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ORIGINAL ARTICLE

Diurnal profile of melatonin concentrations in patients with major depression: relationship to the clinical manifestation and antidepressant treatment

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Abstract

OBJECTIVES: The aim of the study was to establish if there are differences in the 24-hour melatonin secretion profile between patients with major depression (before, and after treatment with clomipramine) compared to those in healthy subjects. Additionally, we determined if there are differences in melatonin concentrations, depending on the severity of depression, and the presence of 24-hour rhythm disturbances.

MATERIAL AND METHODS: Twenty patients with major depression and 24-hour rhythm disturbances, and 14 healthy volunteers took part in the study. Before, and after treatment with clomipramine all subjects had blood samples collected at 08:00, 14:00, 20:00, 24:00, 02:00, 04:00, and 08:00 h, for estimation of melatonin concentrations. Before and after treatment, the severity of depression was evaluated using the following scales: the Hamilton Depression Rating Scale (HADRS), Beck Depression Inventory (BDI), and clinical observation, as well as presence, and if so, severity of 24-hour rhythm disturbances were assessed.

RESULTS: In individuals with major depression with marked disturbances of their diurnal rhythms, melatonin secretion is also disturbed, shown by the higher melatonin concentrations at night as compared to those in healthy individuals. However, melatonin levels were independent of the severity or the clinical manifestation of depression. Moreover, no correlation between the disturbances in their diurnal rhythms (sleep-watchfulness, diurnal mood shifts) and disturbed melatonin pattern was observed.

CONCLUSIONS: Melatonin nocturnal concentrations in patients with major depression were higher than those in healthy individuals. However, the melatonin concentration values do not differentiate the patients in terms of the severity of the depressive symptoms.

Introduction

The relationship between the melatonin rhythm and other circadian rhythms, which are definitely dysregulated in some types of recurrent major depression, has been investigated in many studies with the aim of determining the role of this hormone in the pathogenesis of depressive disorders. During the course of these disorders, aside from depressed mood and anhedonia, the sleep-wakefulness pattern is disturbed, and there are diurnal mood fluctuations.

It is well known that melatonin synthesis is controlled by noradrenergic system [1]. This fact, together with the noradrenergic hypothesis of depression, has induced many researchers to undertake studies directed at examining the concentrations of melatonin in body fluids of individuals with depressive disorders [2]. The studies conducted to date, however, have produced contradictory findings, although most studies indicate the presence of disturbances in melatonin cycles in individuals with major depression. These alterations may be related to disturbances in noradrenergic transmission, although few other potential explanations have been considered. Whether melatonin disturbances appear prior to the depressive symptoms also is unknown.

Some authors reported lowered melatonin levels in individuals with the diagnosis of major depression Beck-Friis et al. [2, 3], Brown et al. [4], and Wetterberg et al. [5, 6], whereas contrary results, namely an increase in melatonin concentrations at night, or during both day and night, have been found by others [7, 8, 9, 10]. It should be noted, however, that in none of the studies conducted thus far a relationship between melatonin levels and depression has been definitely confirmed [2, 9]. There are some studies, which compared in the same patients the melatonin rhythm in the acute phase of major depression and in the remission stage; these data may provide a clue as to the probable causative role of melatonin in the onset of depression, or at least some of its symptoms [9]. Therefore, the aim of the study was to determine: (i) whether there exist distinct differences between the group of subjects with depression (before and after treatment with clomipramine), and the control group of healthy subjects, with regard to the diurnal secretion profile of melatonin, (ii) which, if any, changes can be detected in the diurnal profile of melatonin secretion in patients treated with clomipramine, (iii) are there statistically significant differences with regard to melatonin concentration values, dependent on the severity of depression, and the degree of improvement after the administered pharmacological treatment? (iv) whether the diurnal profile of melatonin concentrations differs in patients in whom there was a diurnal rhythm regulation (sleep-wakefulness pattern, 24-hour mood shifts) after treatment with clomipramine, and those in whom this dysregulation is still present after treatment.

Material and methods

The studied group consisted of 20 patients with the diagnosis of major depression (according to DSM-IV) criteria, hospitalized in the 2nd Psychiatric Clinic, Medical University of Lodz, Poland. The group included 15 women and 5 men (mean age 45.9 ± 8.4 years, range 28–55 years). Among 20 patients included in the study, 14 persons had a relapse of the disease and for 6 patients it was their first episode. The duration of episodes was from a 2 to 5 months. Six persons were without any psychotropic medication for more than one year, 14 persons had the antidepressant withdrawn and underwent subsequent at least 7-day washout period from the last dose before the collection of a blood sample. The control group consisted of 14 healthy volunteers (6 women and 8 men) who were age-matched to the studied group (mean age 41.5 ± 4.0 years, range 32–50 years). All the participants of the study gave their informed consent to participate in the study. The consent of the Ethical Committee, Medical University of Lodz, has also been obtained.

The subjects fulfilling the following criteria were included in the study:

- patients with the diagnosis of major depression (DSM-IV criteria), first, or following episode of depression, with the presence of pronounced diurnal rhythm disturbance,
- age : 28–55 years,
- more than 18 points on the Hamilton Depression Rating Scale on the day of inclusion,
- in case of an episode of depression, which has already been treated with antidepressant medication, at least a 7-day washout period,
- no psychiatric comorbidity,
- no somatic comorbidity.

Patients were qualified for the study during a period of 2 years, the testing, however, was conducted only in the autumn-winter months, to eliminate the seasonal daylight-dependant influence on the secretion of the hormone.

The patients included in the study had an 8 ml blood sample taken 7 times during a 24-hour period (at 08:00, 14:00, 20:00, 24:00, 02:00, 04:00, and 08:00 h) before, and after 8-week treatment with clomipramine (150–225 mg/day). On the day of the blood samples' were collected, the patients were kept in darkness from 22:00 to 06:00 h. The blood was

centrifuged and the plasma was frozen in –20°C. Melatonin concentrations were determined by RIA (DRG-IHRE-29301 kit; intra assay 8%, inter assay 14,8%). An identical procedure of blood sampling and melatonin concentrations measurement was performed in the control group.

Prior to treatment, and after 8 weeks of therapy the psychiatric state of the patients has been evaluated using the following scales: The Hamilton Depression Rating Scale (HADRS), Beck Depression Inventory (BDI), and clinical observation.

The results have been statistically analyzed, using the following: paired Student's t-test, Student's t-test, F-Snedecor test, Aspin-Welsch test, and Mann-Whitney test.

Results

The mean melatonin nocturnal concentrations (24:00, 02:00 and 04:00 h) were higher in persons with depression, than in the healthy subjects (Fig. 1). Also the difference in the area under curve between the two groups was statistically significant (1494.4 ± 159.1 pg/ml/24h vs 986,7 ± 71.8 pg/ml/24h, respectively; mean ± SEM; $p < 0.01$). There were no significant differences between melatonin levels before and after 8 weeks of treatment with clomipramine (Fig. 1).

In order to determine the intensity of depression, all patients were evaluated using the HADRS. The self-evaluation was performed using BDI. The indi-

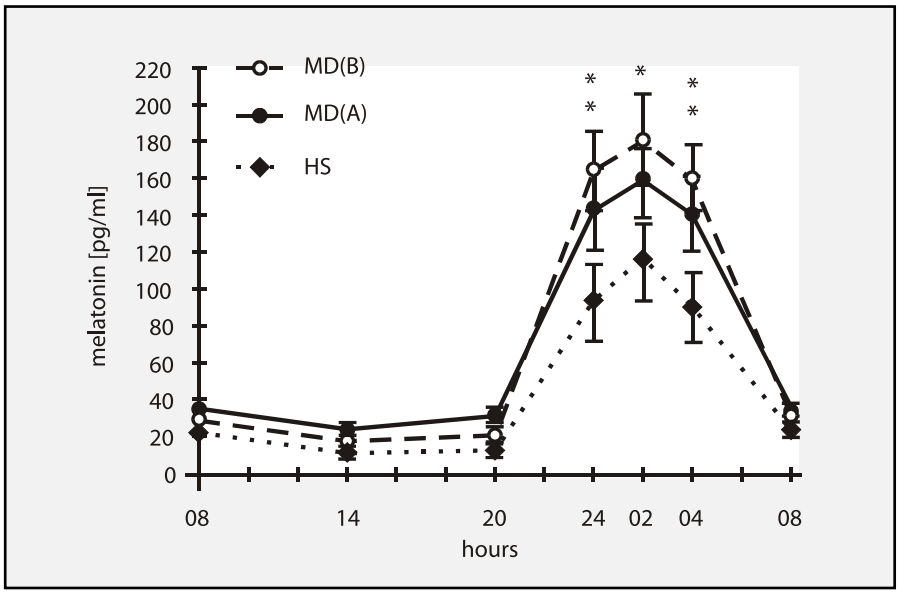

Fig. 1. Diurnal melatonin concentrations in healthy subjects (HS), and individuals with major depression (MD) before (B), and after (A) clomipramine treatment; MD(B) and MD(A) vs HS * $p<0.05$, ** p 0.01; MD(B) vs MD(A) no statistical significance.

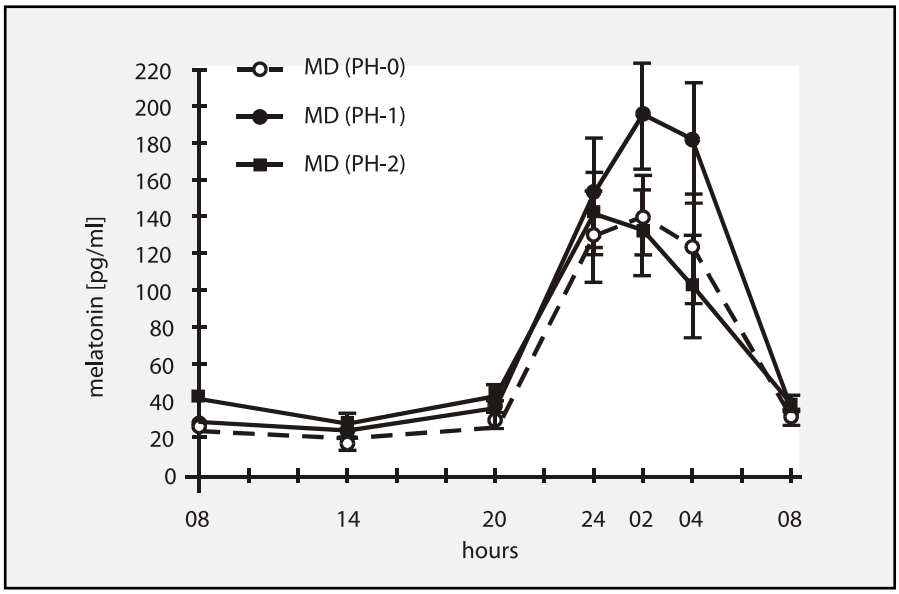

Fig. 2. Mean melatonin concentrations in patients with major depression (MD), depending on the psychiatric state improvement (subgroups: PH-0, PH-1, PH-2), measured by HAMRS; no statistical significance.

viduals included in subgroup H-O were those who obtained 20 to 29 points in the HADRS, whereas those in the H-1 subgroup – 30–40 points in the HADRS. H-0 constituted 55% of the entire population studied. A similar division was observed, based on the BDI self-evaluation, with B-0 20–35 pts and B-1 36–52 pts. The B-0 group constituted 60% of the patients. Table 1 shows the mean melatonin concentrations in persons belonging to different subgroups, depending on the severity of depression in the HADRS. There was no correlation between the severity of depression (judged by HAMRS or BDI scores) and melatonin secretion. The subjects were divided into three subgroups, according to the degree of improvement from baseline in HAMRS and BDI seen after 8 weeks of clomipramine treatment. The PH-0 subgroup (n = 4) were persons, who after 8 weeks of pharmacological treatment had the HAMRS score lowered by 49%; PH-1 – subgroup (n = 8) of patients, whose HAMRS score was lowered by 50–70%, and PH-2 (n = 8)– those, whose HAMRS score was lowered by 71–100%. Similar distinction has been made with regard to the score reduction in BDI (PB-0, n = 4; PB-1, n = 5; PB-2, n = 11; subgroups, respectively). A significant improvement of the psychiatric state is determined by a lowering of HAMRS and BDI scores equal to or greater than 50%. It was determined that 80% of the patients treated with clomipramine had experienced significant improvement, and 20% had not (either no improvement at all, or improvement less than 50%). There were no significant differences in melatonin concentrations between subgroups evaluated in terms of the degree of improvement in the HAMRS scale (PH-0, PH-1, PH-2) were not statistically significant (Fig. 2). A similar analysis performed for the BDI scores also did not reveal statistically significant differences among subgroups PB-0, PB-1 and PB-2 (Fig. 3).

In 17 out of the 20 patients studied, pronounced sleep-wakefulness pattern disturbances were observed (such as waking up too early, difficulty in falling asleep) as shown by clinical observation and answers to chosen questions in HAMRS. After treatment with the antidepressant, in 9 patients (subgroup S-0) from the 17 sleep-wakefulness pattern disturbances remitted completely, whereas in 8 persons (subgroup S-1) they did not. The comparison between mean values of melatonin concentrations in both subgroups did not show significant differences (Fig. 4).

Among the 20 persons included in the study, 17 presented pronounced diurnal mood shifts, reporting greater intensity of depression and anxiety in the morning. After treatment with clomipramine, in 13 treated subjects (subgroup N-0) mood shifts were no longer observed, whereas in 4 persons (subgroup N-1) they remained unchanged. Just as in the case of sleep-wakefulness rhythm analysis, the mean values of melatonin concentrations in patients without pronounced diurnal mood shifts did not differ significantly from those in the subjects, in whom the mood shifts remained unchanged after treatment (Fig. 5).

Discussion

Studies by many authors [3, 4, 7] have claimed low melatonin levels in major depression. The results obtained in those studies should be interpreted with caution, however, due to some methodological shortcomings (small number of patients in the studied group, different age of subjects, testing conducted at various times of the year, non-exclusion of serious somatic conditions, which could have influenced melatonin secretion disturbances). Regardless of these drawbacks, the results obtained in the course of these studies were extremely interesting, leading to a formulation of an interesting concept by Wetterberg et

Table 1. Mean melatonin serum concentrations (pg/ml) and area under curve (pg/ml/24h) in subjects with major depression depending on the intensity of the disease (subgroups H-0, H-1); data are expressed as mean±SEM; no statistical significance.

Subgroup H-0 (n = 11)

Hours							Area under curve
08:00	14:00	20:00	24:00	02:00	04:00	08:00	
29.0±6.9	22.2±5.7	19.7±3.0	150.9±30.9	157.8±30.9	153.8±29.1	30.6±5.8	1434.5±206.2

Subgroup H-1 (n = 9)

Hours							Area under curve
08:00	14:00	20:00	24:00	02:00	04:00	08:00	
29.5±8.0	14.7±2.6	18.5±3.7	181.5±36.2	206.4±37.7	169.5±38.8	28.3±5.1	1567.7±259.7

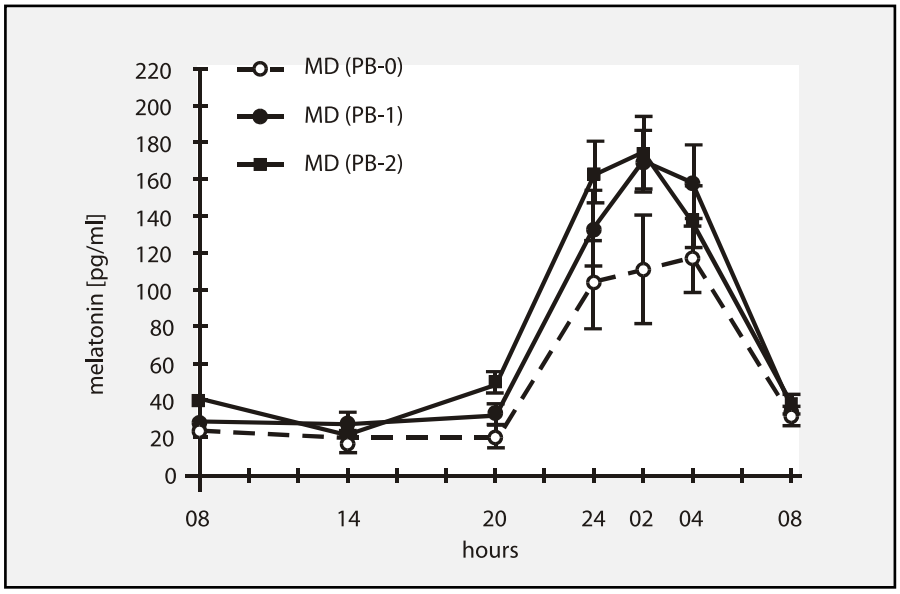

Fig. 3. The mean melatonin concentrations in patients with major depression (MD), dependent on the degree of psychiatric state improvement (subgroups: PB-0, PB-1, PB-2), measured by the BDI; no statistical significance.

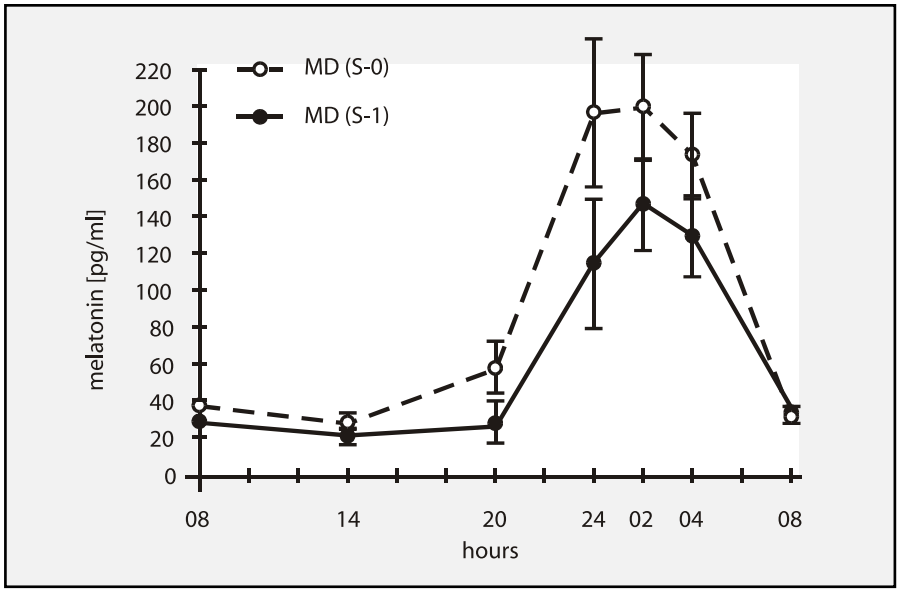

Fig. 4. The mean melatonin concentrations in patients with major depression (MD) with treatment-induced sleep-wakefulness pattern regulation (S-0), and the non-responsive dysregulated rhythm (S-1); no statistical significance.

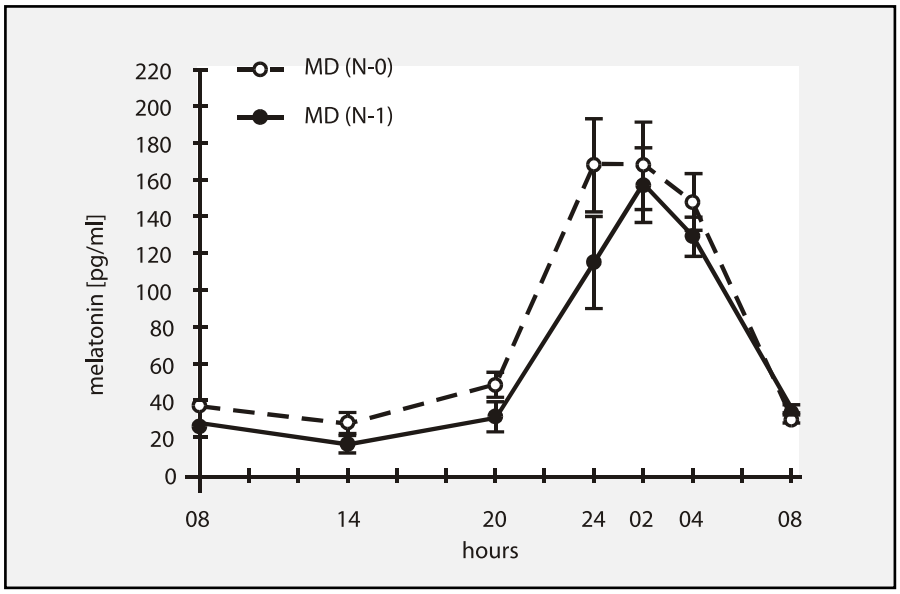

Fig. 5. The mean melatonin concentrations in patients with major depression (MD) without diurnal mood shifts (N-0), and those presenting diurnal mood shifts (N-1); no statistical significance.

al. [5, 6]. They came to believe that low melatonin concentrations could be a biological marker for the susceptibility to major depression.

Mendlewicz et al. [11] have reported that effective antidepressant treatment does not change the diurnal melatonin profile. The results of our study seem to confirm the results obtained by Mendlewicz et al. [11] showing that the melatonin diurnal pattern in patients with depression did not change, even after a marked improvement of their psychiatric state.

Very little information is available about the differences in melatonin concentrations between the individuals with major depression, and the healthy subjects [8, 12, 13].

In our study it was determined that in persons with major depression, melatonin secretion is higher at night than in the healthy control group.

The causes of a discrepancy, obtained by different authors with regard to melatonin levels in patients with major depression, can be numerous. Not all the researchers matched the studied group with the control group according to age, sex, time of the year, and medication taken. Also the body mass of subjects should be taken into consideration, as it may show a negative correlation with melatonin levels. The time of the year during which the study is conducted, also may play a role, especially when one compares the results obtained from patients, tested in various times of the year [14, 15, 16]. Moreover, different circaannual melatonin values have been observed in depressed patients in comparison to healthy controls, namely high summer concentrations and low winter concentrations in depressed patients, and reverse patterns (i.e. low summer and high winter concentrations) in normal healthy volunteers [15]. However, in the later study there was a large age difference between both groups (44.5 years vs 24.2 years, respectively).

In the studies conducted thus far, the correlation between the clinical manifestation of major depression, and the concentration of melatonin in body fluids has not been confirmed. Beck-Friis et al. [2] as well as Rubin et al. [9] did not find a correlation between the clinical manifestation of depression (with melancholy, psychotic, etc), and melatonin levels. They have described, however, higher maximal concentrations of melatonin in depressive individuals with a suicide attempt in anamnesis, and with diurnal mood shifts, as compared with other patients with major depression. Lewy et al. [17] and Wahlund et al. [18] have noted lower melatonin concentrations in persons with psychotic depression, than in those with non-psychotic forms of the disorder, or in healthy individuals. Clearly, patients with depression form a non-homogenous group. In our study it has been determined that after clomipramine treatment the mean melatonin concentrations did not differ statistically significantly from initial values and remained elevated, compared to the healthy population. It can be so, that the altered hormone secretion pattern in individuals with major depression remains altered, regardless of their state improvement. It is difficult to explain this phenomenon. Perhaps the causes of altered melatonin secretion in these patients are related to retino-hypothalamo-pituitary system. It is thought, that patients suffering from major depression have some kind of a biochemical defect, altering the sensitivity of the retina to light. If this sensitivity is lower, it can lead in turn to higher melatonin concentrations, and subsequent diurnal rhythms disturbances. Another explanation of the melatonin secretion disturbances can be the distortion of homeostasis between melatonin, and suprachiasmatic nucleus (SCN) of the hypothalamus. This distortion can be in the form of lower sensitivity of the receptors, and lack of blocking the activity of SCN by the melatonin, secreted to the blood, and cerebrospinal fluid.

Herein no significant correlation was found between melatonin secretion levels, and the severity of major depression. Similar results were obtained by Beck-Friis et al. [2] and Rubin et al. [9]. It should be mentioned, however, that Soutre et al. [19] have found a correlation between low melatonin concentrations, and the severity of depression (measured by HAMDS score), in 16 persons with symptomatic major depression, and 15 in remission phase. Both the patients, who after antidepressive treatment experienced full remission, as well as those, who were only slightly improved, have shown a higher diurnal melatonin secretion, than healthy individuals.

From the results of our study we can conclude that: (i) in persons with major depression, with a marked disturbance of diurnal rhythms, melatonin secretion is also disturbed, shown by the higher hormone synthesis, especially during the night, as compared to healthy individuals, (ii) the melatonin concentration values do not differentiate the patients in terms of the severity of the depressive symptoms, (iii) no connection has been found bet

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