

# Creatine kinase levels in patients with bipolar disorder: depressive, manic, and euthymic phases

## Comparação das fases de depressão, mania e eutímia sobre os níveis de creatina quinase em pacientes bipolares

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### Abstract

**Objective:** Bipolar disorder is a severe, recurrent, and often chronic psychiatric illness associated with significant functional impairment, morbidity, and mortality. Creatine kinase is an important enzyme, particularly for cells with high and fluctuating energy requirements, such as neurons, and is a potential marker of brain injury. The aim of the present study was to compare serum creatine kinase levels between bipolar disorder patients, in the various phases (depressive, manic, and euthymic), and healthy volunteers. **Method:** Forty-eight bipolar patients were recruited: 18 in the euthymic phase; 17 in the manic phase; and 13 in the depressive phase. The control group comprised 41 healthy volunteers. The phases of bipolar disorder were defined as follows: euthymic—not meeting the DSM-IV criteria for a mood episode and scoring < 8 on the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS); manic—scoring < 7 on the HDRS and > 7 on the YMRS; depressive—scoring > 7 on the HDRS and < 7 on the YMRS. Patients in mixed phases were excluded. Blood samples were collected from all participants. **Results:** Creatine kinase levels were higher in the manic patients than in the controls. However, we observed no significant difference between euthymic and depressive patients in terms of the creatine kinase level. **Conclusion:** Our results suggest that the clinical differences among the depressive, manic, and euthymic phases of bipolar disorder are paralleled by contrasting levels of creatine kinase. However, further studies are needed in order to understand the state-dependent differences observed in serum creatine kinase activity.

**Descriptors:** Case-control studies; Bipolar disorder; Water level measurement/adverse effects; Creatine kinase; Depression

### Resumo

**Objetivo:** O transtorno do humor bipolar é uma doença psiquiátrica grave, recorrente e crônica associada a significativo prejuízo funcional, morbidade e mortalidade. A creatina quinase tem sido proposta como um marcador de dano cerebral. A creatina quinase é uma enzima importante principalmente para células que necessitam de uma grande quantidade de energia, como os neurônios. O objetivo do presente estudo foi comparar os níveis de creatina quinase entre as fases depressiva, maníaca e eutímica de pacientes com transtorno do humor bipolar. **Método:** Para avaliação dos níveis de creatina quinase no soro, 48 pacientes bipolares foram recrutados; 18 estavam eutímicos, 17 estavam em mania e 13 em episódio depressivo. Foi feita também uma comparação com um grupo controle que incluiu 41 voluntários saudáveis. Grupo eutímico: foram incluídos os pacientes que não cumpriam os critérios do DSM-IV para episódios de humor e deveriam ter a pontuação inferior a oito nas escalas de avaliação de mania (YMRS) e depressão (HDRS); grupo mania: foram incluídos os pacientes que apresentavam YMRS > 7 e HDRS < 7; grupo depressão: foram incluídos os pacientes que apresentavam HDRS > 7 e YMRS < 7. Os pacientes em episódios mistos não foram incluídos no estudo. Amostras de sangue foram coletadas de todos os participantes. **Resultados:** Durante a mania, os níveis de creatina quinase foram aumentados em comparação com voluntários saudáveis. Entretanto, não houve diferença significativa nos níveis de creatina quinase em pacientes eutímicos e depressivos, quando comparados com o grupo controle. **Conclusão:** Nossos resultados sugerem que as fases maníaca, depressiva e eutímica do transtorno do humor bipolar, além de apresentarem sintomatologia distinta, também podem ser diferenciadas pelo nível de creatina quinase presente no sangue do paciente. Entretanto, mais estudos são necessários para entender as diferenças observadas na atividade da creatina quinase durante as fases do transtorno do humor bipolar.

**Descritores:** Estudos de casos e controles; Transtorno bipolar; Medição de níveis/efeitos adversos; Creatina quinase; Depressão

### Introduction

Bipolar disorder (BD) is a severe, recurrent, and chronic psychiatric disorder that is associated with suicide, as

well as with significant functional impairment and morbidity. Patients with BD typically experience recurrent

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changes in mood, including manic, depressive, and mixed episodes.<sup>1-3</sup>

Creatine kinase (CK), an enzyme that catalyses the reversible transphosphorylation of creatine by adenosine triphosphate, plays a key role in energy buffering and energy transport, particularly in cells with high and fluctuating energy requirements, including neurons.<sup>4</sup> CK is found mainly in the skeletal muscle, heart, and brain; substantially elevated serum levels of CK usually indicate damage or stress in one or more of these. Enhanced serum CK activity is found also in a substantial proportion of patients hospitalized with acute schizophrenia or affective psychosis.<sup>5-10</sup> A recent study of BD patients demonstrated that serum CK levels were higher in manic patients than in depressive patients. Likewise, when tested within the same patient, serum CK levels were found to be higher during the manic phase than in the depressive phase. In agreement with this, it has been demonstrated that CK levels increase in the cerebrospinal fluid and serum of BD patients after an acute episode.<sup>11,12</sup>

Despite recent data indicating that serum CK levels are elevated in BD, we found no studies evaluating CK levels in manic, depressive, and euthymic BD patients. Therefore, this study was designed to investigate whether changes in serum CK levels are associated with mood episodes.

## Method

### 1. Subjects

The present study was approved by the *Ethics Committee* in Human Research of *Universidade do Extremo Sul de Santa Catarina* (UNESC), protocol number: 42/2008. We evaluated 48 patients with BD type I, recruited from among those enrolled in the Bipolar Disorders Program of the *Hospital de Clínicas de Porto Alegre*, located in the city of Porto Alegre, Brazil. Of those 48 patients, 18 were in the euthymic state, 17 were in the manic state, and 13 were in the depressive state. We also recruited a comparison group of 41 healthy volunteers. Psychiatric diagnoses were based on clinical interviews and were confirmed with the structured clinical interview for DSM-IV Axis I personality disorders (SCID-I). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS), respectively. Acute manic or depressive episodes were defined by DSM-IV-TR criteria. Patients were divided into three groups as follows: euthymic—patients who did not meet the DSM-IV criteria for a mood episode and who scored < 8 on the HDRS and YMRS; manic—patients who scored < 7 on the HDRS and > 7 on the YMRS; and depressive—patients who scored > 7 on the HDRS and < 7 on the YMRS. Patients in mixed phases were excluded. The healthy volunteers were screened for psychiatric disorders using the SCID-I, non-patient version. The healthy subjects were not on medication and had no history of major psychiatric disorders, dementia, or mental retardation. Any individual (patient or control) who had a medical condition that could result in elevated CK levels—including acute kidney injury, heart disease and musculoskeletal disorders—was excluded, as were those who had received intramuscular injections.

### 2. Determination of serum CK levels

From each subject, 5 mL of blood were drawn by venipuncture into an anticoagulant-free vacuum tube. The blood was immediately centrifuged at  $3000 \times g$  for 5min, and the serum was stored at

$-80^{\circ}\text{C}$  for subsequent assay. The reaction mixture for CK assay contained 100mmol/L of Tris-HCl buffer, pH 7.5, 30mmol/L of phosphocreatine, 20mmol/L of glucose, 12mmol/L of magnesium acetate, 10  $\mu\text{mol/L}$  of diadenosine pentaphosphate, 15mmol/L of sodium azide, 20mmol/L of *N*-acetylcysteine, 2mmol/L of adenosine diphosphate, 5mmol/L of adenosine monophosphate, 2mmol/L of nicotinamide adenine dinucleotide, 3500U/L of hexokinase, 2000U/L of glucose-6-phosphate dehydrogenase, and approximately 1.5 $\mu\text{g}$  of protein, in a final volume of 1200 $\mu\text{L}$ . The CK activity was calculated based on the appearance (formation) of reduced nicotinamide adenine dinucleotide, monitored with a spectrophotometer at 340nm at  $37^{\circ}\text{C}$ . The upper limit of normal for CK is 150U/L for women and 175U/L for men.<sup>13</sup>

### 3. Statistics

Descriptive analyses are presented as number and percentage. Demographic and clinical characteristics were analyzed using the chi-square test and ANOVA, as necessary. Levels of CK were analyzed by one-way ANOVA, followed by Tukey's post hoc test when the F value was significant, and are expressed as mean and standard deviation. All analyses were performed with the Statistical Package for the Social Sciences 17.0 (SPSS Inc., Chicago, IL, USA). The level of significance was set at  $p < 0.05$ .

### 4. Ethics

The study design was approved by the local research ethics committee, and all participants gave written informed consent.

### Results

Demographic and clinical characteristics of the patients and controls are presented in Table 1. All groups were homogeneous regarding age and sex. No statistical difference was found between the BD phases in terms of years since diagnosis or number of manic or depressive episodes. Serum CK levels were significantly higher in the manic patients than in the controls ( $2.12 \pm 0.42$  vs.  $1.84 \pm 0.26\text{U}/\mu\text{L}$ ,  $p = 0.013$ ; Figure 1). In addition, CK levels were significantly lower in the depressed patients ( $1.72 \pm 0.16$ ) than in the manic patients ( $p = 0.005$ ). Furthermore, CK levels in the depressive and euthymic patients ( $1.89 \pm 0.33$  for the latter) did not differ significantly from those observed for the controls.

### Discussion

Our results show that serum levels of CK are higher in manic BD patients than in healthy control subjects. Although CK levels were higher in the manic patients than in the depressed patients, the levels observed in the latter group did not differ significantly from those obtained for the controls. One of the most important findings of the study is that there was no significant difference between the euthymic patients and the controls in terms of the serum CK levels. In clinical practice, serum CK is measured as a marker of myocardial infarction (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy, and acute kidney injury. In view of this, it should be borne in mind that the elevated serum CK levels seen in the manic patients evaluated here might simply represent increased motor activity.

In agreement with our findings, Segal et al. showed that CK levels are higher in manic patients than in those who are depressed.<sup>11</sup> In addition, cerebrospinal fluid and serum levels of CK have been shown to increase in BD patients after an acute episode.<sup>12,14,15</sup> Furthermore, there is strong evidence that

**Table 1 - Characteristics of the patients and controls**

Characteristic	Control group (n = 41)	Bipolar disorder patients			p-value
		Euthymic (n = 18)	Manic (n = 17)	Depressed (n = 13)	
Female, n (%)	28 (68.3)	15 (83.3)	14 (82.4)	10 (76.9)	0.53*
Age, mean ± SD	42.5 ± 11.39	39.71 ± 3.37	40 ± 11.94	50.33 ± 10.99	0.09**
HDRS score, mean ± SD		3.59 ± 1.42	6.75 ± 2.05	18.23 ± 9.28	0.001**
YMRS score, mean ± SD		5.94 ± 1.09	35.19 ± 9.74	2.38 ± 1.71	0.001**
Years since diagnosis, mean ± SD		17.57 ± 9.19	17.12 ± 8.16	21.6 ± 10.10	0.724**
Number of manic episodes, mean ± SD		13.5 ± 8.48	14.5 ± 8.22	10 ± 7.5	0.543**
Number of depressive episodes, mean ± SD		15.66 ± 12.82	12 ± 3.39	13.57 ± 5.96	0.691**
Creatine kinase levels (U/μL), mean ± SD	1.84 ± 0.26	1.89 ± 0.38	2.12 ± 0.41	1.72 ± 0.15	0.005**

HDRS = Hamilton Depression Rating Scale. YMRS = Young Mania Rating Scale. \*Chi-square test. \*\*One-way ANOVA and Tukey's post hoc test.

metabolic impairment and mitochondrial dysfunction are involved in the pathophysiology of BD.<sup>16-20</sup> The phosphocreatine/CK energy circuit, which is important for maintaining normal energy homeostasis,<sup>21,22</sup> has a number of integrated functions, such as temporary energy buffering and energy transfer, as well as regulating metabolic capacity.<sup>23</sup> In view of these data, we can suggest that the increased CK activity seen in manic BD patients is a compensatory mechanism related to the mitochondrial damage that occurs in BD.

Soni et al. evaluated patients suffering from a variety of psychoses and graded those patients on the basis of the degree of psychomotor activity.<sup>24</sup> Serum creatine phosphokinase (CPK) levels were found to be related to the degree of psychomotor activity, irrespective of the diagnostic category. Retarded patients and withdrawn patients had normal serum CPK, but transitory increases in CPK were observed as those patients returned to normal psychomotor activity, suggesting that nonphysiological motor activity is more directly related to the rise of serum CPK than is motor activity *per se*. However, a postmortem study<sup>25</sup> showed that expression of CK

mRNA is decreased in the hippocampus and dorsolateral prefrontal cortex of BD patients. In addition, decreased CK activity has been reported in a rat model of d-amphetamine-induced mania.<sup>20</sup> That finding could be explained by the fact that increased dopamine activity inhibits CK. In a clinical study of patients with bipolar I or II disorder (BP I or BP II),<sup>26</sup> brain phosphorus metabolism was measured by phosphorus-31 magnetic resonance spectroscopy. The authors found that phosphocreatine levels were significantly lower in the BP II patients, regardless of the BD phase, than in a group of normal controls, suggesting that brain high-energy phosphate metabolism is impaired in BP II and that there are pathophysiological differences between BP I and BP II.

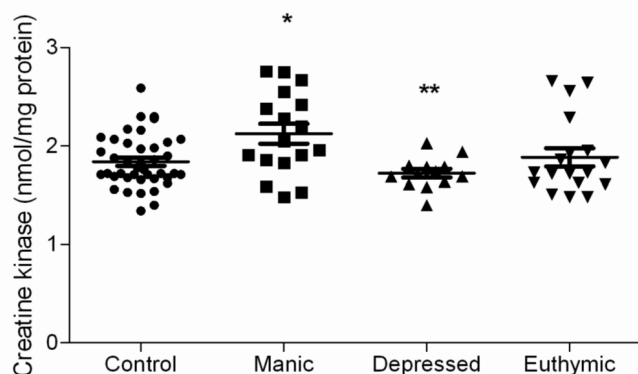
To our knowledge, this is the first study of its type to include euthymic patients. The inclusion of such a group could provide data about the persistence of altered serum CK levels during remission. However, because our sample was small, the present study did not have sufficient power to detect possible differences between the groups. Another limitation of our study is that we did not evaluate the effects that mood stabilizers or other drugs have on CK activity. However, it is of note that we compared the BD (phase) subgroups with the control group. The fact that the levels of the CK in the euthymic BD patients were comparable to those observed for the controls might indicate that alterations in CK levels are associated with acute mood episodes, especially acute mania. Although CK activity does not explain the entire psychiatric profile, it does shed light on certain topics including the potential development of alternative treatments and the possibility that treatment response could be monitored more specifically by measuring the levels of biological markers in plasma.

### Conclusion

In conclusion, our results suggest that the clinical differences among the depressive, manic, and euthymic phases of BD are paralleled by contrasting levels of CK. However, further studies are needed in order to understand the state-dependent differences observed in serum CK activity.

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**Figure 1 - Serum creatine kinase levels in the depressive, manic, and euthymic phases of bipolar disorder and in controls.** Data were analyzed by one-way ANOVA, followed by Tukey's post hoc test when F was significant.

\* $p = 0.013$ , control vs. manic; \*\* $p = 0.005$ , manic vs. depressed.

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## Disclosures

Writing group member	Employment	Research grant <sup>1</sup>	Other research grant or medical continuous education <sup>2</sup>	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other <sup>3</sup>
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\* Modest

\*\* Significant

\*\*\* Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author. Note: UNESC = Universidade do Extremo Sul Catarinense, UFRGS = Universidade Federal do Rio Grande do Sul; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESC = Fundação de Amparo à pesquisa do Estado de Santa Catarina; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

For more information, see Instructions for Authors.

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