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REVIEW ARTICLE

Circadian serum melatonin profiles in patients suffering from chronic renal failure

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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. Very little is known about the circadian plasma melatonin concentrations in patients with chronic renal failure (CRF). 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 with different stages of CRF. **MATERIAL AND METHODS.** Twenty four patients (13 males and 11 females) with CRF aged 35 to 58 years (mean±SEM: 47.0±1.6 years) were included in the study. Patients were divided into two groups: group 1 – patients with compensated CRF (serum creatinine: 2.0-5.0 mg/dL), group 2 – patients with ESRD (serum creatinine: > 8,0 mg/dL). The control group consisted of 20 healthy volunteers (10 males and 10 females) aged 35 to 55 years (mean±SEM: 46.0±1.5 years) checked not to have renal failure [serum creatinine: 0.8-1.4 mg/dL], and matched according to sex and age. Blood samples were collected 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 both groups of patients with chronic renal failure, i.e. in patients with compensated disease and in patients with end-stage renal disease melatonin nocturnal concentrations were significantly lower then those in healthy volunteers. Moreover, in patients with compensated renal failure also day-time melatonin concentrations were significantly depressed. Area under curve was significantly lower in both groups of patients in comparison with the control group. **CONCLUSIONS.** The mechanism of depressed melatonin concentrations in CRF 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. Because the studies on the melatonin secretion in CRF bring about conflicting results, the relationship between renal diseases and melatonin secretion needs further investigations.

Introduction

Melatonin is a major secretory product of the pineal gland. This hormone received recently great deal of interest due to its diversified action, including regulation of biological rhythms [1, 2], free radicals scavengering [3, 4], modulation of the immune system [5, 6], influence on neoplastic disease [7-9], and possible role in aging process [10, 11]. Although the abolished melatonin circadian rhythm and amplitude have been demonstrated in various diseases [12, 13], its precise role in different pathologies is still unknown.

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 hormone is metabolized primarily in the liver and secondarily in the kidney. It undergoes 6-hydroxylation to 6-hydroxymelatonin, followed by sulfate or glucuronide conjugation to 6-hydroxymelatonin sulfate (90-95%) or 6-hydroxymelatonin glucuronide (5-10%). Melatonin also forms some minor metabolites. The main melatonin metabolite, 6-hydroxymelatonin sulfate is excreted in urine [1, 13].

Melatonin synthesis may be influenced by drugs. It is strongly reduced by β-blockers, whereas benzodiazepines, calcium antagonists, dexamethazone, nonsteroidal anti-inflammatory drugs, and clonidine are somewhat less active in this respect. Anti-depressive drugs stimulate melatonin secretion [1, 14].

In spite of broad interest, intensive studies on function of this hormone have not yielded much information about relationships between melatonin and kidneys in health, and particularity in disease. Very little is known about the circadian plasma melatonin concentrations in patients with chronic renal failure (CRF). 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 [15-17].

Therefore, the aim of the present study was to determine the circadian melatonin profiles in patients with different stages of CRF.

Material and methods

Twenty four patients (13 males and 11 females) with CRF aged 35 to 58 years (mean±SEM: 47.0±1.6 years) were included in the study. Patients were divided into two groups: group 1 – patients with compensated CRF (serum creatinine: 2.0-5.0 mg/dL; n = 12; 7 men and 5 women), group 2 – patients with ESRD (serum creatinine: > 8,0 mg/dL; n = 12; 6 men and 6 women).

The primary cause of chronic renal failure was: primary glomerulonephritis in 13 patients (54.2%), polycystic kidney disease in 3 patients (12.5%), lupus nephritis in 2 patients (8.3%), nephrosclerosis in 1 patients (4.2%), whereas in 5 patients (20.8%) renal pathology remained obscure. The majority of patients had one or more secondary disorders, including: arterial hypertension (79.2%), secondary anemia (50%), ischemic heart disease (16.7%), nephrotic syndrome (4.2%), chronic heart failure (4.2%), and viral hepatitis (4.2%). No patient was yet dialyzed.

The control group consisted of 20 healthy volunteers (10 males and 10 females) aged 35 to 55 years (mean±SEM: 46.0±1.5 years) checked not to have renal failure [serum creatinine: 0.8-1.4 mg/dL], and matched according to sex and age.

For last two days 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 48 hours before the study. One day before and during blood sampling the period of darkness in patients' room lasted from 22:00 to 06:00 h. Blood samples were collected 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 ANOVA and LSD (least significant difference) method according to Statgraphic plus V4 computer program.

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 10 patients with CRF no circadian rhythm in melatonin concentrations was detected, and in remaining 14 patients the nocturnal amplitude of melatonin concentrations was much lower than that in the healthy individuals (Fig. 1). In both groups of patients with CRF, i.e. in patients with compensated disease and in patients with end-stage renal disease mean melatonin nocturnal concentrations were significantly lower then those in healthy volunteers (Fig. 2). Moreover, in patients with compensated renal failure also day-time melatonin concentrations were significantly depressed (Fig. 2). Area under curve was significantly lower in both groups of patients in comparison with the control group (Fig. 3).

Both systolic and diastolic, as well as mean arterial blood pressure was significantly higher in patients with CRF in comparison with control group (Table 1). Also creatinine and urea concentrations were significantly elevated in patients with CRF (Table 1). Moreover,

Table 1. Arterial blood pressure and concentrations of creatinine and urea in healthy individuals and patients with chronic renal failure; data are expressed as mean±SEM

	Control	All patients	Group 1	Group 2
Diastolic blood pressure [mmHg]	124.8±2.0[a,b,c]	148.8±4.8	155.4±7.9	142.1±4.9
Systolic blood pressure [mmHg]	75.0±1.0[a,b,d]	87.9±3.2	90.0±4.2	85.8±5.0
Creatinine [mg/dL]	1.0±0.1[a,b,c]	178.517.5	107.7±14.6[c]	249.4±12.6
Urea [mg/dL]	32.5±1.8[a,b,c]	178.517.5	107.7±14.6[c]	249.4±12.6

a – p < 0.001 vs all patients, b – p < 0.001 vs group 1; c – p < 0.001 vs group 2;
d – p < 0.05 vs group 2;

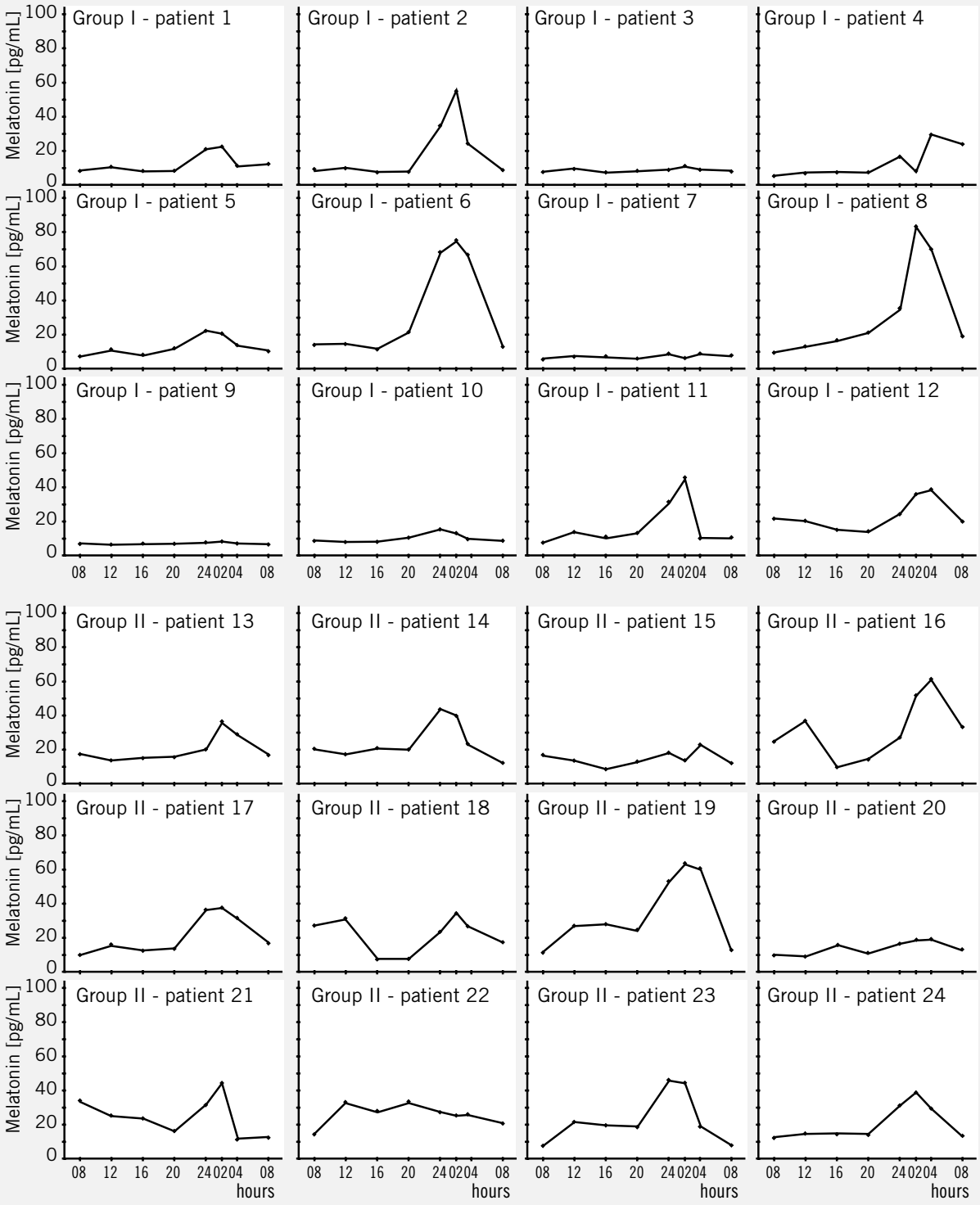

Fig. 1. Individual circadian melatonin profiles in patients with chronic renal failure.

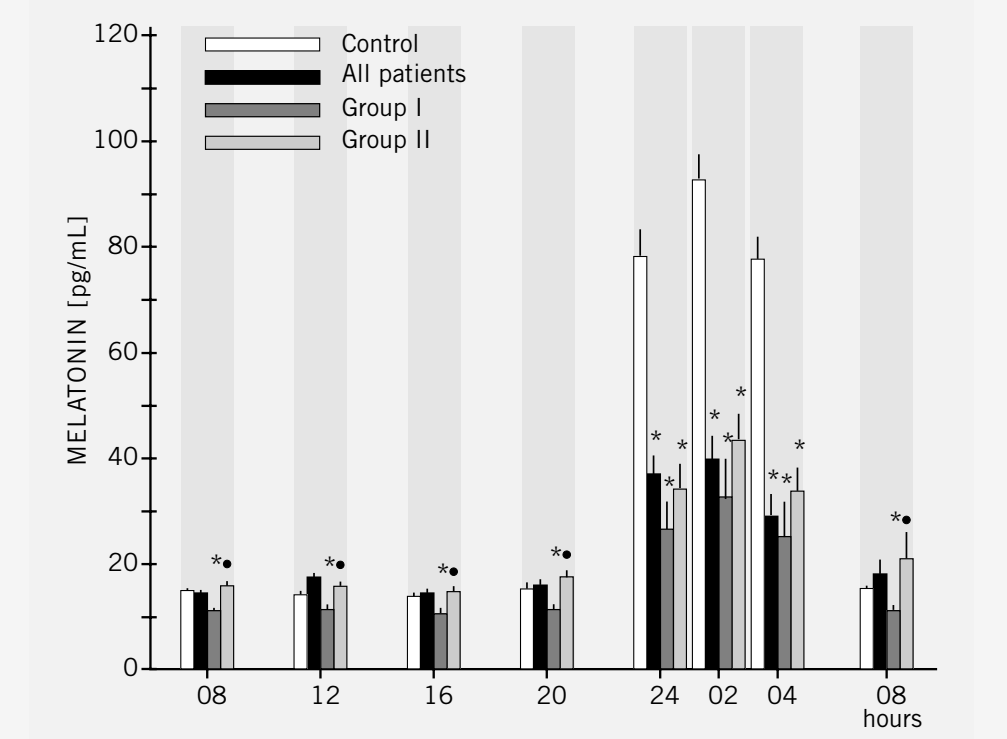

Fig. 2. Mean circadian melatonin concentrations in healthy subjects (control) and patients with chronic renal failure; * $p < 0.05$ vs control; • $p < 0.05$ vs group 1.

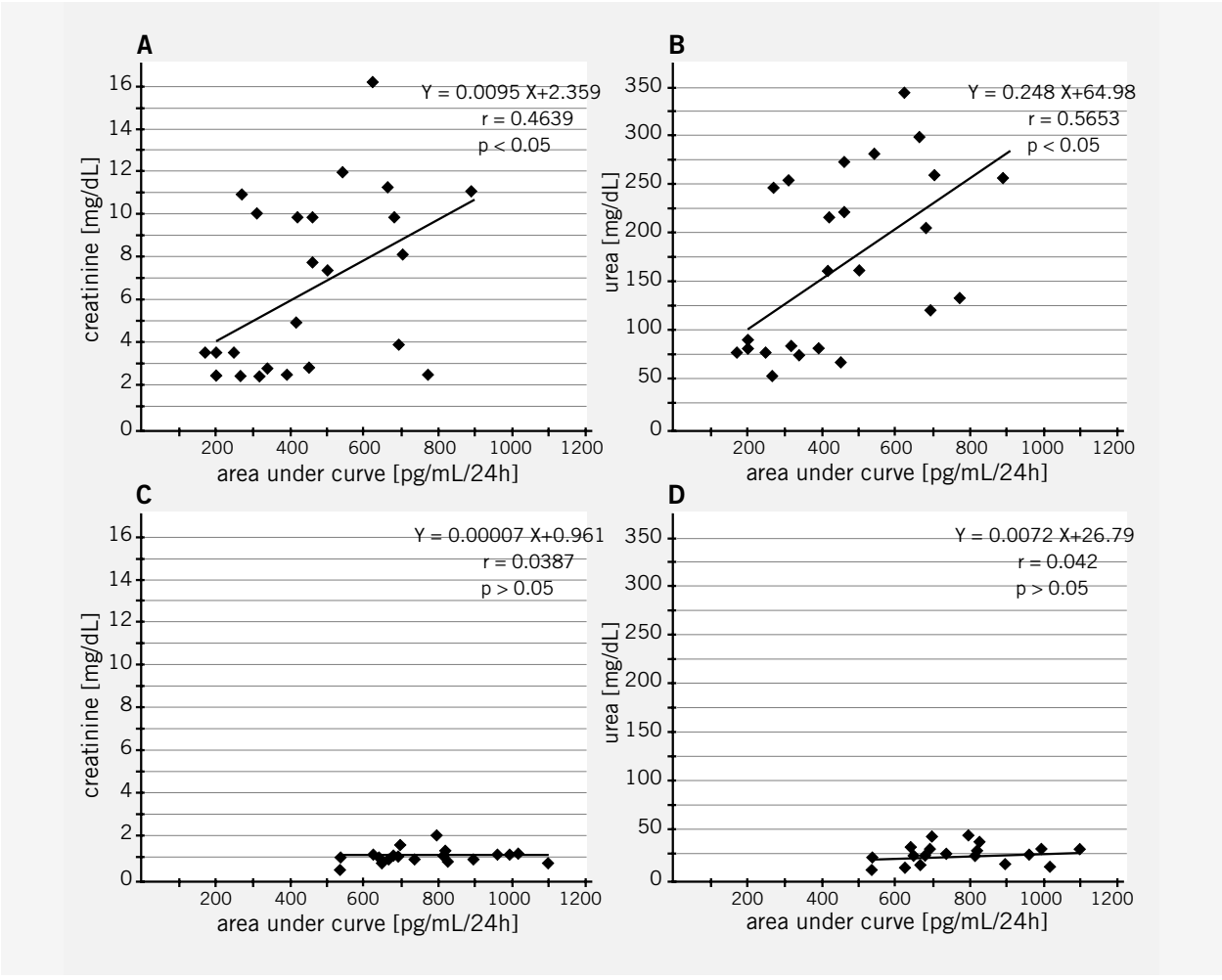

Fig. 4. Correlations between serum creatinine and urea levels and area under curve of circadian melatonin concentrations in patients with chronic renal failure (A and B), and in healthy subjects (C and D).

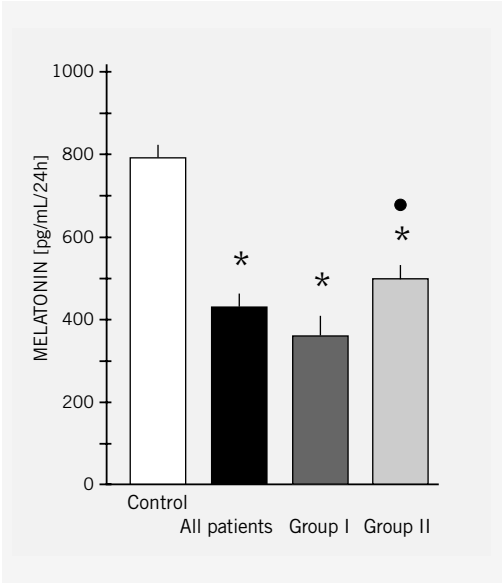

Fig. 3. Area under curve of circadian melatonin concentrations in healthy subjects (control) and patients with chronic renal failure;
* $p < 0.05$ vs control; • $p < 0.05$ vs group 1.

creatinine and urea levels were significantly higher in patients from group 2 in comparison with individuals from group 1 (Table 1).

A positive correlation between creatinine as well as urea levels and area under curve of melatonin concentrations was observed in patients with CRF, although no such correlation has been found in healthy individuals (Fig. 4). No correlation was observed between both systolic and diastolic blood pressure and area under curve of melatonin concentrations, both in healthy subjects and in patients with CRF (data not shown).

Discussion

In contrast to earlier studies [15, 17] we found highly depressed melatonin concentrations in patients suffering from CRF, more pronounced in those with compensated disease. In 45.8% of individuals from both studied groups of patients with CRF no typical circadian rhythm of melatonin concentrations was observed. In 54.2% of patients such rhythm was present, however, the nocturnal amplitude was significantly lower than that in healthy individuals. There are methodological differences between our study and previously published reports. In the present study circadian rhythm of melatonin concentrations was examined in patients with different stages of chronic renal failure, whereas in studies of Viljoen et al. [15] only day-time melatonin levels were examined in various stages of the disease, and nocturnal melatonin concentrations were compared only between patients undergoing hemodialysis and healthy individuals. Also Lüdemann et al. [17] examined day-time melatonin concentrations only in hemodialysed patients. It should be stressed that in our study no patient underwent hemodialysis. Viljoen et al. [15] and Lüdemann et al. [17] observed increased melatonin levels in patients undergoing hemodialysis, and decrease in melatonin concentrations after dialysis. Moreover, Viljoen et al. [15] did not observe any circadian rhythm in the majority of patients, both before and after dialysis. Changes in melatonin, but not 6-hydroxymelatonin sulfate concentrations was observed at 08:00, 15:30, and 18:30 h by Lüdemann et al. [17], and interpreted by these authors as indication of rhythmic release of melatonin. However, because no nocturnal concentrations of melatonin, which are crucial in speaking about melatonin rhythm, were determined, no conclusions can be drawn from the results of Lüdemann et al. [17], at least in terms of existence of melatonin secretion rhythm in their patients. On the other hand, Vaziri et al. [16] did not find differences in serum melatonin and 6-hydroxymelatonin sulfate at 06:00 h in ESRD patients in comparison to normal control group.

It is worthy to note that in experimental model CRF caused by partial nephrectomy in rats resulted in attenuation of the nocturnal surge in serum melatonin concentration as well as in pineal melatonin content [18].The mechanism of depressed melatonin concentrations in CRF 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 [19]. It is well known that adrenergic system plays very important role in melatonin secretion [1, 13]. In patients with CRF reduced densities and response of β2-adrenoceptors has been reported [20]. Moreover, plasma from uremic patients significantly decreased the number of β1- and β2-adrenoceptors [21]. Additionally, suppression of the activity of serotonin N-acetyltrasferase, the key enzyme in melatonin biosynthesis [1, 13] was observed in rats rendered uremic by partial nephrectomy [22].

On the other hand, although no β-blockers were used by our patients at least two days 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.

The observation of depressed melatonin concentrations in CRF may have some clinical implications. Melatonin is a very potent free radical scavenger [3, 4]. Herrera et al. [23] demonstrated that melatonin prevents oxidative stress resulting from iron and erythropoietin administration in doses commonly used to treat anemia in chronic hemodialysis patients, and therefore, according to the authors may be of clinical use. It has been also demonstrated that melatonin attenuates renal failure and oxidative stress induced by mercuric chloride in rats [24]. Melatonin also protects against cyclosporine-induced [25], adriamycin-induced [26, 27], cisplatine-induced [28, 29], and delta-aminolevulinic acid-induced [30] nephrotoxicity, and renal injury induced by extrahepatic cholestasis [31] .

It should be underlined that majority of our patients suffered from arterial hypertension. There are some data that administration of melatonin resulted in a decrease in blood pressure [32, 33]. In recent study Viljoen et al. [24] demonstrated negative correlation between daytime plasma melatonin levels and diastolic but not systolic blood pressure. Although no correlation between both

systolic and diastolic blood pressure and area under curve of 24 h melatonin concentrations has been found in our study it can not be excluded that arterial hypertension per se may influence melatonin secretion.

The patients with chronic renal failure suffer from many symptoms which are related to the primary disease. Sleep disturbances which occur in over 80% patients with ESRD [35] are an example of such symptoms. Considering the strong relationship between melatonin and sleep [36, 37] it is possible that depressed concentrations of melatonin determines, at least in part, the reason of insomnia in patients with CRF.

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

Acknowledgements

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