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Original Research Article

A Comparative Study of Creatine Phosphokinase and its Fractions Among Drug-Naïve Patients with Schizophrenia, Bipolar Mania, Depression and Healthy Controls

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Conflict of interest: Nil

Abstract

Background: Serum CPK levels are elevated by several neural mechanisms mediated by hypothalamic dopamine and by autonomic nervous system. Creatine Kinase is an enzyme found predominantly in the heart, brain, and skeletal muscles, and can be considered a marker of brain injury. It is important to understand whether psychiatric disorders show reliable alterations in creatine metabolism, which is not just solely due to increased activity.

Methods: A cross-sectional hospital-based study was conducted at a tertiary psychiatric care center to measure and compare the serum Creatine kinase levels (CK-MM, CK-MB, CK-BB, and total CK Levels) across various psychiatric disorders. After sample size calculation, 80 participants were included, divided into 4 groups: 20 patients with Schizophrenia, Bipolar mania, and Depression each, and 20 healthy controls. Blood samples were collected and CK-NAC levels and fractions of CK were measured. Clinical assessment was done on BPRS scale. CK-NAC and CK Fractions were compared using appropriate statistical tests.

Results: The findings revealed no significant difference with respect to socio-demographic profile between the groups except for education and occupation. CK-NAC values were seen to be significantly higher in bipolar mania compared to healthy controls (p value-0.039). There was no significant difference among CK-MM, CK-BB & CK-MB fractions among the 4 groups.

Conclusion: Compared to healthy controls, patients with bipolar mania had higher CK-NAC values. No significant difference regarding the CK-fractions among the 4 groups was observed.

Keywords: Creatine kinase (CK), CK Fractions, Schizophrenia, Bipolar Mania, Depression.

Key Message

- The study highlights the biological underpinning of various psychiatric disorders using laboratory investigations like CPK and CK fractions levels.
- All patients and healthy controls were tested for CK-NAC level and the fractions-CK-MM, CK-BB and CK-MB.
- Though the fractions did not show a significant statistical difference, it was seen that the CK-NAC values were significantly higher in the bipolar patients group compared to the healthy control thereby suggesting the relevance of assessing Creatine Kinase in psychiatric disorders.

Introduction

Increased serum creatine phosphokinase (C.P.K.) levels was seen in psychotic patients of acute onset on admission to hospital [1]. Bengzon et al.,1996 reported among a group of 30 patients with schizophrenia, CPK elevations was observed initially which returned to normal during the course of treatment with phenothiazines [2]. The mean creatine phosphokinase level of 41 psychotic patients was significantly elevated than that of 30 nonpsychotic psychiatric patients, as were their MMPI paranoia and schizophrenia scores [3].

Serum creatine phosphokinase (CPK) and aldolase activities tested at admission and throughout hospitalization in 34 patients with Schizophrenia revealed that of the total, 22 patients had increased activity of one or both enzymes [4]. Also in another study, 25 acutely psychotic patients were found who had unexplained elevations of serum creatine phosphokinase (CPK); 14 of the 25, (56%) had a

clinical diagnosis of bipolar affective disorder, manic type [5]. The Creatine Kinase/ Phospho-Creatine system seems to play complex, multifaceted role in cellular energy homeostasis [6]. CK/CPK maintains high intracellular concentrations of ATP by a rapid re-phosphorylation of ADP at the expense of phosphocreatine [7]. Three iso-enzymes of CPK are known: a skeletal muscle type (MM), a cardiac muscle type (MB), and a brain type (BB). Skeletal muscle and brain have almost exclusively MM and BB type CPK, respectively, whereas cardiac muscle has a mixture of all three types [8].

The autonomic nervous system andneural mechanisms mediated by hypothalamic dopamine may be contributing to the elevation of serum creatine kinase [9]. Its substantial elevation was earlier related to injury, intramuscular injections, use of restrains, intense isometric activity, dystonic reactions or stress [10].The aggressive patients with schizophrenia displayed increased serum CK level. It may be useful to include a lab test of CK level in patients with schizophrenia and history of aggression [11].

Also in another study it was seen that 56% of 25 acutely psychotic patients who had unexplained CPK elevations had the diagnosis of bipolar affective disorder, manic type [12]. Also in a study by Feier et al., 2011 the Creatine kinase levels were higher in the manic patients than in the controls. However, no significant difference was observed between euthymic and depressive patients in terms of the creatine kinase level [13]. Post-mortem analyses also have revealed significant down-regulation of brain-type creatine kinase and ubiquitous mitochondrial creatine kinase mRNA levels in the Dorsolateral prefrontal cortex and hippocampus of bipolar patients compared with schizophrenic and healthy controls [14].

Rationale for the Study

This research was attempted to test CPK and its fractions in relation to various psychiatric disorders. Its elevation was previously related to trauma, injuries, use of intramuscular injections, physical restrains or excessive activity. However as seen in various studies, elevation of CPK has been reportedin Schizophrenia and few studies report elevated CPK in mood disorders or depressive disorders as well. Also the fractions of CK have not been extensively studied with respect to psychiatric illness. Hence this research intends to measure and compare the levels of CPK and its fractions among patients with Schizophrenia, Bipolar Mania, Depressive disorder and healthy controls. The current study was done with the hypothesis that CPK levels are higher in psychiatric disorders compared to healthy controls and CK Fractions can vary across psychiatric spectrum like Schizophrenia, Bipolar Mania and Depressive disorder. We aimed at measuring and comparing the CPK and its fractions (CK-MM, BB and MB) across 4 groups namely Schizophrenia. The objectives of the study were to measure and compare the serum creatine kinase levels (all three fractions- CK-MM, CK-MB, CK-BB and CK-NAC) in drug-naïve patients with Schizophrenia, Bipolar mania and Depression as well as in healthy controls and to assess any association with socio-demographic and clinical variables.

Methods

The study was conducted at a tertiary psychiatric care hospital. Patients of either sex of age group of 18 to 60years with diagnosis of schizophrenia, bipolar mania and depression (unipolar/bipolar depression) according to Diagnostic Criteria for Research of ICD-10 (WHO, 1993) and who were drug-naïve and healthy controls who satisfied the inclusion study were selected and divided into four groups accordingly. After sample size calculation 80 patients were recruited of which 20 patients of schizophrenia, 20 patients of bipolar affective disorder current episode manic with or without psychotic symptoms (bipolar mania), 20 patients of depression (both unipolar and bipolar depression) and 20 age and sex matched healthy controls fulfilling inclusion and exclusion criteria were recruited. Controls were screened for any psychiatric or physical abnormality with the help of 12 item General Health Questionnaire. Inclusion criteria for the participants included written informed consent, and for patient group those who met the diagnostic criteria as per ICD 10 DCR. Exclusion criteria for all groups included patients with muscular dystrophy, impaired renal function and history suggestive of Myopathy, Epilepsy, auto immune disease, Malignancy, Trauma, Sepsis, Renal disease, Myocardial infarction, Myocarditis. Intramuscular injections within previous 2 weeks before study participation, alcohol intake within the previous 24 hrs before study participation and history of drug intake like Statins, Fibrates, Dexamethasone, frusemide, and Amphotericin B was also excluded. Necessary socio-demographic and clinical information was collected by using structured socio-demographic sheet.

Blood sample was drawn in the morning. CK-NAC levels were measured using the biochemistry kit - modified procedure of the IFCC (International Federation of Clinical Chemistry) method [15] (Horder et al 1991) and the various fractions of CK was measured using ELISA. The kit used a double-antibody sandwich enzyme-linked immunosorbent one-step process to assay the level of Creatine Kinase – MM, MB and BB in samples.

BPRS-E was administered on the patients as a measure of psychopathology. It is a clinical rating

scale widely used in psychiatric clinical practise. Initially John Overall produced the Brief Psychiatric Rating Scale (BPRS) over a number of years in collaboration with a number of different researchers [16]. While originally only 16 items, the most popular version contained 18 symptom constructs. Later Lukoff et al. (1984) developed an expanded standardized version (BPRS-E) including six extra items (suicidality, elevated mood, bizarre behavior, self-neglect, distractibility and motor hyperactivity) in order to increase the coverage of the instrument and with defined scale points and probe questions in order to increase its interrater reliability which has been used in our study[17]. The 12 item General health questionnaire was applied on healthy controls to rule out psychopathology [18]. It is a self-administered screening test which is sensitive to the presence of psychiatric disorders in individuals presenting in primary care settings and non-psychiatric clinical settings. The GHQ is not designed to detect symptoms that occur with specific psychiatric diagnoses, rather, provide a measure of overall psychological health and wellness. Reference intervals for CK NAC: Male:< 171 U/L and Female:< 145 U/L. Assay range of CK-MM: 15.6pg/ml-1000pg/ml. Assay range of CK-MB: 31.2pg/ml-2000pg/ml. Assay range of CK-BB: 15.6pg/ml-1000pg/ml

Statistical Analysis: Statistical analysis was done using Statistical Package for Social Sciences (SPSS version 20.0). Categorical demographic variables were compared between all the three groups using Chi-Square Test/Fisher's exact test (wherever applicable) and the continuous demographic variables were compared using one-way ANOVA. One-way ANOVA and post-hoc Bonferroni were applied wherever significant difference were observed between the four groups.

Results

The socio-demographic profile (continuous), age of onset and the duration of illness were compared between the four groups using one-way ANOVA. As seen in Table 1 there was no significant difference between the groups with respect to age and age of onset. Post hoc bonferroni reveals there was significant difference between bipolar mania and depression with respect to duration of illness (BM>D, p value<0.05). The study also showed that there was no significant difference with respect to socio-demographic profile between the groups except for education and occupation (p value = 0.029 and 0.018 respectively) as described in table 2. The majority of patients with depression were educated till high school while the other 3 groups majority of them were educated less than high school. Majority of patients with schizophrenia were unemployed (30%) in comparison to the other groups. It was also seen that there was significant difference between the groups with respect to BPRS score (p value < 0.001). POST HOC Bonferroni analysis reveals that the BPRS score were significantly higher in Bipolar mania patients compared to patients with Schizophrenia and Depression (Table 3). Table 4 shows significant difference in CK-NAC value among the four study groups (p value -0.039). POST HOC Bonferroni analysis reveals that CK-NAC value is significantly higher in bipolar mania patients compared to healthy control. However, there was no significant difference between the groups with respect to CK-MM, CK-MB and CK-BB values (Table 5).

Table 1: Comparison of comparison of socio-demographic profile (continuous) between Schizophrenia, Bipolar mania, Depression and Healthy control group

Variables	' SCZ' group (N=20) (Mean ±SD)	'BM' group (N=20) (Mean ±SD)	'D' group (N=20) (Mean ±SD)	'HC' group (N=20) (Mean ±SD)	F	df	P	Post hoc
Age(yrs)	31.45±6.05	32.95 ± 9.85	35.15 ± 12.70	33.25± 8.44	0.505	76	0.68	-
Age of onset(yrs)	26.35 ± 5.78	26.45 ± 8.86	32.60 ± 12.73	-	2.804	53	0.069	-
Duration of illness (months)	60.10 ± 40.68	68.20 ± 63.90	28.28 ± 37.04	-	3.759	57	0.029*	'BM'> 'D'

* Significance at < 0.05. (2 tailed)

SCZ, schizophrenia patient; BM, bipolar mania patient; D, depression patient; HC, healthy controls.

Table 2: Comparison of socio-demographic profile (categorical) between the four groups

Variables		'SCZ' group (N=20) n (%)	'BM' group (N=20) n (%)	'D' group (N=20) n (%)	'HC' group (N=20) n (%)	X2	df	P
Gender	Male	15(75)	12(60)	9(45)	14(70)	0.214	3	0.081
	Female	5(25)	8(40)	11(55)	6(30)			
Education*	Illiterate	3(15)	3(15)	5(25)	1(5)	0.374	12	0.029
	< high school	8(40)	6(30)	2(10)	10(50)			
	High school	5(25)	5(20)	8(40)	5(25)			
	Intermediate	1(5)	1(5)	3(15)	1(5)			
	Graduate	3(15)	5(25)	2(10)	3(15)			
Marital Status	Unmarried	5(25)	5(25)	5(25)	3(15)	0.57	6	0.073
	Married	12(60)	14(70)	13(65)	17(85)			
	Others	3(15)	1(5)	2(10)	0(0)			
Religion	Hindu	15(75)	16(80)	17(85)	18(90)	0.69	6	0.05
	Muslim	3(15)	4(20)	2(10)	2(10)			
	Others	2(10)	0(0)	1(5)	0(0)			
Habitat	Rural	16(80)	18(90)	19(95)	17(85)	0.676	3	0.118
	Urban	4(20)	2(10)	1(5)	3(15)			
Socioeconomic status	Lower	16(80)	14(70)	20(100)	15(75)	0.046	3	0.069
	Middle	4(20)	6(30)	0(0)	5(25)			
	Upper	0(0)	0(0)	0(0)	0(0)			
Family type	Nuclear	16(80)	15(75)	16(80)	12(60)	0.465	3	0.054
	Joint	4(20)	5(25)	4(20)	8(40)			
Occupation*	Unskilled	3(15)	0(0)	0(0)	4(20)	0.082	12	0.018
	Semiskilled	5(25)	8(40)	9(45)	7(35)			
	Skilled	1(5)	3(15)	2(10)	2(10)			
	Unemployed	6(30)	1(5)	1(5)	1(5)			
	Housewife	5(25)	8(40)	6(30)	6(30)			

* Significance at < 0.05. (2 tailed)

SCZ, schizophrenia patient; BM, bipolar mania patient; D, depression patient; HC, healthy controls.

Table 3: Comparison of BPRS Score between 'SCZ', 'BM' and 'D' groups

Variables	'SCZ' group (N=20) (Mean ±SD)	'BM' group (N=20) (Mean ±SD)	'D' group (N=20) (Mean ±SD)	F	df	P	Post hoc
BPRS SCORE	52.20±6.06	60.20±9.89	35.45±5.84	56.805	57	0.000***	BM>SCZ>D

*** Significance at < 0.001 (2 tailed)

SCZ, schizophrenia patient; BM, bipolar mania patient; D, depression patient; HC, healthy controls.

Table 4: **Comparison of CK-NAC value between Schizophrenia, Bipolar mania, Depression and Healthy control group**

Variables	' SCZ' group (N=20) (Mean ±SD)	'BM' group (N=20) (Mean ±SD)	'D' group (N=20) (Mean ±SD)	'HC'group (N=20) (Mean ±SD)	F	Df	P	Post hoc
CK-NAC	519.15±646.64	888.42±1424.90	267.60±792.65	123.48±33.38	2.919	76	0.039*	BM>HC

* Significance at < 0.05 (2 tailed)

SCZ, schizophrenia patient; BM, bipolar mania patient; D, depression patient; HC, healthy controls.

Table 5: **Comparison of CK-MM, CK-MB and CK-BB values between Schizophrenia, Bipolar mania, Depression and Healthy control group**

Variables	' SCZ' group (N=20) (Mean ±SD)	'BM' group (N=20) (Mean ±SD)	'D' group (N=20) (Mean ±SD)	'HC' group (N=20) (Mean ±SD)	F	df	P
CK-MM	589.30±352.08	599.86±433.49	406.88±201.00	501.59±196.34	1.654	76	0.184
CK-MB	1110.96±837.83	1035.79±902.99	1320.10±713.87	999.05±383.64	0.758	76	0.521
CK-BB	722.68±747.25	709.70±751.90	448.94±154.26	459.40±147.30	1.569	76	0.204

SCZ, schizophrenia patient; BM, bipolar mania patient; D, depression patient; HC, healthy controls.

Discussion

Our study showed that there was no significant significance with respect to sociodemographic profile excepting education and occupation. It showed that majority of patients with depression were educated till high school, but the other three groups were educated less than high school. With respect to occupation, majority of patients with schizophrenia were unemployed (30%) as compared to the other groups. This was in accordance with an extensive literature on inadequate social adaptations in schizophrenia patients [16]. Various areas of everyday functioning and daily activities are affected in patients with Schizophrenia. These include significant deficiencies in social, vocational and residential domains, even during periods of remission from active psychosis [17].

In the past, increased serum CK levels are present during acute exacerbations of core psychoses with no evidence of muscle injury or agitation [18]. In a study by Taylor and Abichandani, 1980it was seen that 25 acutely psychotic patients were found to have unexplained elevations of serum CK out of which 56% had diagnosis of bipolar affective disorder, manic type [18]. These findings are consistent with our findings where bipolar mania patients have significant higher CK-NAC value compared to healthy controls. Our study showed statistical significance in CK-NAC value among the four study groups (p value -0.039). POST HOC Bonferroni reveals that CK-NAC Value was significantly elevated in bipolar mania patients, but the healthy control group had normal levels. Also, it was seen that patients with depression had lesser CK-NAC (267.60±792.65) compared to schizophrenia and bipolar mania groups. This was in accordance with previous studies that reported elevated CK levels in manic, depressive, and euthymic phases of bipolar affective disorder [13]. The past research indicates the increased serum CK levels to be present during acute exacerbations of psychoses [10] with no evidence of hyperactivity or trauma. Also, Segal et al. studied serum CK levels in various forms of depression and had reported low normal CK levels, especially in psychotic depressions [20]. Also it was seen that CK serum levels were lower in the depression state compared with the mania state in the same set of study subjects and was hypothesized that differences in CK levels between the manic and depressive state could suggest an interplay of distinct catecholamine activity, mainly of dopamine[20].It has also been studied that in psychiatric conditions, total CK values was increased up to 1500U/Lin 83.7% cases followed by 9.3% cases of psychosis, alcohol dependance, intellectual disability and catatonia had CK values between 1500 and 3000U/L and 6.9% cases of catatonia and alcohol dependence syndrome had total CK values above 3000U/l, irrespective of gender [21]. Thus a easy and rapid detection of serum CK activity provide a reliable additional screening tool in various psychiatric disorders especially in emergency settings and helps in taking immediate management decisions.

In healthy individuals, the total CK activity in the serum consists of CK-MM, nearly 80% [22]. In a study done by Segal et al., the total CK serum level was significantly higher in major depression without psychotic symptoms than in other forms of depression [23] however the individual subtypes of CK were not measured.This study also attempted to study the various variants of CK among the subject groups and it was seen that there was no difference between the groups with respect to CK-MM, CK-MB and CK-BB values statistically. This could be due to the lesser sample size and also there is a lack of literature with regards to the various fractions of CK and correlation to psychiatric illness and invites for further research in this regard.

Also another study was conducted on 102 patients having neurological and psychiatric disorders where data was gathered retrospectively in a tertiary neurosciences centre in a metropolitan city. The Blood samples in plain vial were sent to Emergency Laboratory and total CK levels were measured by automated analyzer. It was observed that CK activity was raised in various psychiatric conditions-acute transient psychotic disorder, alcohol dependence syndrome, delirium, chronic

psychotic, intellectual disability, catatonia, bipolar affective disorder (BAD), depression and mania[24]. The greater proportion of individuals with psychotic or affective disorders could perhaps reflect the greater potential for increased arousal and agitation in these disorders, with abnormally elevated CK activity previously demonstrated in a majority of inpatients with psychosis [25]. The exact mechanisms are unclear, but there is a consistent demonstration of elevated CK in inpatients with psychosis, with a suggestion that it could even function as a biomarker for illness severity [25].

Strengths: The study attempted to measure and compare CK and its fractions across different psychiatric disorders. Considering the paucity of literature regarding the relation of CK fractions to psychiatric disorders, the study attempted to understand the neurobiologic underpinning of psychiatric disorders with respect to Creatine kinase and its fractions which could be used as a tool for early diagnosis and management.

Limitations: The relatively smaller sample size and the Cross sectional nature of the study could be considered a drawback of the study. CPK activity in different phases of bipolar disorder that is manic and depressed phase in same individual (longitudinal course) was not studied. Further research is required to understand the state-dependent differences in serum CPK levels in different phases of bipolar disorder.

Future Directions: Gender difference could be comprehensively studied with respect to CPK and Serum vitamin B12 with a sufficient sample size. Also further studies are required for assessing various fractions of CK- CK-MM, MB and BB in psychiatric illnesses to establish a conclusive finding.

Conclusion

CK-NAC values were seen to be higher in subjects with bipolar mania compared to healthy controls. The individual CK type showed no statistical significance and further research is required to give a conclusive finding. Thus assessing CK levels could be useful in early identification as well as help in management of psychiatric disorders.

Declaration of Conflicting Interests: None.

Ethical Approval and Informed Consent: The study received approval from the Institutional Ethics Committee. Participants who were willing to participate in the study and gave informed consent were recruited in the study.

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