

Original Research Article

# Elevated serum cortisol level and its cut off value in major depressive disorder in an urban metropolitan area: A case control study.

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## ABSTRACT

**Background:** Major depressive disorder (MDD) is associated with several biochemical changes including altered cortisol levels in body fluids which heralds more complications related to the disease. However, this alteration is not uniform and varies depending on several factors. The present study was undertaken to ascertain any change in serum cortisol levels in MDD patients in our study population along with an effort to find out a cut off value for it for delineating between these patients and normal healthy subjects.

**Methodology :** In a case control study, serum cortisol levels were measured by ELISA technique from morning blood samples in 37 MDD cases and 39 matched control subjects. A receiver operating characteristic (ROC) curve analysis was used for determining the cut off value of serum cortisol levels between the case and control groups.

**Results :** Serum cortisol levels were found significantly higher ( $14.1 \pm 3.90 \mu\text{g/dL}$ ) in the MDD group compared to the values in the control subjects ( $7.85 \pm 2.5 \mu\text{g/dL}$ ). ROC analysis showed a cut off value of  $9.95 \mu\text{g/dL}$  for serum cortisol level in the MDD patients.

**Conclusion:** The present study observed significantly raised serum cortisol levels in an urban MDD patient group residing in a metropolitan area. Raised serum cortisol values indicate a more severe state of MDD and thus accounts for an aggressive management at an earlier state. A cut off value of  $9.95 \mu\text{g/dL}$  as indicated in our present study may help in finding hypercortisolic MDD patients at an early stage and formulate an appropriate management protocol appropriately for a better clinical outcome.

## Introduction:

Major depressive disorders (MDD) is one of the commonest psychiatric disorders in the world with a prevalence varying from 8% to 12% throughout the world. In the United States, it is one of those having the worst impact on biomedical disability while in Europe it is the third leading cause for such. MDD is characterized by depressed mood, lack of interest in the surroundings, sleep disturbances, memory bias to negative information, feelings of undue fatigue and guilt and most importantly lack of initiation for work and feeling of worthlessness that is sometimes accompanied by recurrent suicidal thoughts. Several biochemical parameters are altered in major depression. Low levels of serum total cholesterol, low levels of LDL cholesterol in blood, low magnesium levels, deranged catecholamines e.g. serotonin, nor-epinephrine and dopamine in the central neuronal circuit, altered neuroendocrine status like decreased oxytocin and increased cortisol levels have been reported in various studies throughout the world. As major depression is supposed to alter the Hypothalamic-Pituitary-Adrenal (HPA) system as evidenced by the dexamethasone suppression test, it is associated with several clinical features linked to a deranged HPA axis e.g. cognitive dysfunction, changes in diurnal variations etc.

However, different studies reported elevated cortisol levels in different body fluids. Hoifodt et al (2019) reported increased salivary cortisol levels without any elevated morning blood cortisol level in MDD patients. On the other hand, Tang et al (2019) reported a definite

inverse relationship with plasma cortisol level and quality of life in MDD. But importantly, both of these observations indicate towards elevation of cortisol in body fluids in MDD patients that may be monitored effectively as an overall management protocol in these patients. It is quite understandable from these studies that regarding the association between cortisol level and the severity of MDD, it is the variability of different stress factors, environmental factors and ethnic factors that counts more rather than the magnitude of the cortisol response associated with MDD. Hence, cut off values for determining hypercortisolic states should also vary significantly among different geographical areas based on the environmental and ethnic factors. However, we got only a few studies regarding any cut off value of serum cortisol levels between MDD patients and normal persons that could enable this monitoring more effectively.

Keeping these facts in mind, we hypothesized to find a higher serum cortisol level in our study population. We also tried to find out a definite cut off value of cortisol levels in blood that could help to differentiate the MDD subjects with their matched control subjects without any such disorder.

## Materials And Methods :

### Study design :

The present study was designed as a case control analytical study undertaken from January 2020 to July 2020 in the Departments of Psychiatry and Biochemistry of a tertiary care hospital in Eastern India.

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**Selection of study subjects :**

Cases were selected following the method of convenience from the Psychiatry outpatient department (OPD) of a tertiary care hospital of a metropolitan city in Eastern India i.e all subjects attending the concerned OPD fulfilling the inclusion and exclusion criteria within the stipulated study period were selected. Diagnosis of MDD and exclusion of other psychiatric disorders were made by qualified psychiatrists using the DSM-V guidelines and its severity was assessed by using the Hamilton Depression rating scale. The inclusion criteria for the cases were: i) MDD diagnosed according to the DSM-V guidelines, ii) patients diagnosed as MDD for the first time who did not receive any treatment for it earlier, iii) both male and female MDD patients falling in the adult age group with a matured HPA axis i.e form 20 yrs to 45 yrs of age group. On the other hand, the exclusion criteria followed were: i) patients suffering from any other psychiatric disorder than MDD and mental retardation, ii) patients suffering form any metabolic or endocrine disorders or abnormal BMI, iii) patients suffering from any acute or chronic inflammatory diseases or any malignant disorders, iv) pregnant population and females on OCP therapy, v) patients having any history of any substance abuse.

Control subjects were selected from the healthy population in a age and sex matched manner from the same geographical area having similar socioeconomic and nutritional status using a pre-designed questionnaire.

**Ethical consideration :**

The study was undertaken after obtaining the ethical permission from the institutional ethics committee. Informed consent was taken from each participant. The study adhered strictly to the Helsinki Declaration and ICMR guidelines for human studies.

**Estimation of biochemical parameters:**

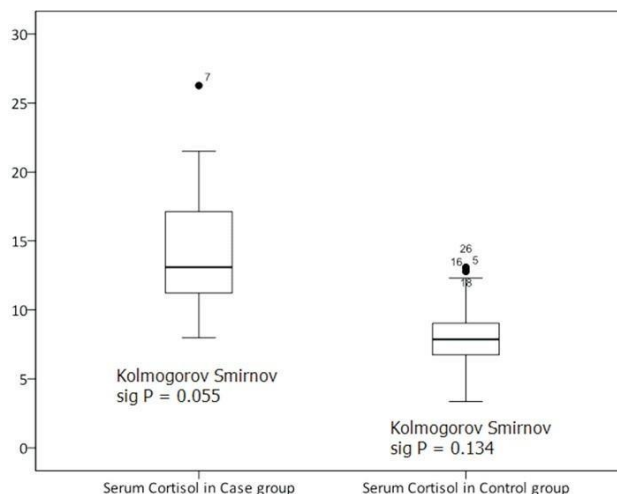
Serum total cortisol was estimated from the morning blood sample drawn between 8 am to 9 am after an overnight fast of 8 – 10 hours, using immunoassay technique. 5 ml of venous blood was collected in aseptic conditions and serum was allowed to separate and collected. The serum was stored at -200 centigrade till the assay was performed. Serum cortisol was measured using competitive ELISA technique using reagents kits obtained from Accubind, USA and were stored at 2 to 80 C for a maximum period of 2 months after reagent preparation as recommended. A calibration curve was obtained using the provided calibrators of 0, 1.0, 4.0, 10.0, 20.0 and 50.0 µg/dl concentrations. The measurement was done using the automated ELISA reader and washer from Tecan, Austria. The samples showing values of 50 µg/dl were re-measured by diluting them further 1:5 and 1:10 using cortisol 0 µg/dl calibrator reference materials. The detection limit of this assay system was 0.366 µg/dl and the cross reactivity with other gonadal steroids was minimal or not detectable. Precision of the assay technique was monitored by maintaining the coefficient of variation (CV) below 5 percent throughout the study period. The reference range of the morning samples was noted to be 5-23 µg/dl with this reagent kit.

**Statistical methodology:**

Data were collected and handled as per standard guidelines. The data obtained from the case and control subjects were compared for their serum cortisol levels and were analyzed further to find out a cut off value that could differentiate between the serum cortisol levels between the case and control groups with a maximum sensitivity and minimum false positivity. Data were first analysed for their pattern of distribution and were found to follow normal distribution pattern as determined by the Smirnov Kolmogorov test (P > 0.05). For the comparison between two data groups student t test was performed whereas for obtaining the cut off value receiver operating characteristic curve (ROC) was used. All statistical analyses were performed using SPSS software version 20.0 for Windows. For all statistical analyses P value was considered to be significant at a value of less than 0.05 for a 95% confidence interval.

**Result Analysis :**

After fulfilling the inclusion and exclusion criteria 37 cases and 39 control subjects were finally selected for the study. Both groups were age matched (P = 0.868, Table 1) and matched for gender distribution (Chi square value = 0.229, P = 0.632, data not shown in Tables). Overall distribution of the cortisol values in different quartiles in both case and control subjects has been illustrated using boxplot in figure 1 where it is found to follow almost a normal distribution pattern as P values for both are more than 0.05 according to the Smirnov-Kolmogorov test.



**Figure 1 :** Boxplot showing distribution of cortisol values (µg/dL) in the case (n = 37) and control (n = 39) groups.

The comparative analysis of the serum cortisol levels between the case and control groups has been shown in the Table 1 where serum cortisol value was found to be higher in the case group than the control group (t = 8.28), the difference being statistically significant (P < 0.001)

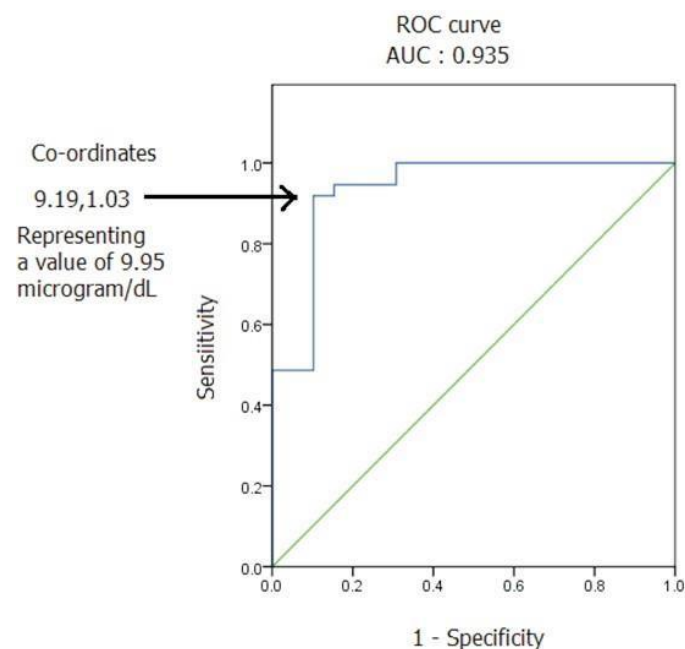
**Table 1:**

Unpaired independent t test showing the comparative analysis of age and serum cortisol values between the case and control groups.

	Case (n = 37)	Control (n = 39)	t value	P value
Age in yrs	36.0	35.71	0.166	0.868
Serum cortisol (µg/dL)	14.1 ± 3.90	7.85 ± 2.5	8.28	P < 0.001*

\*P value is considered to be significant at P < 0.05 for 95% confidence interval.

For obtaining a cut off value of serum cortisol level that could delineate between the patients suffering from MDD and the normal control population, we performed the ROC curve analysis where the sensitivity and false positivity (1-specificity) for each value falling in the case group was calculated (Figure 2). The value with the maximum true positivity and minimum false positivity i.e. the value at the left uppermost corner of 9.95 µg/dL was selected as the cut off value above which all the values are expected to represent that of MDD patients. An area under curve (AUC) value of 0.935 indicated the robustness of use of ROC analysis for this purpose.



**Figure 2 :**

ROC curve showing the cut off value of serum cortisol level between the MDD patients and normal healthy control subjects.

#### Discussion :

In the present study serum cortisol levels were found to be significantly higher in the MDD patients in comparison to the normal healthy control subjects (Table 1). In spite of the contradicting reports regarding elevation of serum cortisol levels in major depression there are ample evidences which suggest a persistently elevated cortisol level in MDD with a higher set up value that produces a persistently stimulated HPA axis in some MDD patients. In fact, a dysregulated glucocorticoid signalling mechanism has been reported in MDD patients resulting in constant hypersecretion of the corticotrophin releasing hormone. This explains the high value of serum cortisol level in the MDD in our study group also. However, the conflicting results regarding changes in the cortisol value are also important for understanding the relationship between the pathophysiology of the MDD and changes in cortisol level. Although an altered suppression mechanism of HPAaxis has been observed in MDD patients in response to pharmacological and psychological tests in early well established reports, the association between cortisol levels and MDD in humans is influenced by numerous confounding factors like severity and duration of the disease, stage of the illness and an early life stress etc. An elevated cortisol level may not always accompany the MDD. Rather constantly increased baseline levels of cortisol in blood or saliva reflect a higher stage of the disease with more severe form which is often accompanied with psychotic symptoms. This association between the type of depression and cortisol response is very important in understanding and predicting the ongoing course of MDD and can be explained at the receptor level. In melancholic and psychotic depression an altered expression of the glucocorticoid receptors (GR) brings out an imbalance in the HPA axis leading to hypercortisolism that in turn induce changes in serotonin receptors and dopaminergic activity in the brain which ultimately increase the severity and psychotic elements in the course of MDD. In milder cases and atypical MDD cases absence of hypercortisolism does not influence the changes in serotonergic and dopaminergic activities in the brain leading to less severe psychotic and associated symptoms of MDD.

In the present study we observed the mean value of serum cortisol to be 14.1 ug/dL in the patient group with an SD of about 3.9 that was found to be significantly higher than the corresponding values of 7.85 ±

2.5 ug/dL found in the control subjects (Table 1). In the ROC curve analysis an area under curve of 0.935 indicated an excellent representation of the data included for finding out a cut off value for the MDD group (Fig 2). Using ROC, we found a cut off value of 9.95 ug/dL for the serum cortisol level in the present study population that could importantly indicate the boundary of this parameter between the normal healthy group and the MDD patients in our study area. Serum cortisol levels beyond this value in MDD patients may indicate a persistent hypercortisolism and its associated complications in them. Although, some studies have indicated higher cut off values of serum cortisol in MDD others have reported lower levels for diagnosing an hypercortisol state'. So, the cut off value of cortisol level in blood may exhibit significant variation depending on several factors like environmental factors, racial factors, nutritional factors etc.

#### Conclusion :

The present study observed significantly raised serum cortisol levels in an urban MDD patient group residing in a metropolitan area. Raised serum cortisol values indicate a more severe state of MDD and thus accounts for an aggressive management at an earlier state. Earlier reports emphasize that chronic treatment with appropriate anti-depressants along with cortisol agents that inhibit cortisol synthesis alleviate symptoms of MDD more rapidly with lowering of serum cortisol levels. A cut off value of 9.95 µg/dL as indicated in our present study may help in finding hypercortisol MDD patients at an early stage and formulate an appropriate management protocol appropriately for a better clinical outcome.

#### Limitations :

The major limitation of the present study is its sample size. Although, the sample size is sufficient to draw statistical inferences, however a larger sample size including different ethnic groups from wider study areas is needed in future for a better conclusion applicable for our country that consists of different ethnic groups spread in diverse geographical areas.

#### Conflict Of Interest :

There is no conflict of interest regarding any academic, financial or administrative matter related to this work.

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