicarbonate across the blood–brain barrier. Disequilibrium syndrome causes cerebral edema, which may depress the CNS. This depression causes a decrease in alertness and arousal (23,24) Therefore, the depression of the CNS in dialysis patients can lead to daytime sleepiness and result in an impaired sleep–wake rhythm (25).

Secondly, the hemodialysis procedure is a significant physical and psychological stressor. The stress response triggered by emotional arousal resulting in reactions like anxiety, depression and increased daytime sleepiness (26,27).

Thirdly, hemodialysis may also affect the sleep–wake cycle by altering exposure to *zeitgebers* (time cues) that help set or entrain the circadian system. The time of day that treatment is given can affect an individual's wake-up time, time for physical activity, meal times, light exposure, social activities (28) and even survival (29). This study of Bliwise *et al.* has shown that morning-shift hemodialysis patients survived significantly longer than afternoon-shift hemodialysis patients. The authors suggested that this effect included salutary effects of sleep in the morning or less efficient biochemical exchange during afternoon dialysis (29).

Finally, hemodialysis may induce sleep propensity by raising body temperature (30). This seems interesting since there is a reciprocal relationship in circadian profiles whereby the temperature nadir ('dip') correlates closely to the peak of melatonin (1). In the past, immunogenic reactions during hemodialysis caused chills and fever. From studies in the nineties, when dialyzer membranes were less biocompatible and the water used for hemodialysis was of less microbiological quality than nowadays, it was suggested that interleukin-1 (IL-1), IL-6 or tumor necrosis factor (TNF) produced by peripheral blood mononuclear cells in the bloodstream were recognized as a pyrogenic signal by specific centers within the central nervous system (CNS). Such signals may induce the synthesis of prostaglandins that represent the central mediators of the coordinated response which may lead to a rise in core body temperature (28,31,32,33). IL-1 was found to be involved in both surges in body temperature and sleep induction (31). However, a slight increase in body temperature has also been observed in patients undergoing hemodialysis with uncontaminated dialysate (33). Body temperature may also rise as a result of heat load from the dialysis bath. Because of the known association between body cooling and sleep onset (34,35)

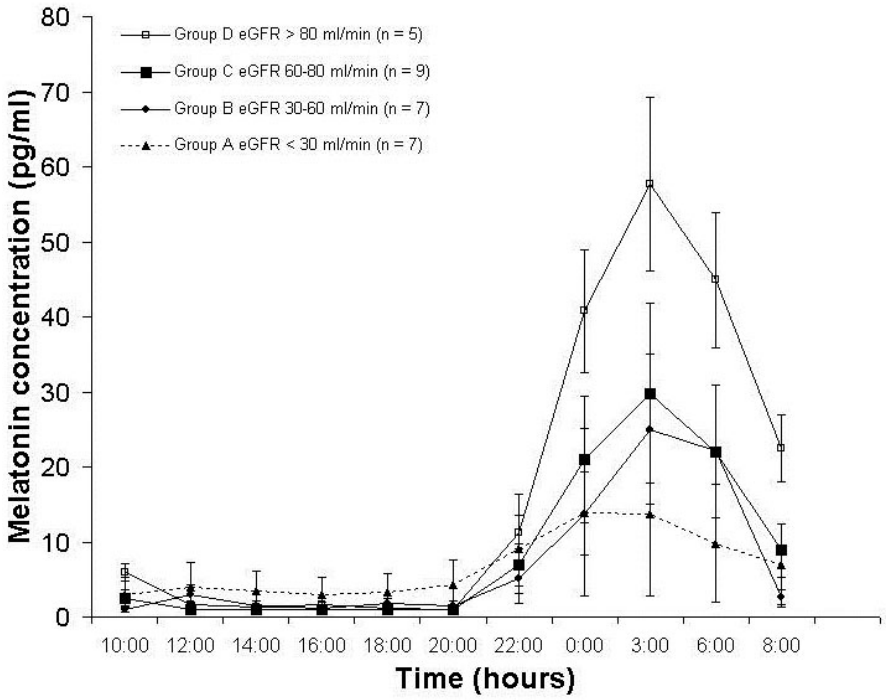

Figure 2. Mean serum melatonin concentrations in 4 groups with increasingly affected renal functions (n=28). The error bars reflect the standard deviations. The horizontal axis reflects the time of day (in hours). The vertical axis reflects the mean melatonin concentration in blood (in pg/ml). Reproduced with permission from (38).

hemodialysis-associated elevations in body temperature might activate cooling mechanisms that enhance daytime sleep propensity, particularly during the post-hemodialysis period. Chronic, episodic elevations in body temperature in association with hemodialysis might therefore lead to alterations in the sleep propensity rhythm (30).

After kidney transplantation many sleep disorders, such as sleep-disordered breathing, improve compared to hemodialysis (36). However, sleep quality remains low and the prevalence of sleep complaints remains higher than in the general population (37).

4.1.2. Nocturnal melatonin levels in CKD patients

Koch *et al.* have described a direct association between a decrease in renal function and a decrease in melatonin production (Figure 2) (38).

Figure 2 illustrates that patients with a GFR<30 ml/min, i.e. the group with the worst renal function in this study, still expressed a melatonin curve with a criterion concentration in blood of at least 10 pg/ml. The time at which the value of 10 pg/ml in blood is reached is called the Dim Light Melatonin Onset (DLMO) and is the best characterisation of the 24-h melatonin rhythm, which is strongly associated with the circadian sleep-wake rhythm) (38,39,40). However, in many CKD stage 5 (hemodialysis) patients, the normal rise above this value was not evident. In one of our studies in CKD patients, the nocturnal melatonin rise in daytime hemodialysis patients was absent (41). In a different study by Koch *et al.* it was shown that the melatonin rhythm differs depending on the type of dialysis (22). In nocturnal hemodialysis patients some nocturnal melatonin rise was found, while in daytime hemodialysis and APD patients this rise was absent. Since APD is also performed nocturnally like nocturnal hemodialysis, we had expected a nocturnal melatonin rise in this patient group as well. Given that APD patients had the best sleep of the three groups studied, we concluded that melatonin might play a subordinate role in the sleep-wake rhythm of APD patients (22). The absence of normal nocturnal melatonin levels in end-stage renal disease (ESRD) suggests a possible role for exogenous melatonin to restore the melatonin rhythm in CKD and daytime hemodialysis patients (41).

5. RESTORING CIRCADIAN RHYTHM DISORDERS IN RENAL DISEASE

5.1. Use of exogenous melatonin to treat sleep disorders in CKD

Melatonin can be used to treat sleep disorders by reducing sleep onset latency. The *hypnotic* effect of melatonin on sleep onset latency in healthy subjects with and without insomnia (42,43) and in subjects with primary sleep disorders (44) is described in three meta-analyses of controlled trials (42,43,44). From these studies it is concluded that exogenous melatonin is a safe and effective drug in these populations.

Melatonin also exerts a *chronobiotic* regulatory effect on the 'sleep wake cycle'. This aspect of melatonin is

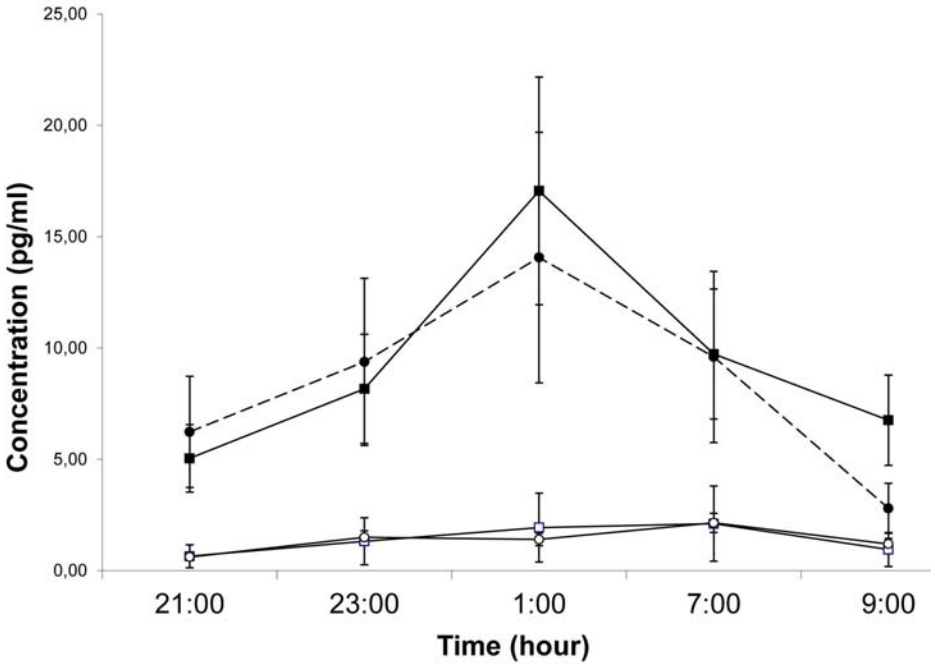

Figure 3. Mean melatonin concentrations in saliva on the day of dialysis and the consecutive day. The horizontal axis reflects time of day (in hours); the vertical axis reflects melatonin concentrations in saliva (in pg/ml). Lines with open bullets represent the measurements before melatonin treatment. Lines with closed bullets represent the measurements after melatonin treatment. Squares represent measurements on nights following dialysis, circles represent measurements on nights after a non-dialysis day. Vertical lines at the bullets represent the standard deviation error bars. Treatment consisted of melatonin 3 mg daily at 10 pm for 6 weeks. Reproduced with permission from (41).

reviewed by Cochrane Systematic Review (45). The mechanism by which melatonin regulates the sleep wake cycle has not yet been determined. It may be due to either an intrinsic property or to the combination of two other physiological effects: i.e. reduction of sleep onset latency and improvement of sleep quality (46). Several authors claim that the chronobiotic effects of melatonin occur only if melatonin is administered at the right time of the day in relation to the Dim Light Melatonin Onset (DLMO) (39,40,47,48).

ESRD, when renal replacement therapy is required, is associated with the worst sleep quality of all CKD patients (2). Koch *et al* have studied the effect of administration of melatonin 3 mg on the sleep of patients undergoing conventional daytime dialysis (41). The purpose of this study was to investigate the effects of exogenous melatonin on the sleep of patients on conventional daytime hemodialysis. In this study it was observed that treatment with melatonin resulted in normalization of sleep onset latency and a significant improvement of total sleep time, sleep efficiency and sleep fragmentation. In addition to these objective measurements subjective sleep parameters improved as well. Furthermore the normal nocturnal melatonin rise that was absent was recovered after a few weeks of melatonin treatment (see (Figure 3)). This endogenous rise in melatonin concentration was seen 1-2 days after patients had ceased taking their study medication.

To investigate the *long-term* effects of melatonin administration, our group has followed 67 daytime hemodialysis patients for one year. Although a beneficial effect on sleep onset latency during the first three months of treatment was observed, this effect decreased with time. The possible reasons for this decreased efficacy have not yet been established (unpublished data).

5.2. Effect of timing of dialysis related to sleep disorders in CKD

Another interventional study of Koch *et al.* on sleep disorders in hemodialysis patients concerned the change from daytime dialysis to nocturnal dialysis (49). In this study 18 patients were followed during their change from daytime hemodialysis to nocturnal dialysis. This study showed significantly improved and normalized sleep efficiency and proportions of sleep stages 3 and 4 (deep sleep) with polysomnography after 6 months of in-centre nocturnal in hospital dialysis compared to conventional daytime hemodialysis. Patients reported improved daytime function and sleep quality when on in-centre nocturnal hemodialysis therapy in comparison to conventional daytime hemodialysis. The salivary nocturnal melatonin surge was restored with melatonin concentrations greater than DLMO levels of 4 pg/ml when on in-centre nocturnal hemodialysis therapy as is illustrated in (Figure 4).

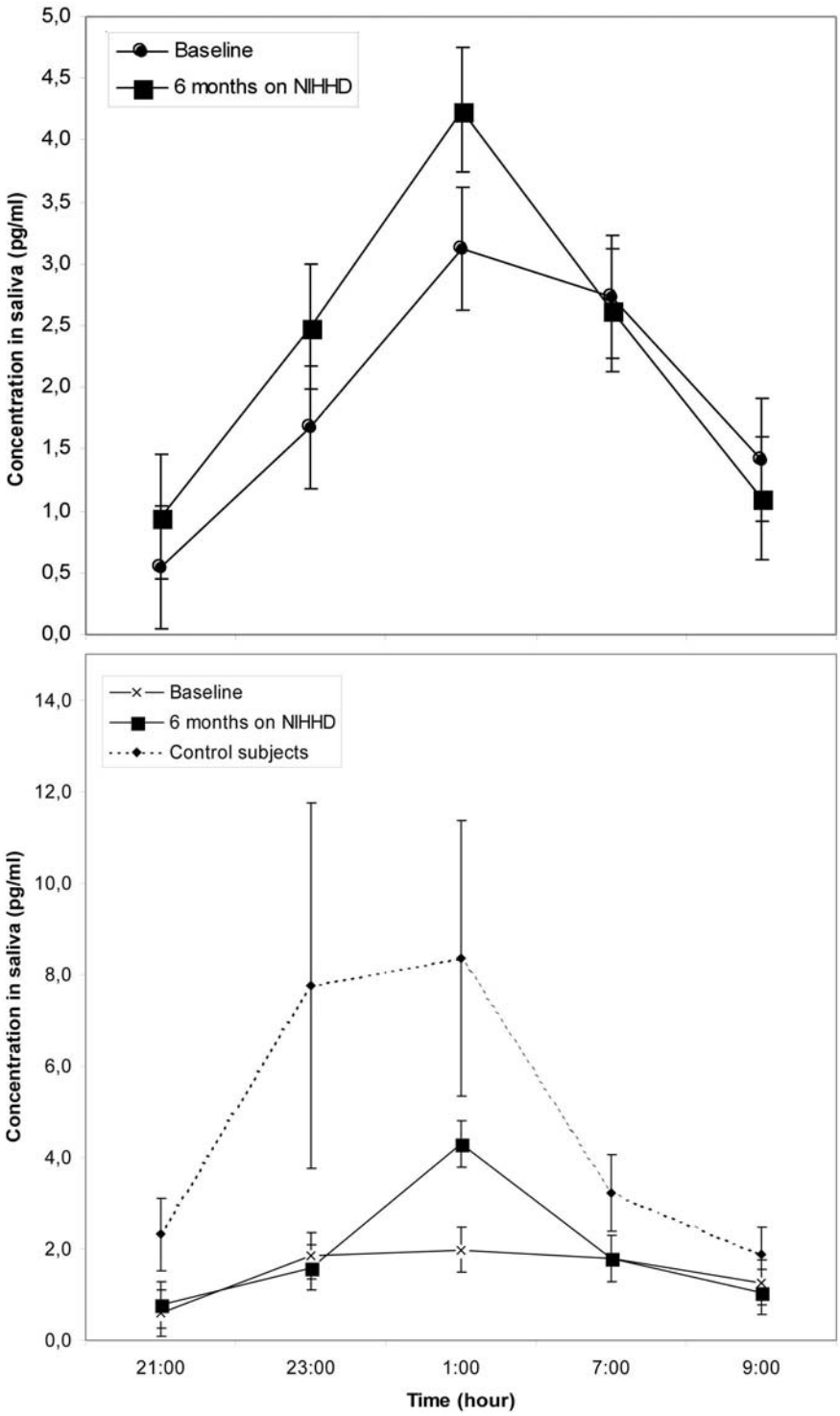

Figure 4. Average melatonin concentration in saliva on (upper panel) the day of dialysis (n=12) and (lower panel) the day after dialysis (n=12). The horizontal axis reflects time of day (in hours), the vertical axis reflects melatonin concentrations in saliva (pg/ml); baseline, measurements at t= 0. Abbreviation: NIHHD, nocturnal in-hospital hemodialysis. Data shown in lower panel for control individuals (n=30) are unpublished and courtesy of Bühlmann Laboratories (Schönenbuch, Switzerland). Reproduced with permission from (49).

Nocturnal dialysis has an important advantage over daytime dialysis: the sleep promoting mechanisms of the dialysis treatment coincide with appropriate and conventional time of day. In this way the shift to nocturnal dialysis could restore the normal temporal relationship between the sleep period and other rhythms of the circadian system. Very likely this will result in an improved quality of both sleep and daytime functioning. These improvements could be enhanced by a markedly increased dialysis efficiency and fluid removal.

5.3. The effect of melatonin on blood pressure rhythm in CKD

In CKD patients cardiovascular mortality is the commonest cause of death. Apart from traditional risk factors of cardiovascular disease (50,51) it is hypothesized that non-traditional risk factors, such as oxidative stress, continuous inflammation, vascular calcifications, endothelial dysfunction and anaemia contribute to the excess cardiovascular mortality in renal disease (52).

In this respect circadian rhythm of blood pressure is clinically relevant. Blood pressure shows 24-hour periodicity. Early during the night, blood pressure typically drops to its lowest values ('dip') to rise the next morning to its highest level ('surge'). Individuals who have an excessive morning surge or who lack the nocturnal dip tend to show worse cardiovascular outcomes (53,54).

A relatively high proportion of CKD patients show an impaired diurnal blood pressure profile (55). The prevalence of non-dipping in patients with underlying kidney disease (CKD, hemodialysis (HD) and peritoneal dialysis (PD)) is higher than in patients with essential hypertension: 53% versus 30%. Even after successful kidney transplantation, this difference persists (56). The pathogenesis of the non-dipping phenomenon is unclear, but a relation between reduced nocturnal melatonin levels and non-dipping blood pressure can be hypothesized. This is interesting, since we have found previously that nocturnal melatonin concentrations are reduced in patients with chronic kidney disease (38).

Although no specific evidence is available on blood pressure lowering effects of melatonin in patients with CKD, clinical trials to elucidate this would be interesting, since some hypotheses can be drawn from existing animal studies and small studies in humans. Melatonin is proposed as an additive to regular antihypertensive drugs in patients with non-dipping blood pressure profile or with night-time hypertension because of its supposed antihypertensive effect. Firstly, in animal studies low melatonin levels are related to the development of hypertension. Pinealectomized rats or rats that are exposed to continuous light become melatonin deficient. This is accompanied by peripheral vasoconstriction and hypertension (reviewed in: 57). Rats with renovascular hypertension that received melatonin treatment, showed reduced blood pressure, improved left-ventricular function and alleviated oxidative injury of the kidney, heart and brain (58). Secondly, in humans it was shown that a nocturnal surge in melatonin concentrations reflected by the increase of the urinary melatonin metabolite 6-sulfatoxymelatonin was observed only in patients with a nocturnal blood pressure dipping profile (59). Administration of 2.5 mg exogenous melatonin in hypertensive patients decreased both the systolic and diastolic blood pressure, during day and night (60). The mechanism by which melatonin lowers blood pressure is not fully elucidated. Possibly the free radical scavenging and anti-oxidative properties of melatonin play a role by preserving endothelial function, stimulating NO synthesis and inhibiting NO degradation, which results in vasodilatation and hypotensive effects. Furthermore, melatonin is thought to help lowering the nocturnal blood pressure through its anti-adrenergic effect. Thirdly, via specific melatonin receptors in peripheral tissue or blood pressure modulating structures in the central nervous system, melatonin might influence blood pressure (reviewed in: 57). Finally, melatonin alters blood flow to assorted vascular beds by the activation of different melatonin receptors (61).

6. THE EFFECT OF MELATONIN ON OXIDATIVE STRESS IN CKD

In addition to its use as a chronobiotic or hypnotic to influence or restore disturbances in circadian processes in renal patients such as sleep problems, hypothetically the strong anti-oxidative properties of melatonin might be used to lower the risk of deterioration of kidney function. Melatonin exerts its anti-oxidative properties directly by scavenging free radicals, such as reactive oxygen species (ROS). It indirectly protects the function of membranous or cytosolic proteins and DNA in the cell nucleus by stimulating the upregulation of anti-oxidative enzymes and reducing lipid peroxidation (62).

Hardly any data are available on distinct renoprotective effects of melatonin in humans. However, there is considerable evidence that oxidative stress contributes to renal injury and the administration of antioxidants exhibits beneficial effects in a number of animal models of kidney diseases (Reviewed in: 63). The therapeutic and protective effect of melatonin against this type of kidney damage has repeatedly been shown in animals (64,65,66).

In pinealectomized rats, the animals experienced significant kidney damage that could be prevented by the administration of exogenous melatonin (67).

Many studies have been undertaken in animal models in which oxidative stress was induced by drug toxicity. As an example, the nephrotoxic drug cisplatin induces kidney damage which can be measured by an increase in plasma creatinine and blood urea and a decreased kidney level of the antioxidant glutathione. Co-treatment with melatonin protected against the oxidative damage associated with cisplatin (68).

However, the majority of the animal studies in which the anti-oxidative effect of melatonin has been shown, was done with relatively high melatonin doses, up to 40 mg/kg. A good interpolation to corresponding human

dosages is difficult. However, Agapito *et al.* showed that a low pharmacological dose of 50 µg/kg, which corresponds to common human dosages of 1 to 5 mg, could attenuate oxidative stress (expressed by the reduced to oxidized glutathione ratio) and the amount of lipid peroxidation products that was induced by an injection of adriamycin in rats (69).

Although on the basis of *in vitro* and animal studies melatonin could theoretically be a valuable supplement to attempt to prevent deterioration of kidney function by using its anti-oxidative properties, evidence in humans is scarce. While there is some evidence for the protective effect of melatonin against oxidative stress for example due to the administration of intravenous iron and recombinant human erythropoietin in hemodialysis patients (70), there is insufficient proof to recommend taking melatonin or other anti-oxidative supplements with renal injury.

7. INFLAMMATION IN CKD IN RELATION TO CIRCADIAN DISTURBANCES

The continuous inflammatory state of ESRD patients predisposes them to develop sleep disturbances. In the general population, subjects with sleep disturbance or healthy volunteers experiencing sleep deprivation have enhanced inflammatory responses (71,72). Some inflammatory cytokines, especially the interleukin–1 (IL-1) family, have critical roles in the regulation of physiological sleep (73). Several authors have demonstrated that hemodialysis patients with sleep problems have higher IL-18 and high sensitive C-reactive protein levels (74,75). Moreover, treatment for sleep disturbances partially eliminates the large amount of inflammatory cytokines in peritoneal dialysis patients (76). Importantly, recently it was shown in hemodialysis patients that an improvement in sleeping pattern by cognitive-behavioral therapy was associated with a decrease in inflammatory activity and oxidative stress (77). Interestingly this supports the exciting idea that non-pharmacological interventions may be helpful in the prevention of worsening of CKD. All of this evidence implies a connection between sleep disturbance and inflammation in CKD patients.

Previously, we have measured melatonin rhythms and levels of the inflammatory markers IL-6 and TNFα. However no evidence was found to support the association between higher melatonin levels in patients with CKD and lower levels of the inflammatory markers (38,78).

8. REMAINING QUESTIONS AND FUTURE RESEARCH

In CKD a number of disturbances in (the regulation of) circadian rhythm exist. A remarkable decrease in melatonin secretion is seen in CKD patients, related to the severity of the kidney disease. The low melatonin concentrations in serum and saliva during the night, without reaching a threshold concentration of 10 pg/ml in serum or 4 pg/ml in saliva, may be the basic feature of sleep related circadian rhythm disorders in CKD patients. This may result in several concurrent pathophysiological conditions that feature CKD: high nocturnal blood pressure and oxidative stress.

The fact that administration of exogenous melatonin to hemodialysis patients improves several sleep parameters and possibly reverses non-dipping blood pressure and reduces oxidative stress, stresses the therapeutic potential of exogenous melatonin in CKD. In a study on the long term effects of melatonin in hemodialysis patients (unpublished data), it seems that this beneficial effect on sleep diminishes after daily use during more than three months. It is not known if other benefits of melatonin such as the effects on blood pressure profile and oxidative stress persist. Future research is necessary to elucidate why the sleep-related benefits of exogenous melatonin decrease. This may be related to accumulation of exogenous melatonin in CKD and therefore the loss of effect on the sleep gate (79) or may be due to melatonin receptor down regulation, which has been described before (80).

Since there are promising short term effects of melatonin on disturbed sleep in hemodialysis patients it is important to perform studies to develop the optimal melatonin treatment scheme in CKD patients, especially in patients with ESRD in whom circadian rhythm disorders are most prominent. However, to design such a study we suggest that more basic knowledge on pharmacokinetics of melatonin is needed as well as the influence of light therapy on melatonin production in this particular patient group.

Up to now, the causes of the lower melatonin levels in patients with CKD are unknown. Is it a result of impairment in adrenergic function that occurs in renal failure, as suggested by Karasek? (81) Or is it due to a disturbance of the genetic functioning of the biological clock? A relatively new field of research is the involvement of the genetic biological clock in the origin or consequence of renal disease. Circadian rhythms in renal function have been well documented, including renal blood flow, glomerular filtration, tubular reabsorption and tubular secretion. These rhythms are not only reactive to given circumstances, but exist in a self-sustained mechanism, enabling the kidney to anticipate various predictable circadian challenges to homeostasis. The molecular make-up of the renal peripheral clock is know and its effect on control of water and electrolyte balance in the kidney is slowly being unraveled (15,82). The significance of the molecular clock on functioning of the kidney has only partly been clarified. For example, Doi *et al.* found that in mice disruption of two core clock elements leads to salt-dependent hypertension and non-dipper blood pressure profile through modification of the aldosterone synthesis pathway. A human equivalent of this pathway was suggested. Here, a direct link between disruption of the biological clock and disruption of the circadian blood pressure profile through kidney dysfunction is made (83). There are more signs that disturbances of the biological clock are involved in the development of chronic disease, such as the onset of diabetes (84).

Melatonin is one of the hormones that is produced under circadian regulation; it is often described as

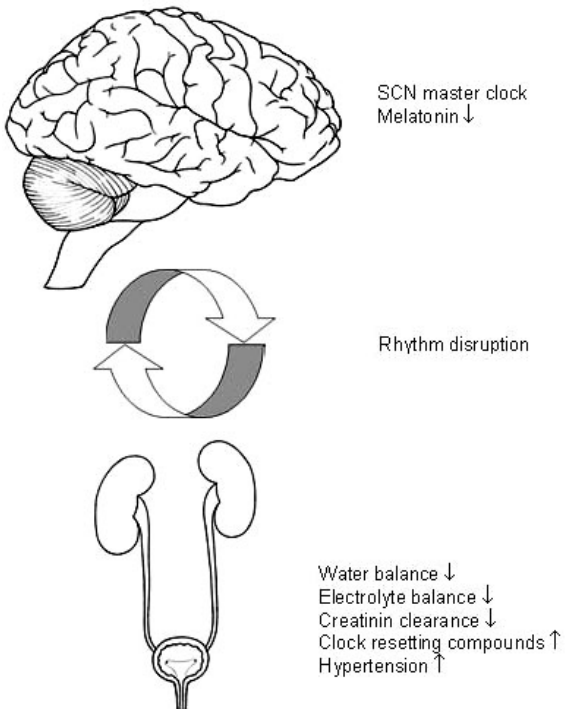

Figure 5. Hypothesis: relation circadian rhythm disorders and CKD

a clock-hand of the biological clock. We postulate that disruption of the master biological clock, the suprachiasmatic nucleus, through impaired interaction with the peripheral biological clocks in the kidney (82), may result in a peripheral circadian rhythm impairment. Perhaps an impaired melatonin secretion could be seen as an indicator for disruption of the biological clock like creatinine clearance is the indicator of the degree of kidney function. Hypothetically accumulation of clock-resetting compounds in the blood due to lack of proper filtration by the kidneys could lead to altered clock gene expression. If the basis for this interrelationship between kidney function and circadian regulation is laid in the genes or in other factors that can be pointed out, this might be an important target for research or future drugs. This hypothesis is illustrated by (Figure 5).

As previously stated, CKD patients suffer from chronic inflammation and a high level of oxidative stress. This results in a vicious circle of degradation of kidney tissue and deterioration of the kidney functions. It is known that melatonin has strong anti-oxidative properties and is able to decrease the negative results of oxidative stress in animal studies. Whether melatonin could be a clinically effective treatment to stop the vicious circle of oxidative stress and deterioration of kidney function remains to be elucidated.

Future research must be focused on clarification of the origin of circadian rhythm disorders in CKD and the role and impact of melatonin in the (prevention of) circadian rhythm disorders in CKD. The usage of exogenous melatonin in these disorders is a promising area of research.

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