

Serum creatine kinase level in unmedicated nonpsychotic, psychotic, bipolar and schizoaffective depressed patients

Michael Segal ^{a,*}, Avi Avital ^{b,c,1}, Marina Drobot ^a, Aida Lukanin ^a,
Andrei Derevenski ^a, Sergio Sandbank ^a, Abraham Weizman ^{d,e}

^a Flügelman's (Mazra) Mental Health Medical Center, Acre, Israel

^b Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

^c The Max Stern Academic College of Emek Yezreel, Israel

^d Research Unit, Gehah Medical Center and Felsenstein Medical Research Center, Petach Tiqva, Israel

^e Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Abstract Creatine kinase (CK) level was previously found to be increased in the majority of hospitalized acute psychotic patients. We aimed to assess the possible differences in CK level in various forms of depression: major with and without psychotic symptoms, of bipolar depression and schizoaffective depression. Unmedicated hospitalized patients participated: nonpsychotic major depression ($n=39$), psychotic major depression ($n=23$), bipolar depression ($n=23$) and schizoaffective depression ($n=24$). The severity of depression was assessed by the Hamilton Depression Rating Scale (Ham-D) and blood samples were collected in the morning of admission day, prior to any treatment. Ham-D yielded a significantly higher score for psychotic major depression group, compared with all other groups which showed similar score. CK serum level was significantly higher in nonpsychotic major depression than in all other forms of depression. The results indicate a biological difference between the nonpsychotic major depression and the “psychotic” cluster of depressive syndromes.

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1. Introduction

Nosologically, psychotic depression does not constitute a single diagnostic category. According to the Research Diagnostic Criteria (Spitzer et al., 1978; RDC), depressed

patients who manifest certain types of psychotic symptoms (i.e., the archetypal symptoms of schizophrenia, or first-rank symptoms) are classified as having schizoaffective disorder whereas those without such symptoms are classified as having psychotic major depression. Likewise, patients diagnosed as having major depression and those falling in the psychotic subtype are subclassified according to their psychiatric history as bipolar or unipolar. In contrast to major depression, schizoaffective disorder is not formally divided into bipolar and unipolar, although such a distinction

* Corresponding author. Tel.: +972 4 8321354; fax: +972 4 9812092.

E-mail address: mdsegalpsy@hotmail.co.il (M. Segal).

¹ Equal contribution.

may be useful for this disorder as is for classical bipolar and unipolar one (Breslau and Meltzer, 1988).

The assumption that major depression psychotic (MD psychotic) is a distinct syndrome from nonpsychotic MD is supported by reports of its familial transmission, association with poorer premorbid function, presenting features, biological measures, longer depressive episodes, lower responsiveness to antidepressant medication and worse prognosis (Sands and Harrow, 1994; Meyers, 1995). MD psychotic is estimated to be presented in up to 25% of consecutively depressed patients admitted to the hospital. The patients with psychotic depression were more likely to have bipolar depression, psychomotor disturbances, a family history of schizophrenia and a more severely disordered hypothalamic-pituitary-adrenocortical axis (Coryell et al., 1984). However, psychotic features in depressed patients often go overlooked because clinicians fail to adequately assess for these symptoms, and some patients may be underreported due to paranoid symptoms (Lykouras et al., 1986). Ohayon and Schatzberg (2002) observed that nearly 19% of subjects with major depression had psychotic features, consistent with other estimates of MD nonpsychotic and MD psychotic (Johnson et al., 1991). Psychotic symptoms such as nihilistic, guilty or somatic delusions and auditory hallucinations by definition are only present during depressive episodes, making MD nonpsychotic distinct from schizoaffective depression (SA depressed; Schatzberg and Rothschild, 1992).

In practice, relatively few studies have evaluated the neuropsychological functioning in MD psychotic compared with MD nonpsychotic patients. The clinical admixture of psychomotor-retarded melancholic signs and symptoms, "atypical" features and psychosis (less frequent) may provide a "bipolar signature" in clinical scenarios when there is uncertainty concerning the polarity of a depressive presentation (Mitchell et al., 2001). When investigated, three structural depressive subtypes (psychotic, melancholic and non-melancholic) appear functionally underpinned by differential contributions of serotonergic, noradrenergic and dopaminergic neurotransmitters, but understanding of the etiology of depression has been hampered by the absence of direct measurements of monoamines in humans (Delgado, 2000).

Existing data are inconsistent, often methodologically limited, and potentially confounded by the effects of chronic disease, age, hospitalization, severity of depression and exposure to antipsychotic treatments. Empirical evidence suggests that, compared with MD nonpsychotic, MD psychotic is associated with a higher rate of neurobiological alterations, such as structural brain abnormalities (Lesser et al., 1991; Rothschild et al., 1989; Shiraishi et al., 1992) and excessive

hypothalamic-pituitary-adrenal axis activity (Schatzberg et al., 1983; Anton, 1987). Increased levels of cortisol have been related to neurological changes that include cortical atrophy, ventricular enlargement and smaller hippocampi (Gomez et al., 2006). The monoamine hypothesis of depression predicts that the underlying pathophysiologic basis of depression is depletion in the levels of serotonin, norepinephrine and/or dopamine in the central nervous system. However, intensive investigation has failed to find convincing evidence of a primary dysfunction of a specific monoamine system in patients with major depressive disorders (Duval et al., 2000).

One possibility for a better understanding of the neurobiological dysfunction associated with psychotic depression involves comparison with clinically related conditions like nonpsychotic depression, with which it shares affective symptoms (Hill et al., 2004) or the bipolar depression and the schizoaffective disorder with which it shares affective and/or psychotic symptoms.

Patients with major depression showed higher levels of plasma catecholamine and serum cortisol in Dexamethasone Suppression Test (DST). Interestingly, these patients showed also lower serum creatine kinase (CK) activity (Sora et al., 1986).

Furthermore, increased serum CK activity was found in the majority of hospitalized acutely disturbed schizophrenia patients and patients with affective psychoses (Blumensohn et al., 1998).

It is probable that some of these increases do not result from nonspecific factors such as activity, trauma or stress, which do cause an increase in some cases (Meltzer et al., 1980).

Therefore, in the present study, we aim to assess the possible differences of CK serum level in various forms of depression: with and without psychotic symptoms, as well as of bipolar and schizoaffective origin.

2. Experimental procedures

Inpatients at least 18 years of age from the different psychiatric wards of Flügelman's (Mazra) Mental Health Medical Center participated in the study.

Subjects were 109 consecutively admitted unmedicated patients (1st episode and recurrent): 39 nonpsychotic major depression (MD nonpsychotic), 23 with psychotic major depression (MD psychotic), 23 bipolar depressed (BP depressed) and 24 schizoaffective depressed (SA depressed). All participants underwent a Structured Diagnostic Interview for DSM-IV (SCID) (First et al., 1994) and met the DSM-IV criteria (American Psychiatric Association, 2000) for a first episode or recurrent major depression. All patients had a score

Table 1 The mean age ($\pm$ S.D.) and the gender of the patients in the different groups

		Age		Gender	
		Mean	S.D.	Female	Male
MD nonpsychotic	1st ($n=21$)	48.43	± 13.59	9	12
	Recurr ($n=18$)	53.61	± 11.62	10	8
MD psychotic	1st ($n=15$)	43.67	± 19.25	10	5
	Recurr ($n=8$)	45.13	± 10.17	8	0
BP depressed	1st ($n=23$)	49.70	± 12.76	13	10
SA depressed	1st ($n=24$)	37.58	± 11.88	16	8

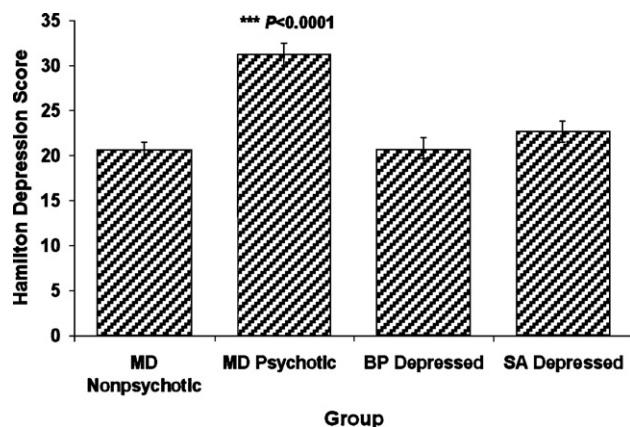


Figure 1 The psychotic depression group showed a significant higher score in Hamilton Depression Rating Scale yielded, compared with all other three groups which showed similar score.

of at least 14 on the 17-item Hamilton Depression Rating Scale (Hamilton, 1960).

The Ham-D's items of retardation (psychomotor slowness) or agitation and the CK level were examined in order to look for any correlation between these measures.

The patients were in good physical health as determined by a physical examination, routine laboratory assessment and a 12-lead ECG.

Patients were excluded from the study if they had a current DSM-IV axis I diagnosis other than major depression (psychotic or nonpsychotic), bipolar or schizoaffective disorder currently depressed. Other forms of schizophrenia, alcohol or drug abuse within 3 months, physical illness including any endocrine or cerebral pathology, drug or alcohol abuse and pregnancy and post-partum depression were also excluded.

All the first-episode MD nonpsychotic and MD psychotic subjects were untreated; the recurrent patients had received no antidepressants or mood stabilizers for at least 1 month, oral antipsychotic treatment for at least 3 months and no depot antipsychotics for at least 6 months. None of the patients has a history of MAOI treatment.

Ham-D was completed on admission. Blood samples for serum CK determination were collected between 8 and 9 a.m. in the admission day on a routine blood chemistry screening, prior to any medication. The diagnosis of various forms of depression was made by two senior psychiatrists, who were blinded to CK serum levels, according to the DSM-IV-TR criteria.

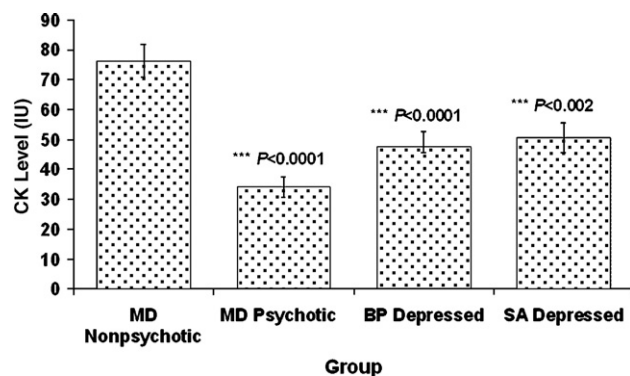


Figure 2 CK level was significantly higher in MD nonpsychotic group than in all other forms of depression, i.e.: MD psychotic, BP depressed and SA depressed groups.

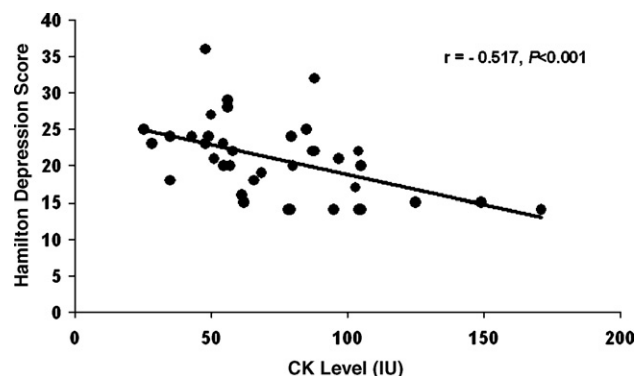


Figure 3 A significant correlation [$R_p = -0.517$, $P < 0.001$] was found between the severity of the depressive episode (i.e., Hamilton Depression Rating Scale score) and the CK level in MD nonpsychotic patients.

The study protocol was approved by the Ethical Local Board Committee of Flügelman's (Mazra) Mental Health Center, Acre.

After complete description of the study to the subjects, written informed consent was obtained from all participants.

3. Results

Table 1 shows the mean age ($\pm$ S.D.) and the gender of the patients in the different groups.

Ham-D scale yielded a significant higher score for the psychotic depression group, compared with all other three groups which showed similar score (Fig. 1, $P < 0.0001$).

CK serum levels were found to be within the normal range. However, a significant difference was found between the groups [Fig. 2; $F(3,105) = 13.55$, $P < 0.0001$]. Specifically, CK level was significantly higher in MD nonpsychotic group than in all other forms of depression, i.e., MD psychotic ($P < 0.0001$), BP depressed ($P < 0.0001$) and SA depressed ($P < 0.002$) groups. There were no significant differences in CK levels between the MD psychotic, BP depressed and SA depressed patients.

Moreover, a significant correlation [$R_p = -0.517$, $P < 0.001$] was found between the severity of the depressive episode (i.e., Ham-D's score) and the CK level in MD nonpsychotic patients (Fig. 3).

No significant correlation was found between CK levels and Ham-D's motor-activity items. Finally, no significant difference was found between first episode and recurrent patients in all measures.

4. Discussion

Our results on CK serum level indicate for the first time a clear biological distinction between the nonpsychotic and the psychotic forms of depression. It seems that like the MD psychotic, the SA depressed and the BP depressed have a common pattern illustrated by a similar CK level in unmedicated patients. Contrary to previous reports on high CK level of new admitted psychotic patients (Zweig et al., 1981; Blumensohn et al., 1998; Terao et al., 1999), we show a relatively "low-normal" CK levels in unmedicated patients. Thus, we suggest the existence of a psychotic depressions

cluster (MD psychotic, BP depressed and SA depressed) with different pathophysiological traits than that of the MD Nonpsychotic. Our results are in accordance with the study of Breslau and Meltzer (1988) in which they found that patients with psychotic depression diagnosed according to RDC (Spitzer et al., 1978) as schizoaffective, bipolar or unipolar were indistinguishable in gender, race and age at onset. They found little support for the validity of separating symptomatic psychotically depressed patients into those with schizoaffective or nonschizoaffective psychotic depression. They concluded that schizoaffective depression, mainly affective, is closely related to unipolar and bipolar psychotic depression and that the last two affective psychoses are essentially similar in depressive and psychotic symptoms, with the exception of hypomania, that is more common in bipolar patients.

Alternatively, Halbreich (2006) hypothesized that endocrine abnormalities may be more specific to clusters of symptoms (syndromes or dimensions) across current nosological entities. We suggest that CK level albeit being in the normal range may be referred to as one of the "biological markers" of MD nonpsychotic. Another hypothesis (Halbreich, 2006) views the endocrine abnormalities as a generalized nonspecific imbalance of the central nervous system. Creatine was recently (Andres et al., 2005) identified as a potent natural survival and neuroprotective factor for developing nigral dopaminergic neurons. Creatine supplementation improves the function of the creatine kinase/phosphocreatine system by increasing cellular creatine and phosphocreatine levels, the rate of ATP re-synthesis and maintaining cellular-energy homeostasis (Jost et al., 2002). Miura et al. (1999) showed that CK was sharply inhibited by dopa and dopamine in the presence of ferrylmyoglobin. Neural mechanisms mediated by hypothalamic dopamine activity and by the autonomic nervous system may be contributors to the elevation of serum CK in Parkinson's disease (Takubo et al., 2003), especially in advanced cases, where dopamine control may be unstable in a few locations of their brain. Some pathological phenomenon related to the disease may elicit imbalance of dopamine in patients' brain and induce CK elevation as in the similar condition in which neuroleptics are administered (Shimoda-Matsubayashi et al., 1996). Massive increases of CK were reported during the course of treatment with antipsychotic drugs (Meltzer et al., 1996).

The Meltzer's hypothesis was that increase of CK might be related to serotonin (5-HT), because the drugs that produced this type of increase in serum CK activity shared relatively more potent 5-HT_{2A} than dopamine D₂ antagonism (Meltzer et al., 1989). Fluctuating levels of endogenous 5-HT_{2A} modulating activity, at the level of gene expression, receptor synthesis or turnover, might cause the increase in CK activity during acute psychosis (Meltzer, 2000).

Our results showed "low-normal" CK levels, especially for the psychotic depressions. Thus, we postulate that in these cases CK is activated in an opposite direction by the "low serotonergic-high dopaminergic" imbalance. Furthermore, the inverse correlation between the Ham-D scores and the CK level in MD nonpsychotic patients suggests a relatively higher serotonin activity and less depressive symptoms. Taken together, pre-treatment serum CK level may serve as a peripheral biological indicator for the severity of depression and for the serotonin-dopamine balance in depression.

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