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## Serum melatonin and urinary 6-sulfatoxymelatonin in major depression

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### Abstract

In this study, serum melatonin and urinary 6-sulfatoxymelatonin (aMT6s) were measured in 14 major depressive inpatients, compared to 14 matched controls according to age, gender, season and hormonal treatment in women. Moreover, the relationship between serum melatonin and urinary aMT6s levels was analysed in the two groups. Results indicated that the two groups of subjects showed a clear melatonin rhythm without significant difference in the mean level of melatonin or aMT6s, in the area under the curve of melatonin or in the melatonin peak. However, the time of the nocturnal melatonin peak secretion was significantly delayed in depressive subjects as compared to healthy controls. Moreover, the depressed patients showed urinary aMT6s concentrations enhanced in the morning compared to night time levels, while these concentrations were lowered from the night to the morning in the control group. These results suggest that the melatonin production is phase-shifted in major depression.

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*Keywords:* Depression; Melatonin; Urinary 6-sulfatoxymelatonin; Circadian rhythm

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## 1. Introduction

The rhythm of melatonin, a pineal indoleamine derived from serotonin, is a robust marker of circadian phase in humans, with high concentrations during the night and low or undetectable levels during the day. Disturbances in the melatonin circadian profile in depression have been already evidenced in 1979 (Arendt et al., 1979; Mendlewicz et al., 1979; Wetterberg et al., 1979). Several authors have reported altered circadian rhythms of melatonin. The first studies described abnormalities of secretion rhythms with advanced phases and/or decrease in nocturnal amplitude of melatonin rhythm in depression (Branchey et al., 1982; Claustrat et al., 1984; Nair et al., 1984; Beck-Friis et al., 1985; Frazer et al., 1986; Brown et al., 1987; Checkley and Park, 1987; Zetin et al., 1987; Miles and Philbrick, 1988; Kennedy et al., 1989).

Souetre et al. (1989), did not find a significant difference in the nocturnal melatonin peak in the depressive patients compared to controls. In contrast, Thompson et al. (1988), found different results, with a 46% increase in nocturnal melatonin secretion in depressive patients compared to matched controls. Steward and Halbreich (1989), reported an increased melatonin nocturnal peak in patients who received antidepressant treatment. Sekula et al. (1997) also found higher mean nocturnal melatonin levels in female depressives compared to their matched controls and a trend toward a later offset time, by about 40 min.

In the Rubin et al. study (1992), compared with their matched controls, the depressed patients showed a trend toward a significantly elevated average nocturnal melatonin concentration that was accounted for primarily by the 14 premenopausal women. The postmenopausal female and male depressive patients did not differ significantly from their respective controls. The average diurnal melatonin concentration also showed a trend toward being higher in both the female and male depressed patients.

Several factors could explain those discrepancies. First, the onset of the disease, i.e. remission or relapse, must be considered, because of the different results reported. Secondly, authors do not always specify whether their patients are drug-free (review in Pacchierotti et al., 2001). Some authors have considered melatonin as a trait marker of depression since alteration in the rhythm of melatonin is also present in remission phase (Beck-Friis, 1985; Brown, 1985; Claustrat et al., 1990). For other authors, melatonin is considered like a state marker (Fanget et al., 1990).

Moreover, there is a need to control for other factors than the specific psychiatric conditions that might influence melatonin levels, like light, age and drugs (review in Beck-Friis et al., 1985). Light play an important role as a major synchronizer of circadian and circannual rhythms in humans. It is well known that light (Wetterberg et al., 1979; Lewy, 1983) influences melatonin levels. Therefore, both season and light exposure should be considered in melatonin studies. Another difficulty is to investigate patients with no antidepressive treatment or beta-blocker treatment that may influence melatonin levels (Hanssen et al., 1977; Moore and Paunier Sizonenko, 1979) and also to consider oral contraceptive use in women.

6-sulfatoxymelatonin (aMT6s) is a major urinary metabolite of the pineal hormone melatonin. Its measurement in urine appears to provide a robust, simple and reliable

assessment of melatonin secretion (Bojkowski and Arendt, 1990). Several authors provided data indicating a relationship between serum or plasma melatonin levels and aMT6s in 24 h urine samples in healthy volunteers (Arendt et al., 1985; Markey et al., 1985; Bojkowski et al., 1987; Nowak et al., 1987; Bartsch et al., 1992; Graham et al., 1998). Measurement of aMT6s is a noninvasive method to study melatonin because repeated urine fractions can be obtained during a long period without disturbing the person but the relationship between serum melatonin and aMT6s in urine was never verified in psychiatric populations, particularly in depressive patients.

The nature of melatonin secretion rhythm disturbances in depression remains unclear. Therefore there is a need to control for factors that influence melatonin production. It could be more convenient to use urine samples rather than blood samples. There is a need to check if urinary measures reflect integrated peak blood concentrations of melatonin in depressive patients, as compared to healthy subjects.

Until now, no study has compared the relation between serum melatonin and urinary aMT6s levels in depressive patients. The purpose of this study was to compare serum melatonin and aMT6s levels in drug-free major depressive inpatients and in control subjects matched for age, gender and season.

## **2. Methods**

### *2.1. Subjects*

Fourteen DSM IV major depressive inpatients were included in this study. They scored more than 21 in the 17-item Hamilton Depression Rating Scale (mean score $\pm$ SD=33.5 $\pm$ 5.5) (Hamilton, 1960). They were at the end of a drug-free period of at least 2 weeks (3 weeks, if they had been treated with fluoxetine). Previous treatments included SSRIs (three patients), MAOIs (two patients), tricyclics (two patients) and nothing (seven patients). The washout of antidepressant treatments was supervised in hospital. Only occasional low doses of benzodiazepine were allowed in six patients (nothing in eight patients).

The patients were between 38 and 69 years old, with a mean age $\pm$ SD of 52 $\pm$ 8 years. Body Mass Index (BMI) was 25.7 $\pm$ 1.72 (SEM).

The depressive group comprised seven men and seven women. Among the women, three received substitutive hormonal therapy and one took oral contraceptives. Three women were without estrogen replacement therapy (one pre-menopausal and two menopausal). Mean ages were 61 $\pm$ 8 for the men and 47 $\pm$ 5 years for the women.

The control group consisted of healthy subjects recruited in the same area and chosen to match the patients. Persons with chronic insomnia, who performed time-shift work and/or who had recently gone on transmeridian travel were excluded. Controls were submitted to a medical examination, blood sample and psychiatric interview to exclude any psychiatric disorder. In addition, they scored <10 on the 17-item Hamilton Depression Rating Scale. The control group was chosen to match to the depressive patients for both age and gender.

Fourteen subjects participated in this study (six men; mean age=59 $\pm$ 8 years and

eight women; mean age=46±5 years). They were free of present or past psychiatric illness, even in their first degree relatives. They were also free of medical illness. All of them scored <10 on the Hamilton Depression Scale. They all had normal laboratory tests for serum electrolytes determinations, renal, hepatic, thyroid tests, adrenal tests and they did not take any medication. BMI was 25.8±1.05 (SEM).

Among the women, four had no hormonal therapy (three pre-menopausal and one menopausal), one had oral contraceptives and two had substitutive therapy (menopausal).

Patients and controls were checked for alcohol use during the entire washout period for inpatients and for the 2 days period of data collection for control subjects. No patient or control subject with history of alcohol dependence or abuse was accepted in this study.

## 2.2. *Experimental protocol*

All subjects spent two consecutive nights in the hospital research ward, one habituation followed by one experimental night. A particular effort was made to match the sampling month between patients and controls.

As of 1700 h, subjects were at bed rest with a light exposure of 50 lux to 2300 h. They remained recumbent in total darkness from 2300 h to 0700 h. All subjects had normal meals at the usual time delivered by the hospital at normal mealtimes. They left the room at 1100 h on day 2.

At 1800 h, an indwelling catheter was inserted into a forearm vein. Blood samples of 10 ml were drawn over a 15 h period at 1800 h, 2000 h, 2200 h and every hour from 2300 h to 0600 h and at 0800 h and 1000 h. Urine was collected over a 24h divided into 4 periods, 1100 h–1900 h, 1900 h–2300h, 2300 h–0700 h day 1 and 0700 h–1100 h day 2. Urine volumes were recorded each time.

This protocol was approved by the Ethics Committee of the University of Liège Medical School and all participants gave written informed consent.

## 2.3. *Hormonal assays*

Each blood sample was immediately centrifuged and serum samples were frozen at –20°C until RIA (Stockgrand Ltd). The lower limit of sensitivity was 2 pg/ml, the average intraassay coefficient of variation 10% and the average interassay coefficient of variation 15% in the range of physiological concentrations (Van Caeter et al., 1994). Serum melatonin levels are given in pg/ml.

Each urine sample was immediately frozen at –20° until RIA (Stockgrand Ltd, UK). For a aMT6s concentration of 300 pmol/l, the intra-assay CV was 8% and the inter-assay CV was 12%. Since the volume of urine production is different in each individual and because patterns of aMT6s excretion are affected by water consumption and renal function (see Klante et al., 1997), aMT6 concentrations were corrected for volume and calculated per hour of urine sampling (ng/h) as in earlier studies (Crasson et al., 2001; Hendrick et al., 2002). Due to the fact that the sampling of urine was always carefully controlled, the exact volume of urine was known and

there was no need to use urinary creatinine as a substitute for urine volume, as pointed out by Klante et al. (1997).

#### 2.4. Data analysis

Each serum melatonin determination (1800 h, 2000 h, 2200 h, every hour from 2300 h to 0600 h, 0800 h, 1000 h) as well as each urinary measures of aMT6s (1100 h–1900 h, 1900 h–2300 h, 2300 h–0700 h day 1 and 0700 h–1100 h day 2) were compared between patients and controls.

The area under the curve (AUC) was taken as the index of nocturnal melatonin secretion (from 1800 h to 1000 h). The melatonin peak was the highest mean level and the peak time was the time corresponding to the highest level.

Kolmogorov–Smirnov tests indicated that these data were not inconsistent with a Gaussian distribution, allowing parametric analyses, like in previous publications (Bojkowski et al., 1987, Bojkowski and Arendt, 1990; Gibertini et al., 1999).

ANOVA and repeated ANOVA measures were used to assess the differences between patients and control subjects and to assess the role of gender and sampling time for the different variables considered. Post-hoc analysis was undertaken when significant results emerged in order to specifically determine between which conditions statistical differences existed.

Parametric regression statistics were performed to analyse the correlation between serum and urinary measures. Gender and BMI were also controlled in the analyses.

### 3. Results

#### 3.1. Plasma melatonin levels

One hundred eighty-two samples were obtained in each group of subjects. All data were sampled from February to September.

Fig. 1 shows the mean plasma melatonin profiles observed in the two groups and Table 1 indicates values of each variable in depressive patients and their matched controls.

Anovas performed on hourly values of serum melatonin indicated that there was no difference between patients and controls ( $p$  between 0.12 and 0.91,  $df=1, 27$ ) or between males and females ( $p$  between 0; 25 and 0.97,  $df=1, 27$ ) in each group in most of the melatonin determinations.

The only variable that indicates a significant difference was the melatonin peak time. The peak time was 77 min later in patients (0330 h $\pm$ 23 min) than in controls (0213 h $\pm$ 25 min) ( $p=0.03$ ,  $F=5.59$ ,  $df=1,24$ ).

Using a double ANOVA with gender and groups as classification variable, without interactions between these two variables, differences between patients and control subjects were found as well as differences between men and women emerged related to melatonin peak time. Since men are older than women, age was used as covariate in the analyses and it appears that this gender difference can be explained by age

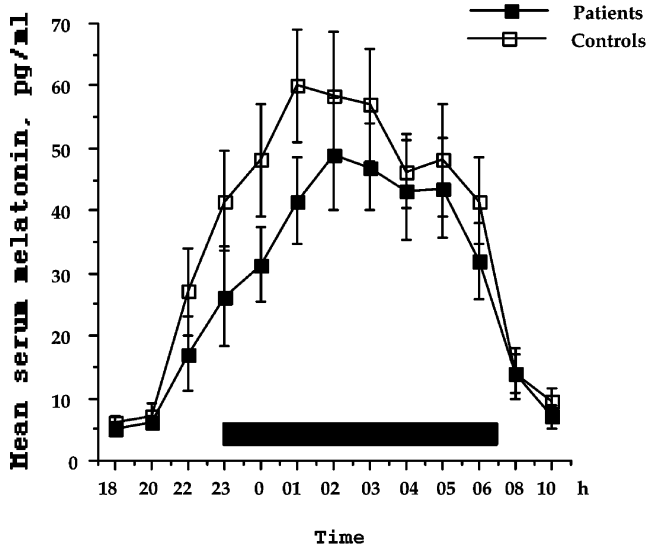


Fig. 1. Mean (+SEM) plasma melatonin concentration at the time of each blood sampling for the patients (■) and normal controls (□). The time of darkness is marked by an horizontal bar.

Table 1

Mean (+SEM) plasma melatonin values (pg/ml) at each sampling time and AUC values for 14 depressed patients compared with their matched controls

Criteria	Patients (n=14)	Controls (n=14)
1800 h	5.37±0.94	6.21±1.11
2000 h	6.06±1.21	7.26±2.12
2200 h	17.14±6.11	27.15±6.64
2300 h	26.23±7.62	41.48±7.56
0000 h	31.43±5.81	48.13±8.84
0100 h	41.52±7.11	60.01±9.34
0200 h	49.07±9.34	58.58±9.56
0300 h	47.00±7.07	57.08±9.42
0400 h	43.17±7.80	46.35±6.22
0500 h	43.58±7.77	48.17±9.32
0600 h	31.94±5.52	41.55±7.38
0800 h	14.43±3.58	13.92±2.57
1000 h	7.15±1.96	9.59±1.99
AUC	25499±5483	30331±5657
Peak value	56.04±9.10	67.32±9.18
Peak time <sup>a</sup>	0330 h±22 min	0213 h±24 min

<sup>a</sup> ANOVA,  $p=0.03$ .

difference between men and women. There were too few cells in each case to compare pre-menopausal and post-menopausal females who were or not receiving estrogen replacement therapy.

### 3.2. Urinary aMT6s levels

Fifty-six samples were obtained in each group of subjects.

There were no statistical differences in mean urinary aMT6s concentration between patients and controls when each sampling period was considered separately.

There were no differences between males and females of each group.

However, repeated ANOVA measures with group as classification and aMT6s repeated measures at different sampling time as dependent variable indicated a significant interaction between the groups and sampling time ( $p=0.0095$ ,  $F=4.43$ ,  $df=3$ , 36). Urinary aMT6s concentration enhanced in the patient group (from  $651\pm 194$  to  $1451\pm 482$  ng/h), while it lowered in the control group ( $1280\pm 370$  to  $514\pm 104$  ng/h) from the night time period (2300 h–0700 h) to the morning period (0700 h–1100 h). Fig. 2 illustrates this interaction.

### 3.3. Relationship of serum melatonin and urinary aMT6s measures

The relation between serum melatonin and urinary aMT6s concentration was compared through regression analysis in the patients and in the control group. To limit

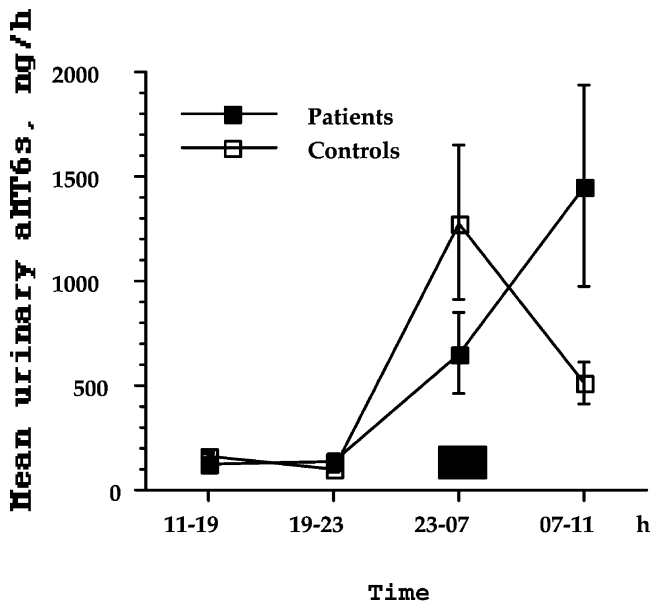


Fig. 2. Mean (+SEM) urinary aMT6s concentration for each sampling period in the patients group (■) and in the normal controls group (□). The time of darkness is marked by an horizontal bar (2300 h–0700 h).

the number of correlations in the analyses, we choose two blood parameters: the melatonin AUC and the peak value.

### 3.3.1. *The control group*

In the control group, the melatonin AUC value and night time excretion of aMT6s (2300 h–0700 h) were highly correlated ( $r=0.82$ ,  $p=0.007$ ). Melatonin peak was also highly correlated with night time excretion of aMT6s (2300 h–0700 h) ( $r=0.78$ ,  $p=0.004$ ). These data indicate that night time urinary excretion of aMT6s (from 2300 h to 0700 h) is a good correlate of the total amount of serum melatonin secreted over the night and of its peak value. The regression analysis of melatonin AUC values with morning excretion of aMT6s (0700 h–1100 h) indicated a tendency ( $p=0.06$ ,  $r=0.61$ ,  $F=4.73$ ,  $df=1, 9$ ) and the regression analysis for melatonin peak values showed a significant correlation with morning excretion of aMT6s concentrations (0700 h–1100 h) ( $p=0.055$ ,  $r=0.57$ ,  $F=4.70$ ,  $df=1, 11$ ) indicating, although to a lesser extent, that the higher the levels of melatonin during the night, the higher the concentration of aMT6s in the urine collected from 0700 h to 1100 h.

### 3.3.2. *The patient group*

In the patient group, there was no correlation between serum melatonin AUC or serum melatonin peak level and urinary excretion of aMT6s measures.

Considering that BMI was not different between the group of patients and the group of control subjects ( $p=0.96$ ,  $F=0.003$ ,  $df=1, 23$ ) nor between men and women ( $p=0.80$ ,  $F=0.06$ ,  $df=1, 23$ ), we decided not to include this variable as covariate in the analysis of serum melatonin and aMT6s concentrations.

## 4. Discussion

The results of this study support a phase-shift in the pineal secretion of melatonin in major depression. Indeed, depressive patients showed a 77 min peak time delay of serum melatonin secretion as compared to normal control matched for age and month of sampling. This delay in melatonin production is also reflected in urinary aMT6s concentrations which was enhanced instead of lowered from the night time period (2300 h–0700 h) to the morning period (0700 h–1100 h) in depressive patients as compared to control subjects.

These results are in accordance with Rubin et al. (1992) data indicating a trend toward a later peak time in a group of depressed patients compared with that in their controls. However, here we matched controls to patients by season of the year, unlike Rubin's study.

Our results did not confirm 'low melatonin syndrome' hypothesis suggested in some studies (Branchey et al., 1982; Claustrat et al., 1984; Nair et al., 1984; Beck-Friis et al., 1985; Frazer et al., 1986; Brown et al., 1987; Checkley and Park., 1987; Zetin et al., 1987; Miles and Philbrick, 1988; Kennedy et al., 1989). But, as pointed out by Rubin et al. (1992), the earlier studies used relatively small sample sizes,



patients and controls were not always comparable regarding age, not always drug-free and the early melatonin assays were questionable.

The analysis of the relationship between serum melatonin and urinary aMT6s in control subjects indicated a high and consistent association between melatonin AUC value or melatonin peak value and night time urinary aMT6s (2300 h–0700 h). The correlations were 0.82 and 0.78 ( $p < 0.01$ ). These correlations were also seen with morning aMT6s concentrations (0700 h–1100 h) but to a lesser extent. These results are in agreement with published studies where significant relationships, ranging from  $r = 0.62$  to  $r = 0.84$  were typically found between aMT6s and either AUC or peak plasma melatonin values (Arendt et al., 1985; Markey et al., 1985; Bojkowski et al., 1987; Graham et al., 1998), even in older subjects (Cook et al., 2000).

In the patient group, no correlation was observed between serum melatonin AUC or serum melatonin peak level and urinary excretions of aMT6s measures. This gap between the correlations observed in patients and controls is difficult to understand. It might reflect clearance difference between aMT6s and melatonin (Harthe et al., 1991) since the time for melatonin to aMT6s urinary excretion depends on hepatic processing and renal clearance (Graham et al., 1998). Metabolic processing of melatonin in the liver and its ultimate clearance occurs over a 1–2 h period (Klante et al., 1997). Further pharmacokinetic research would help to understand the observed discrepancy. Creatinine-corrected aMT6s values would be of interest in this type of study (Klante et al., 1997), or urinary melatonin because of its independence of hepatic degradation pathways (Cook et al., 2000).

While the blood measures of melatonin appeared to be slightly phase-shifted and the urinary aMT6s concentrations significantly delayed as compared to control subjects, the discrepancy observed in regression analysis between blood and urinary measures in depressives seems to be independent of pineal function and points out rather metabolic or clearance related explanations.

Some limitations concerning this study have to be raised. Previous antidepressant treatment could have influenced melatonin metabolism through its inhibition of cytochrome activities (e.g. fluvoxamine on CYP1A2 and CYP2C19 (von Bahr et al., 2000; Hartter et al., 2001)). However, all patients had been drug-free for at least two weeks (3 weeks for fluoxetine treated patients) which limits this possible bias. Some patients occasionally took low doses of benzodiazepines during the washout period, but never during the days of data collection. Benzodiazepines could diminish melatonin secretion if used chronically at high doses, which was not the case for our patients. In contrast, short-acting benzodiazepines like triazolam do not have any effect on melatonin secretion (Kabuto et al., 1986; Copinschi et al., 1990). Single doses of zopiclone and temazepam did not alter the nocturnal melatonin secretion (Norman et al., 2001). On the other hand, hypercortisolemia associated with depression could decrease melatonin secretion and therefore modify the relationship found in healthy controls (Claustrat et al., 1984).

Another limitation of this study would be that some women were taking hormonal therapy but according to recent data (Cook et al., 2000; Hendrick et al., 2002), neither menopausal status or hormonal replacement therapy alter 6-hydroxymelatonin-sulfate values in morning void urine. As pointed out in a recent study (Cook et al., 2000),

pre- and post-menopausal women, with or without hormone replacement therapy, did not differ according to their morning aMT6s values, suggesting that the various hormonal statuses do not play a major role.

This study also pointed out the necessity to control for confounding variables like gender and age. There was a higher peak time of melatonin in males than females. This difference, however, seems mainly due to the relation between age and gender, since it disappeared after adjustment for age.

In conclusion, this study shows a delayed phase-shift of melatonin secretion in drug-free depressive patients compared to control subjects, indicating circadian rhythm abnormalities. Urinary aMT6s excretion rates remains a good estimate to detect phase-shift in the circadian rhythm of depressive patients compared to control healthy subjects.

The study provides a confirmation for the inclusion of night time urine samples as a reliable tool of overnight plasma melatonin in studies involving healthy subjects, even in older populations. Although it does not provide direct information about the timing of the peak value, this parameter should be further investigated in its relation to plasma melatonin in psychiatric populations, according to the observed discrepancies in the depressive group in the relationship between serum and urinary measures. Obviously, one will have to consider the different steps of the complete retino-hypothalamo-sympathic-pineal adrenergic neuronal pathway and the pineal serotonin metabolism leading to melatonin synthesis together with kidney and hepatic melatonin clearance for future psycho-endocrine studies.

The design of this study, extending the sampling time to a broader time schedule (including night time (2300 h–0700 h) and morning time (0700 h–1100 h) sampling) provides evidence of the relevance of including night time as well as morning urine samples as a tool in circadian rhythm disturbance studies involving depressive patients.

As pointed out by Pacchierotti et al. (2001), further determination of the role of melatonin in psychiatric disorders could help to better understand the biological basis of these disorders and to define the potential for light therapy in their treatment.

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