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ORIGINAL ARTICLE

# Decreased melatonin nocturnal concentrations in hemodialyzed patients

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**Abstract**

**OBJECTIVES:** In spite of broad interest, intensive studies on function of melatonin have not yielded much information about relationships between this hormone and kidneys in health, and particularity, in disease. There are only a few studies dealing with melatonin concentrations in renal diseases, mainly performed in hemodialyzed patients with end-stage renal disease (ESRD). Moreover, the most melatonin assays were performed during the daytime, and the results are conflicting. Therefore, the aim of the present study was to determine the circadian melatonin profiles in patients ESRD before and after hemodialysis.
**MATERIAL AND METHODS:** Thirty patients (19 males and 11 females) with ESRD undergoing dialysis, aged 22 to 64 years (mean±SEM: 49.1.0±1.9 years) were included in the study. The control group consisted of 20 healthy volunteers (13 males and 7 females) aged 35 to 55 years (mean±SEM: 46.2±1.4 years) matched according to sex and age. Blood samples were collected on the day preceding hemodialysis and one day following dialysis at 08:00, 12:00, 16:00, 20:00, 24:00, 02:00, 04:00, and 08:00 h. Melatonin concentration was measured by enzyme immunoassay.
**RESULTS:** In patients with renal insufficiency undergoing dialysis mean melatonin nocturnal concentrations were significantly lower then those in healthy volunteers. The presence of the circadian rhythm in melatonin concentrations (although of significantly lower nocturnal amplitude) was detected only in 8 patients with renal failure undergoing hemodialysis, whereas in remaining 22 patients no such rhythm was found. Hemodialysis did not influence melatonin concentrations.
**CONCLUSIONS:** The mechanism of depressed melatonin concentrations in hemodialyzed patients observed in our study remains unclear. However, it seems possible that decline in melatonin levels is due to impairment in adrenergic function that occurs in renal failure. Because the studies on the melatonin secretion in chronic renal failure bring about conflicting results, the relationship between renal diseases and melatonin secretion needs further investigations.

## Introduction

Melatonin, a major secretory product of the pineal gland, received recently great deal of interest, and is a subject of intense clinical studies. Melatonin secretion exhibits typical circadian rhythm with low concentrations during the daytime (10–20 pg/mL) and high concentrations at night (70–120 pg/mL). The abolished melatonin circadian rhythm and amplitude have been demonstrated in various diseases [4, 6]. However, precise role of melatonin in different pathologies is still unknown.

Studies dealing with melatonin concentrations in renal diseases are rare, and were mainly performed in hemodialyzed patients with end-stage renal disease (ESRD). Moreover, the most melatonin assays were performed during the daytime, and the results are conflicting [10, 12, 13].

In our previous study [7] we have found decreased melatonin concentrations in patients with chronic renal failure (CRF) and ESRD, not yet dialyzed, however. Therefore, the aim of the present study was to determine the circadian melatonin profiles in patients with ESRD undergoing hemodialysis.

## Material and methods

Thirty patients (19 males and 11 females) with ESRD aged 22 to 64 years (mean±SEM: 49.1.0±1.9 years) were included in the study.

The primary cause of chronic renal failure was: primary glomerulonephritis in 11 patients (36.67%), polycystic kidney disease in 5 patients (16.67%), diabetic nephropathy in 4 patients (13.33%), hypertensive nephropathy in 2 patients (6.67%), chronic pyelonephritis in 1 patient (3.33%), interstitial nephritis in 2 patient (6.66%), light chain disease in 1 patient (3.33%), reflux nephropathy in 1 patient (3.33%), toxic kidney damage in 1 patient (3.33%), whereas in 2 patients (6.67%) renal pathology remained obscure. The majority of patients had one or more secondary disorders, including: arterial hypertension, secondary anemia, ischemic heart disease, nephrotic syndrome, and congestive heart failure.

Hemodialyzed subjects received treatments three times a week and were adequately dialyzed (Kt/V>1.2), equivalent to a weekly glomerular filtration rate of 10–15 mL/min. Hemodialysis was performed using a dialyzer model F 6,7,8-Fresenius and GFS-Gambro.

The control group consisted of 20 healthy volunteers (13 males and 7 females) aged 35 to 55 years (mean±SEM: 46.2±1.4 years) matched according to sex and age.

One day prior to the study the examined individuals had not received any drugs known to influence melatonin secretion and metabolism.

Patients and volunteers were admitted to the hospital at least 24 hours before the study. During blood sampling the period of darkness in patients' room lasted from 22:00 to 06:00 h. Blood samples were collected on the day preceding hemodialysis and one day following dialysis at 08:00, 12:00, 16:00, 20:00, 24:00, 02:00, 04:00, and 08:00 h; the nighttime samples were taken under dim red light. All blood samples were allowed to clot for 45 min, serum was removed after centrifugation, and stored at –20°C until assayed. Melatonin concentration was measured by enzyme immunoassay, using ELISA kits (IBL, Hamburg; Cat. No. RE 540 21, sensitivity 3.0 pg/mL, intra assay CV – 3.3–10.5%, inter assay CV – 6.9–15.7%).

Statistical analysis of the data was performed using Student's t test and paired Student's t test.

The study was approved by the Regional Committee for Studies with Human Subjects. The experimental protocol was explained to each patient, and informed consent was obtained.

## Results

In patients with renal insufficiency undergoing dialysis mean melatonin nocturnal concentrations were significantly lower then those in healthy volunteers (Fig. 1). The presence of the circadian rhythm in melatonin concentrations (although of significantly lower nocturnal amplitude) was detected only in 8 patients with ESRD undergoing hemodialysis, whereas in remaining 22 patients no such rhythm was found. Area under curve was significantly lower in dialyzed patients in comparison with the control group (Fig. 2). No differences were observed in melatonin concentrations between patients before and following dialysis (Figs. 1 and 2).

Creatinine concentrations were normal in control group (1.0±0.1 mg/dL) and significantly elevated in dialyzed patients (9.3±0.4 mg/dL; $p < 0.001$ vs Control). Also urea levels were within normal range in control subjects (33.2±1.9 mg/dL) but were significantly higher in dialyzed patients before dialysis (143.4±12.1 mg/dL; $p < 0.001$ vs Control), and although were significantly lower after dialysis (40.1±2.0 mg/dL; $p < 0.001$ vs patients before dialysis), still remained significantly higher than in those in control group ($p < 0.01$ vs Control). No differences in both systolic and diastolic arterial blood pressure were found between hemodialyzed patients and control group (mean±SEM = 133.0±3.9/79.5±1.9 mmHg vs 125.0±74.8±0.9 mmHg, respectively).

## Discussion

The results of the present study confirm our previous observations [7] of decreased nocturnal melatonin concentrations in patients suffering from advanced stage of renal diseases. Like in previous study, we found completely abolished circadian rhythm of melatonin in majority of patients undergoing hemodialysis. Moreover, even in these patients in whom the rhythm was present (8 out of 30) the amplitude of nocturnal rise of melatonin levels was significantly lower than that in healthy individuals. In comparison with patients suffering from CRF without dialysis the abolishment in melatonin circadian rhythm in patients undergoing dialysis was even more marked (45.8% vs 73.3% of

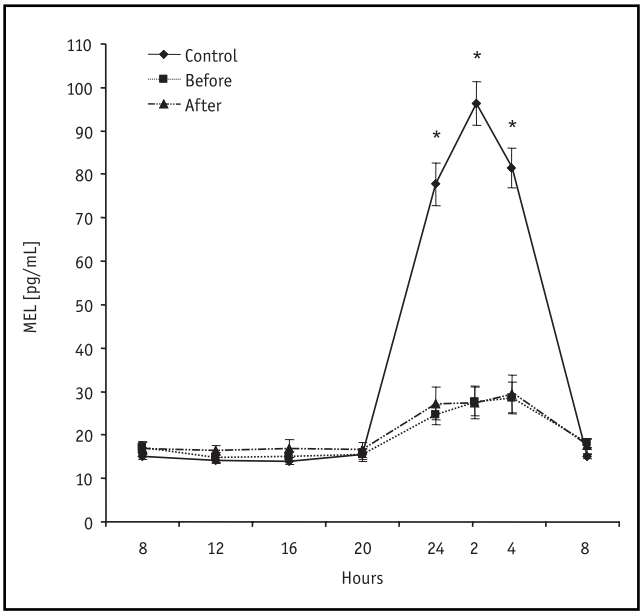


**Figure 1.** Mean circadian melatonin concentrations in healthy subjects (control) and in patients before and after hemodialysis; * p < 0.001 vs control group

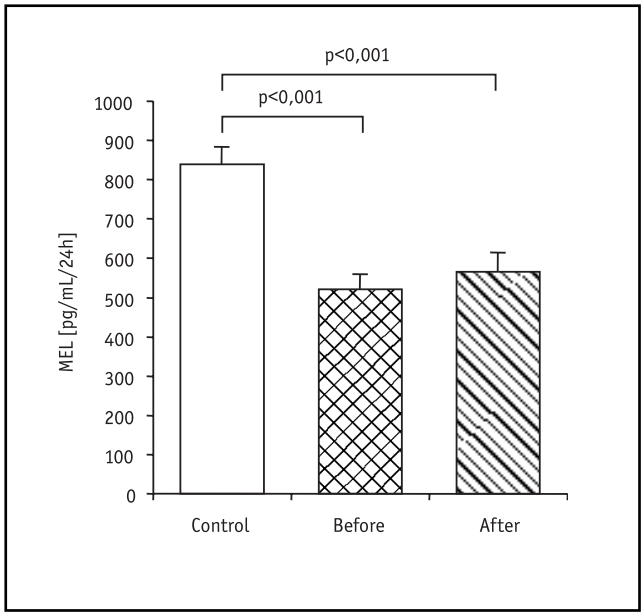


**Figure 2.** Area under curve of circadian melatonin concentrations in healthy subjects (control) and in patients before and after hemodialysis; * p < 0.001 vs control group.

patients without rhythm, respectively). No significant differences in melatonin concentrations were observed between patients one day before and one day after hemodialysis.

In contrast to earlier studies [10, 12, 13] we found highly depressed melatonin concentrations in patients suffering from renal insufficiency. In 73.3%% of individuals undergoing hemodialysis no typical circadian rhythm of melatonin concentrations was observed. In 26.7% of patients such rhythm was present, however, the nocturnal amplitude was significantly lower than that in healthy individuals. Viljoen et al. [13] observed increased melatonin levels in patients undergoing hemodialysis and decrease in melatonin concentrations after dialysis. Moreover, the authors did not observe any circadian rhythm in the majority patients. Increased day-time (08:00, 15:30, and 18:30 h) melatonin levels (but not 6-hydroxymelatonin sulfate concentrations) in dialyzed patients and their decrease after dialysis was observed by Lüdemann et al. [10]. There are some methodological differences between our study and previously published reports. In the present study circadian rhythm of melatonin concentrations was examined in patients one day before and one day after hemodialysis, whereas in studies of Viljoen et al. [13] nocturnal melatonin concentrations were estimated immediately before and hemodialysis. Lüdemann et al. [10] examined only day-time melatonin concentrations in hemodialyzed patients.

The mechanism of depressed melatonin concentrations in patients with CRF undergoing hemodyalisis observed in our study remains unclear. However, it seems possible that decline in melatonin levels is due to impairment in adrenergic function that occurs in CRF [11]. Adrenergic system plays very important role in melatonin secretion [1, 6]. It has been demonstrated that patients undergoing long-term hemodialysis showed certain signs of dysregulation of autonomic nervous system [9]. In patients with CRF reduced densities and response of β2-adrenoceptors has been reported [2]. Moreover, plasma from uremic patients significantly decreased the number of β1- and β2-adrenoceptors [3]. Additionally, suppression of the activity of serotonin N-acetyltrasferase, the key enzyme in melatonin biosynthesis [1, 6] was observed in rats rendered uremic by partial nephrectomy [5]. Low concentration of serum melatonin in patients before and after hemodialysis and lack of circadian melatonin profiles similarly to our previous observations [14] suggests, that main causes of melatonin deficiency is probably depression of its production provoked by uremic toxins. In addition, melatonin is known to bind to alpha-1-acid glycoprotein and albumin and therefore it is not dialyzable in this form (to high molecular wight) [8] We should also keep in mind that although no β-blockers were used by our patients one day before melatonin estimation, majority of our patients, before entering the study received β-blockers because of arterial hypertension. Therefore, changes in adrenergic system caused by long-term use of β-blockers can not be excluded.

Summarizing, the studies on the melatonin secretion in hemodialyzed patients with renal insufficiency bring about conflicting results, and therefore, the relationship between renal diseases and melatonin secretion needs further investigations.

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