Circadian rhythm and the phenotype of major depressive disorder: an Egyptian study

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Introduction
For many years, researchers have suggested that abnormalities in circadian rhythms may underlie the development of mood disorders, such as major depression. The objectives behind this study were to investigate whether cortisol circadian rhythm could be considered as a biomarker for major depression, to identify whether different circadian rhythm alterations in patients with major depression is interrelated with syndrome presentation (either with or without psychotic features) and symptom profile (typical and atypical depressive symptoms) and to investigate whether there are alterations in the cortisol circadian rhythm and whether it could be a possible endophenotype among first-degree relatives of patients.

Methods
Fourteen patients, aged between 25 and 50 years, in a major depressive episode or in a depressed phase of bipolar disorder, six controls and six first-degree relatives were screened using psychometric questionnaires, and a blood sample was withdrawn from consenting participants at four time points during the day, for the assessment of plasma cortisol secretion. The patients were diagnosed by a clinical psychiatric interview and a semistructured psychiatric interview based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria for diagnosis, and a psychometric assessment was made. Serum cortisol levels were assayed using a validated commercial kit.

Results
There was a statistically significant difference between serum cortisol levels of the three studied groups at four consecutive sampling points over 24 h. The elevated plasma cortisol levels of patients correlated positively with phenotypic features, such as suicidality ($P=0.029$), positive family history of psychiatric disorder ($P=0.024$), chronotype of the patients ($P=0.017$) and their scores on Beck Depression Inventory ($P=0.029$) and Hamilton Depression Rating Scale ($P=0.05$). In addition, there is no statistically significant difference between patients and their first-degree relatives on the scores of Bipolar Affective Disorder Dimension Scale.

Conclusion
The increase in cortisol secretion and shift in its circadian phase and chronotypes of depressed patients and their first-degree relatives suggest that cortisol level is probably a state marker in mood disorder. In addition, different phenomenology and symptomatology of depression was closely interrelated to cortisol levels. Further genetic studies are recommended to establish its predictive significance.

Keywords:
cortisol circadian rhythm, hypothalamic–pituitary–adrenal axis abnormalities, major depressive disorder, phenotype

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Introduction

For many years, researchers have suggested that abnormalities in circadian rhythms may underlie the development of mood disorder, such as major depression, bipolar disorder and seasonal affective disorder. Furthermore, some of the treatments that are currently used to treat mood disorders are thought to act by shifting or resetting the circadian clock. Recent genetic, molecular and behavioural studies implicate individual genes that make up the clock in mood regulation [1]. Circadian rhythms are periodic variations over approximately 24 h in many biological and physiological processes and are controlled by the internal clock. Markers of circadian rhythms are sleep/wake cycle, chronotype, body temperature, melatonin secretion, cortisol secretion and activity of the clock genes [2]. Wichers *et al.* [3] hypothesized that genetical and environmental susceptibilities to depression are

expressed, in part, as alterations in cortisol day curves. Cortisol abnormalities are not merely the consequence of depressive states or the stressors associated with its onset. Alteration of diurnal secretion of cortisol is a possible endophenotype of depression, as depressed patients show alterations in cortisol dynamics over the day [3]. In addition to elevated cortisol levels, disturbances in the temporal pattern of secretion have been observed, including a flattened circadian curve of cortisol, a reduction in the length of the nocturnal quiescent period, an earlier nadir, an elevated nadir and changes in the duration, amplitude and frequency of pulsatile episodes. These findings provide evidence that normal periodicities in hypothalamic–pituitary–adrenal (HPA) axis activity are disturbed, one of the criteria for a dysregulated biological system [4]. Recent research [5] has showed reliable HPA changes associated with adult major depressive disorder (MDD). These changes might be evident before clinical manifestation of the illness in at-risk persons (first-degree relatives). Studies have reported relationships between HPA axis abnormalities and severity, endogenicity, psychotic features, melancholic features and chronicity [6–8]. These observations of course pose the question of whether the persisting abnormalities are trait markers for depression, indicating an increased vulnerability for an affective disorder. Thus, a promising strategy is the investigation of healthy relatives of depressed patients as one can assume that genetically predisposed individuals show trait markers indicative for an increased susceptibility to depression even in the premorbid state. Our aim was to identify whether cortisol circadian rhythm alterations in patients with mood disorder are interrelated with syndrome presentation (either with or without psychotic features) and symptom profile (typical and atypical depressive symptoms) and to investigate whether cortisol circadian rhythm could be a possible endophenotype for mood disorders among first-degree relatives of patients.

Materials and methods

Participants were recruited from the Psychiatry outpatient clinic of Mansoura University Hospital, during a period of 6 months. The total number of participants was 26 and was divided into three groups, 14 patients (patient group), six participants from first-degree relatives of the patients (relatives group) and six nonpsychiatric participants (control group). All the patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria for a current major depressive episode, either of the unipolar or bipolar type, with or without psychotic features and were free of drug treatment for at least 3 months. The patients were recruited according to certain inclusion and exclusion criteria.

The sample included patients of both sexes, with age groups ranging from 25 to 50 years and whose first-degree relatives were available. A written informed consent, for participating in the study, was taken from the patient and his first-degree relative.

The sample excluded patients who were meeting criteria for any comorbid axis I psychiatric disorder or had a history of substance abuse, patients who received antidepressants or mood stabilizers and electroconvulsive therapy during the previous 3 months, women during the menstrual cycle, menopause, pregnancy or lactation, patients with chronic medical illnesses and debilitating conditions, a history of seizures or major head trauma, unstable or untreated hypertension, cardiovascular disease or endocrine disorders, abnormal clinical laboratory tests (e.g. disturbed kidney, liver functions), patients on steroids (i.e. prednisone or steroidal inhalers) and patients treated with medications that interact with cortisol metabolism or patients engaged in shift work.

A cross-sectional survey was carried out on the patient group, the relatives group and the control group. All the selected patients were subjected to: (i) psychiatric assessment through history evaluation and mental state examination by a clinical psychiatric interview along with a semistructured psychiatric interview based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria [9] for diagnosis of the current major depressive episode, either of the unipolar or bipolar type. (ii) Beck Depression Inventory (BDI) [10] to screen for the presence/absence of the clinically significant depressive symptoms and severity. The standard cut-offs are 0–9 (not depressed)/10–18 (mild depressed)/19–29 (moderate) and 30–63 (severe depression). (iii) Hamilton Depression Rating Scale (HADRS) [11] that is an observer-rated scale consisting of 17–21 items (including two-part items, weight and diurnal variation). Eight items are scored on a five-point scale ranging from 0 = none/absent to 4 = most severe. Nine items are scored from 0 = absent/none to 2 = severe. The sum of the scores from the first 17 items are: 0–7 = normal, 8–13 = mild depression, 14–18 = moderate, 19–22 = severe and 23 or more = very severe depression. (iv) Bipolar Disorder Dimension Scale [12]: Bipolar Affective Disorder Dimension Scale (BADDS) is a dimensional rating scheme that retains and builds on current categorical classifications. BADDS consists of four dimensions: M: mania, D: depression, P: psychosis and I: incongruence. Each dimension is rated using integer scores on a 0–100 scale. Each rating reflects a mixture of the severity and frequency of clinical features. (v) Morningness and Eveningness Questionnaire (MEQ) [13]: it is a self-assessment questionnaire, to give an idea about the chronotype of the patient. It has 19 questions; some questions have a scale instead of a selection of answers. The scores are added together and the sum is converted into a five–point Morningness–Eveningness Scale, namely Definitely Morning Type = 70–86, Moderately Morning Type = 59–69, Neither Type = 42–58, Moderately Evening Type = 31–41 and Definitely Evening Type = 16–30.

Each patient was then admitted. The blood samples were directly withdrawn from the patients on the first 24 h of admission according to the designed timetable of sampling. On collection of the sample during night, the

Table 1 Demographic data of the total sample

Demographic data	Cases % (*N*)	Controls % (*N*)	First-degree relatives % (*N*)	Pearson's χ^2 test	Significance
Age					
Mean ± SD	42.8 ± 6.3	45.3 ± 7.1	33.5 ± 19.5	18.9	0.143
Sex					
Female	42.9% (6)	16.7% (1)	50% (3)	1.65	0.437
Male	57.1% (8)	83.3% (5)	50% (3)		
Occupation					
Not working	21.4% (3)	16.7% (1)	33.3% (2)		
Manual workers	57.1% (8)	50% (3)	33.3% (2)	1.21	0.876
Employed	21.4% (3)	33.3% (2)	33.3% (2)		
Marital groups					
Unmarried	35.7% (5)	66.7% (4)	100%	7.36	0.025
Married	64.3% (9)	33.3% (2)			

SD, standard deviation.

nurses were instructed and trained not to wake the patient from sleep, and to use minimal lighting during the withdrawal procedure. All these precautions were taken to ensure accuracy of the sampling procedure and to increase levels of sampling reliability.

The relatives group

Each relative was subjected to a clinical interview to exclude relatives with overt psychiatric disorders, BADDS that accommodates subclinical features, MEQ and cortisol blood levels collected by the same methods mentioned before.

The control group

Controls were matched for age and sex and were subjected to the analysis of MEQ and plasma cortisol levels.

The cortisol assay procedures

Blood samples, at the following times during the day, 8:00–10 : 00 a.m. (awakening sample, once the patient wake up or within an hour of that timing) 2 : 00–4 : 00 p.m., 8 : 00–10 : 00 p.m. and 2 : 00 a.m., and awakening sample, once the patient woke up or within an hour of that timing, were collected. All standards, samples and controls were run in duplicate concurrently, by the enzyme-linked immunosorbent assay technique according to manufacturer's recommendations.

Statistical study and cortisol calculations

Calculation of cortisol results

The average absorbance values for each set of standards, controls and patient samples were calculated. A standard curve was constructed by plotting the mean absorbance obtained from each standard against its concentration with the absorbance value on the vertical (Y) axis and concentration on the horizontal (X) axis. Using the mean absorbance value for each sample, the corresponding concentration from the standard curve was determined. Expected cortisol values in the serum or plasma ranges from 50 to 230 ng/ml (138–635 nmol/l) between 8 : 00 and 10 : 00 a.m. and from 30 to 150 ng/ml (82.8–414 nmol/l) at 4 : 00 p.m. [14].

Statistical methods

Data were analysed by using the statistical package for social sciences software version 17 (New York, USA) [15]. Data were presented as mean ± standard deviation for quantitative variables and as number and percentage for qualitative variables. Student's *t*-test, χ^2 test and Mann–Whitney test were used. *P* value less than 0.05 was considered to be significant. Cortisol levels correlated for pairs of studied samples and with the phenotypic features of the patients by Pearson's correlation.

Results

Table 1 shows that there is no statistically significant difference for the demographic data among the three groups, except for marital status, as all first-degree relatives were unmarried.

Table 2 shows that the majority of patients had a positive family history of psychiatric illness (71.4%) followed by severe guilt and suicidal symptoms (64.3%) and atypical symptoms (57.1%). The number of patients with psychomotor retardation exceeded those with psychomotor hyperactivity. The majority of the patients' chronotype was of neither the morningness nor eveningness type (50%), as scored by MEQ and the smallest percentage had a definite morningness chronotype (14.3%). The same applied for the first-degree relatives group in which the majority was of neither the morningness nor eveningness chronotype and there was no participant with definite morningness chronotype. The majority of the controls had morningness chronotypes (66.6%), whereas the rest of the controls were nearly equally distributed between the remaining chronotypes (Table 3).

Table 2 Descriptive data for phenotypic features of the patient group

Symptoms	Guilt	Suicide	Positive family history	Psychomotor agitation	Psychotic symptoms	Atypical symptoms
With *N* (%)	9 (64.3)	9 (64.3)	10 (71.4)	6 (42.8)	4 (28.5)	8 (57.1)
Without *N* (%)	5 (35.7)	5 (35.7)	4 (28.6)	8 (57.1)	10 (71.4)	6 (42.8)

Table 3 Frequency distribution of the Morningness and Eveningness Questionnaire grouping among the total sample

	Groups			
MEQ scores	Cases *N* (%)	Controls *N* (%)	Relatives *N* (%)	Total *N* (%)
Morningness (70–86)	2 (14.3)	2 (33.3)	0	4 (15.3)
Morningness>eveningness (59–69)	4 (28.6)	2 (33.3)	2 (33.3)	8 (30.7)
Neither morningness or eveningness (42–58)	7 (50)	1 (16.6)	3 (50)	11 (42.3)
Eveningness>morningness (31–41)	1 (7.1)	1 (16.6)	1 (16.7)	3 (11.5)
Total *N* (%)	14 (100)	6 (100)	6 (100)	26 (100)

MEQ, Morningness and Eveningness Questionnaire.

Table 4 The difference between patients and their relatives on the Bipolar Affective Disorder Dimension Scale

BADDS	Patients	First-degree relatives	Chi-square value	Significance
Mania	19.56±27.3	0	1.23	0.22
Depression	65.25±28.04	34.16±17.4	0.94	0.35
Psychotic features	20.62±35.9	3±7.08	1.34	0.18
Incongruity	39±13.9	34±4.9	0.11	0.91

BADDS, Bipolar Affective Disorder Dimension Scale.

Table 4 shows that there was no statistically significant difference between the patients and their first-degree relatives on scores of different dimensions of BADDS.

Table 5 shows that the patient group had scores of severe and very severe depressions as detected by scores of HADRS and BDI. The cortisol level of the patients was higher than that of the first-degree relatives, and also higher than that of the controls in the consecutively timed blood samples over a 24 h collection. In addition, the blood cortisol level of the first-degree relatives was higher than that of the controls in all the collected blood samples according to time table mentioned before. This detected difference in the blood hormone level was of statistical significance Table 6.

In Table 7, the statistical significance was calculated by dividing the studied sample into comparative pairs of cases versus controls, cases versus relatives and relatives versus controls. The *P* value was highly significant in the four consecutively timed samples, except, in cases versus relatives pairs.

Table 8 shows that there is positive correlation for the plasma cortisol levels at different times with the phenotype of depression.

Figure 1 shows that the cortisol levels of controls dropped after awakening until the noon sample after which it reached a steady state during sleep, but 2 h after sleep, it started to rise again until dawn and had a stable level until the awakening sample of the next day.

Figure 2 shows the first-degree relatives' cortisol levels across four time points during the day. The majority of the sample shows maximum cortisol levels in the afternoon. The hormonal level of the first-degree relatives was considerably low on awakening, and started to rise directly after the patient awakened, and continued to rise sharply until the noon sample, after which it dropped gradually until the patient fell asleep. The hormone level continued to fall gradually to reach its lowest level during the day at the time of the next awakening sample.

Figure 3 shows that the cortisol secretion of the patients was the highest on awakening and then gradually decreased in the noon sample and the sleeping sample, after which it started to rise sharply for the early dawn sample and reached the peak just before and on awakening the next morning.

Table 5 Beck Depression Inventory and HADRS scores of the patient group

	Mean±SD	Male *N* (%)	Female *N* (%)	Total (%)
BDI scores				
Severe (30–63)	47.5±9.5	8 (57.5)	6 (42.5)	14 (100)
HARDS scores				
Severe (19–22)	20.75±1.5	3 (75)	1 (25)	4 (28.6)
Very severe (≥23)	35.2±6.6	5 (50)	5 (50)	10 (71.4)

BDI, Beck Depression Inventory; HADRS, Hamilton Depression Rating Scale; SD, standard deviation.

Table 6 Plasma cortisol level of the total sample

Cortisol (μg/dl)	Mean±SD	Chi-square value	*P* value
Awakening			
Cases	58.8±19.5	18.90	0.00
Controls	9.8±2.8		
Relatives	19.8±3		
Noon level			
Cases	34.3±17.3	13.16	0.001
Controls	7.5±1.6		
Relatives	32.3±12.2		
Sleeping level			
Cases	25.5±13.8	11.07	0.004
Controls	7.3±3.5		
Relatives	27.1±18.5		
Early dawn level			
Cases	31.2±15.7	11.71	0.003
Controls	9.6±4.9		
Relatives	16.5±6.8		

SD, standard deviation.

Table 7 Correlative significance of cortisol levels among pairs of the studied sample

Mann–Whitney pairs	Awakening *Z* value	Awakening cortisol (*P*)	Noon *Z* value	Noon cortisol (*P*)	Sleeping *Z* value	Sleeping cortisol (*P*)	Early *Z* value	Early dawn cortisol (*P*)
Cases/controls	3.6	0.001	3.4	0.001	2.9	0.003	2.9	0.003
Cases/relatives	3.05	0.001	0.24	0.841	2.8	0.444	1.9	0.051
Controls/relatives	2.88	0.002	2.89	0.002	2.8	0.002	2.2	0.026

Table 8 Correlation of the plasma cortisol levels to the phenotypic features of the patients

Cortisol phenotypic correlations	Guilt *Z* (*P* value)	Suicide *Z* (*P* value)	Positive FH *Z* (*P* value)	Psychotic features *Z* (*P*)	Chronotype *Z* (*P* value)	BDI *Z* (*P* value)	Atypical features *Z* (*P* value)	HADRS *Z* (*P* value)
Awakening cortisol	1.31 (0.19)	2.18 (0.029)	1.03 (0.304)	0.63 (0.95)	2.38 (0.017)	2.18 (0.029)	0.65 (0.573)	0.19 (0.51)
Noon cortisol	0.9 (0.364)	2.18 (0.029)	0.21 (0.839)	0.18 (0.852)	2.51 (0.01)	2.22 (0.026)	0.82 (0.414)	0.29 (0.31)
Sleeping cortisol	1.04 (0.298)	0.51 (0.606)	0.64 (0.539)	2.55 (0.014)	0.39 (0.686)	0.61 (0.54)	0.00 (1.00)	0.049 (1.96)
Early dawn cortisol	0 (1.00)	0.00 (1.00)	2.25 (0.024)	0.68 (0.491)	0.46 (0.641)	0.42 (0.673)	0.56 (0.573)	0.12 (0.67)

BDI, Beck Depression Inventory; FH, family history.

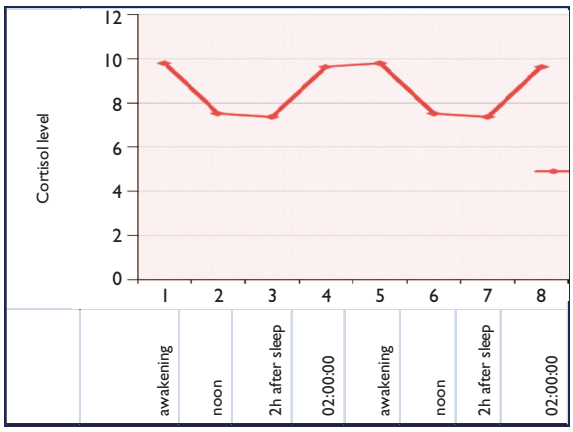
Discussion

HPA axis dysregulation is often seen in major depression and is thought to represent a trait vulnerability-rather than merely an illness marker-for depressive disorder. Vulnerability traits associated with stress-related disorders might reflect increased sensitivity for the development of psychopathology through an association with HPA axis activity [16].

Cortisol levels of the control group obtained in our study are within the normal reference range, 5–25 μg/dl (a.m.) and 2.5–12.5 μg/dl (p.m.). The levels obtained from the relatives group were to some extent elevated above the normal range. This is consistent with a study by Rao *et al.* [5] to identify depression-related HPA changes in healthy adolescents at high risk of depression and compared with normal controls with no personal or family history of psychiatric disorder. They found that elevated nocturnal urinary free cortisol was associated with the development of depression during follow-up. The finding that elevated HPA activity occurs before the onset of depression in at-risk adolescents suggests that this variable serves as a vulnerability marker for the illness. The patient group in this study showed definite hypercortisolism with their plasma cortisol levels far more exceeding the baseline level. Numerous studies documented HPA dysregulation in adult depression, including higher basal corticotropin-releasing hormone and cortisol secretion and nonsuppression of cortisol in response to dexamethasone administration [16,17]. Cervantes *et al.* [18] found that the increase in cortisol secretion in patients in both the depressed and manic phases of bipolar disorder suggests that cortisol level is probably not a state marker in bipolar disorder. In addition, they reported that Pearson's correlation between symptom rating scores of BDI and HADRS and cortisol secretion variables were not significant.

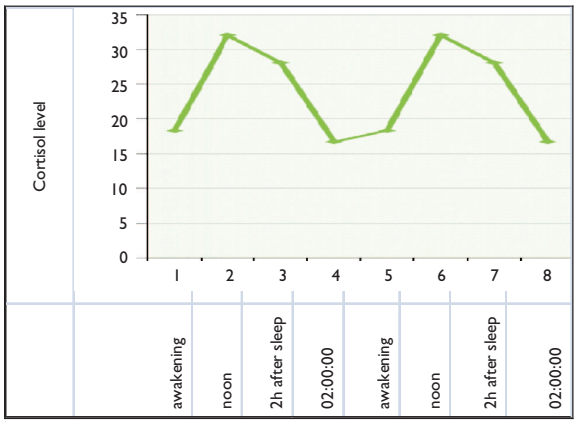
In this study, the cortisol level correlated positively with some of the phenotypic features of depression especially, guilt, suicide, positive family history, psychosis and scores on BDI and HADRS. These data are consistent with the study by Keller *et al.* [6] who found that major depression

Figure 1



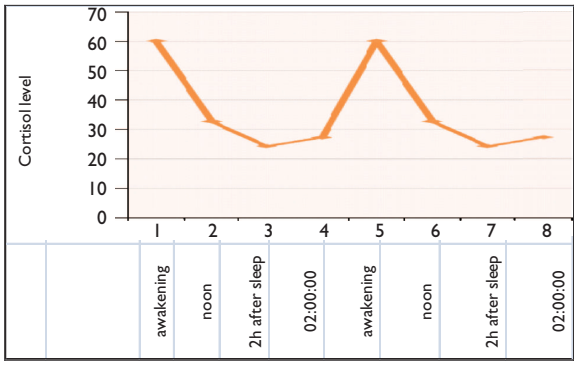
Forty-eight hour curve for the means of control group cortisol levels across four time points during the day.

Figure 2



Forty-eight hour curve for the means of the first-degree relatives' cortisol levels across four time points during the day.

Figure 3



Forty-eight hour curve for the means of the patient cortisol levels across four time points during the day.

with psychosis had higher cortisol levels during the quiescent hours. Enhanced cortisol activity, particularly a higher nadir, was related to depression severity and the interaction of depressive and psychotic symptoms. However, Vreeburg *et al.* in their study [19] disagree with our results. They found that higher cortisol awakening levels were not associated with most depression characteristics, such as severity, chronicity and the symptom profile. They concluded that higher cortisol response was observed among both patients with current MDD and patients with remitted MDD. This may be indicative of an increased biological vulnerability for depression in general. Recently, a study of depression done by Van Santen *et al.* [16] in Netherlands, found that persons scoring high on vulnerability traits show an elevated cortisol awakening curve. Dysregulation of the HPA axis function is associated with suicidal behaviour. Suicide correlated positively with cortisol levels in this study. This is further confirmed by the study by Jokinen *et al.* [20] who found that in suicide attempters with mood disorder, the nonsuppressor status in the dexamethasone suppression test is associated with suicide, indicating that HPA axis hyperactivity is a biological risk factor for suicide and may be a useful predictor.

Our findings showed that the curve of cortisol circadian rhythm of controls followed the normal patterns of secretion, whereas erratic patterns were noticed to some extent in the first-degree relatives group, and definitely evident in the curve belonging to the patient group. Disturbed circadian rhythm found in our study is consistent with the study by Peeters *et al.* [4]. They found that secretory patterns of cortisol were particularly erratic in patients with more severe or recurrent episodes instead of high levels of cortisol secretion. In addition, a study [3] using a cross-twin cross-trait design, found that probands of cotwins with lifetime depression have a different diurnal cortisol profile than those without, suggesting that altered HPA axis functioning is an indicator of depression susceptibility. Recently, Taylor *et al.* [21] documented relationships between adult reports of parental affection in childhood and adult diurnal cortisol rhythms. MDD is a heritable psychiatric syndrome that seems to be associated with subtle cellular and molecular alterations in a complex neural network [22]. The susceptibility findings among first-degree relatives mentioned above were further evident by the insignificant difference between the patient group and relatives group on scores of Bipolar Disorder Dimension Scale. This indicates that the first-degree relatives had subclinical symptoms.

Rhythm disturbances are a frequent clinical manifestation of depression. In recent years, a possible relationship between depression and chronotypes has emerged. Specifically, eveningness has been proposed as a vulnerability factor [23]. In addition, in another study, patients with MDD have also been reported to be significantly more of the evening type than controls [24]. MEQ is a stable, quantifiable measure reflecting preferred circadian phase and used for the indirect evaluation of circadian rhythm. The chronotype of our studied sample among the patients and the relatives (neither type = 50%) varied extensively from the distribution of chronotypes in the control group (neither type = 16.6%). This is in line with the study by Gaspar-Barba *et al.* [23] on 100 patients diagnosed with MDD. They found that according to MEQ scores, 60% of patients was of neither type, 18% was of eveningness type and 21% was of morningness type. In addition, McClung [1] found that even individuals that are genetically predisposed towards 'eveningness' (a preference for the evening) versus 'morningness' (a preference for the morning) are more likely to develop depression.

Conclusion

Results of this study found that different symptomatology of major depression are associated with distinct patterns of HPA axis activity. Cortisol abnormalities are not merely the consequence of depressive states or the stressors associated with its onset, as evident by data collected from the patient group, and depression plays a major role in the determination of the cortisol levels and vice versa. Thus, alteration of diurnal secretion of cortisol is a possible endophenotype of depression, as depressed patients show alterations in cortisol dynamics over the day as concluded from earlier studies.

The genetical and environmental susceptibilities to depression are expressed, in part, as (i) alterations in cortisol day curves evident by the elevated levels of cortisol secretion in the relatives group, and by the insignificant difference between them and patient group on scores of BADDS (low level of symptoms). (ii) The chronotype of the relatives group are mostly of neither morningness nor eveningness chronotype and eveningness chronotype is more than morningness chronotype. This finding is nearly alike in all patients group. Thus, hypersecretion of cortisol can be detected in asymptomatic individuals at genetic risk of depression and may represent an illness endophenotype.

We recommended that further studies are needed to find out whether increased cortisol levels can predict indivi-

dual risk of illness and whether the increased cortisol secretion has implications for general health and cognitive function.

There is no conflict of interest to declare.

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الملخص العربى

العلاقه بين النظم المداريه اليوميه و الصوره الاكلينيكبه لمرض الاكتئاب الجسيم:

دراسه على عينة مصريه

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حاول فريق البحث فحص مدى امكانيه اعتبار النظام المدارى اليومى لافراز هرمون الكورتيزول مؤشر حيوى يعتمد عليه فى حدوث مرض الاكتئاب الجسيم. وقد هدفنا فى هذا البحث لدراسه الاعتلالات المداريه اليوميه وارتباطها بالصوره الاكلينيكيه للمرض, سواء كان الاكتئاب مصحوبا باعراض ذهانيه ام لا او كان الاكتئاب ذو نسق ظاهرى تقليدى او غير تقليدى. ولتحقيق هذا الهدف تم فحص 14 مريضا بالاكتئاب الجسيم ترددوا للكشف بالعيادات الخارجيه لمستشفى جامعه المنصوره. و استطاع فريق البحث الحصول على موافقه 6 من أقارب المرضى المشاركين بعد الكشف عليهم لإستبعاد إصابتهم بأى إضطراب نفسى فعلى و6 من المتطوعين كمجموعه ضابطه. و قد تم سحب عينات دم من المرضى و أقاربهم و كذلك من المجموعه الضابطه على فترات متتاليه و متساويه أثناء اليوم (كل سته ساعات بدءا من الساعه الثانيه بعد الظهر ولمده 24 ساعه) لمتابعه النظام المدارى اليومى لإفراز الكورتيزول.و تم تطبيق مقياس بيك و هاملتون للإكتئاب على مجموعه المرضى وكذلك إختبار الميل الليلى و النهارى و إختبار المدى الطولى للإضطراب الوجدانى ثنائى القطب على مجموعه المرضى و أقاربهم. و خلصت نتائج البحث إلى وجود فرق إحصائى واضح بين مستويات إفراز الكورتيزول بين مجموعه المرضى و مجموعه الاقارب من الدرجه الأولى و كذلك المجموعه الضابطه. كما وجدنا علاقه ترابطيه واضحه بين مستويات الكورتيزول و أعراض مرض الإكتئاب الجسيم المختلفه كالميول الإنتحاريه و الميول الليليه و النهاريه. كما كانت العلاقه الترابطيه الواضحه مع الدرجات التى حصل عليها المرضى على مقياس بيك و مقياس هاملتون فى اكثر من توقيت لإفراز هرمون الكورتيزول , مؤشر حيوى يعتمد عليه فى مرض الإكتئاب الجسيم. ولكن تاكيد هذه النتائج يحتاج بعض الدراسات الجينيه التطبيقيه التى يمكن إجرائها مستقبلا.