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Biochemistry Section

# Assessment of Hyperprolactinemia in Drug Naive Patients with Depression

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## ABSTRACT

**Introduction:** Patients with hyperprolactinemia often present with emotional difficulties, which occasionally persist even after treatment with dopamine agonists. There is an unusual prevalence of hyperprolactinemia in patients with depressive disorder. Prolactin is a hormone of the anterior pituitary and its secretion is regulated by Thyrotropin-Releasing Hormone (TRH) and Dopamine. Several studies have shown that antidepressants that inhibit serotonin reuptake can cause hyperprolactinemia which in turn leads to several complications like galactorrhoea, sexual dysfunction and several hormonal imbalances. This study was envisaged to assess baseline prolactin levels before administering any antidepressants like Selective Serotonin Reuptake Inhibitors (SSRIs) in patients with depression.

**Aim:** To assess serum prolactin level in drug naive patients with depression attending psychiatric Out Patient Department (OPD) of a tertiary care hospital and to compare its level with healthy controls.

**Materials and Methods:** The present study was a cross-sectional, descriptive hospital based study. The duration of the study was 12 months. The study was conducted at the Department of Biochemistry and Psychiatry OPD of College of Medicine and Sagore Dutta Hospital, Kolkata, West Bengal, India. Forty drug naive depression patients were selected as cases and 40 age and sex matched healthy individuals randomly were taken as controls.

**Results:** A total of 40 Major Depressive Disorder (MDD) patients were studied with a gender distribution of 10 males (25%) and 30 females (75%), age ranging from 21-50 years with the majority (90%) of the participants belonging to Hindu community. Among cases (n=40) Median value of prolactin concentration was 19.7 ng/mL (Z=-2.879,p=0.004) among controls (n=40) Median value of prolactin concentration was 13.6 ng/mL.There was significant positive correlation between HAM-D and serum Prolactin levels.

**Conclusion:** There should be restrictive use of SSRI in hyperprolactinemia in patients suffering from depression.

**Keywords:** Major depressive disorders, Prolactin, Selective serotonin reuptake inhibitors

## INTRODUCTION

Hyperprolactinemia is described as the persistent increase in blood prolactin level, exceeding its normal level (Females: <25 ng/mL, Males: <20 ng/mL), regardless of presence of symptoms. Several conditions can lead to hyperprolactinemia such as physiological factors like pregnancy, lactation and stress and use of antipsychotics, sedatives, antidepressants and calcium channel blockers. Also, prolactin secreting tumours (adenomas) arising from pituitary gland can lead to raised prolactin levels.

Hyperprolactinemia is associated with abnormal carbohydrate and lipid metabolism. Decreased glucose tolerance, hyperinsulinemia, increased lipid synthesis and increased food intake have been demonstrated in patients with hyperprolactinemia. Hence, long-term hyperprolactinemia is often accompanied by weight gain in humans. Sustained elevation of prolactin, caused by either antipsychotic drugs or prolactinomas leads to increased weight which can be ameliorated by normalisation of serum prolactin in particular. There is also increasing evidence that prolactin plays a role in whole body insulin sensitivity by stimulating insulin release and regulating adipokine release [1].

Of late, MDD is emerging as a major public health problem affecting a large number of human populations of any age. According to World Health Organisation (WHO), in young people neuropsychiatric disorders are the leading causes of worldwide disability and second leading cause of death [2].

Recent studies have clearly shown that antidepressants used in treatment of MDD inhibit Serotonin Reuptake (SSRI) which can cause hyperprolactinemia leading to several complications like galactorrhoea, sexual dysfunction and hormonal imbalances [3]. Thus, it becomes important to distinguish between hyperprolactinemia in drug naive patients and patients taking antidepressants. Moreover, administration of SSRIs in MDD further aggravates already existing hyperprolactinemia. Currently, there is no data about the baseline prolactin level in drug naive patients with depression. Therefore, this study was undertaken to assess the presence of hyperprolactinemia in drug naive MDD patients before prescribing SSRIs for the treatment.

## MATERIALS AND METHODS

The present study was a cross-sectional, descriptive hospital based study. The study was conducted at the Department of Biochemistry and Psychiatry OPD of College of Medicine and Sagore Dutta Hospital, Kolkata, West Bengal, India. Patients who matched the inclusion criteria within the stipulated time duration (12 months) were included in the study population. At the end of 12 months, the number of patients was found to be 40.

**Study population:** Forty drug naive patients between 21-50 years with depression attending the psychiatric OPD from September 2018 to August 2019 were included in the study. Forty age and sex matched healthy persons were taken as controls. Institutional ethical clearance (No. IEC/COMSDH/11.11.17) was obtained before commencement of the study. Detailed informed consent was taken from both cases and controls.

**Inclusion criteria:** Drug naive patients (male/female) with depression between 21-50 years attending the psychiatric OPD were randomly selected. Patients suffering from depression were screened with Mini International Neuropsychiatric Interview (MINI Bengali version 5.0.0) and confirmed with Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR). Hamilton Rating Scale for Depression (HRSD) was used for assessing severity of depression [4].

**Exclusion criteria:** Either patient/caregiver who didn't provide written consent, patients suffering from any concurrent medical or endocrine disorder and extremes of age group, pregnant or lactating mothers and postmenopausal women were excluded from the study. Detailed drug history was also obtained. Patients taking any medications that were likely to alter prolactin levels were excluded. Presence of any other psychiatric morbidity, which is likely to interfere with diagnosis, thyroid disorders, history of major substance abuse and history of chronic inflammatory diseases were also excluded.

**Sample size:** As the place of study was a medical college, providing mostly tertiary care to the patients attending the hospital, so most patients attending the psychiatry OPD had earlier got initial treatment with one or other psychotropic drug. Therefore, number of drug naive patients attended the psychiatry OPD and diagnosed to be suffering from major depression was only 40. Hence, as they fulfilled the pre-determined exclusion and inclusion criteria these 40 patients were included in the study.

**Laboratory analysis:** Biochemical parameter Prolactin was measured by Electrochemiluminescence Immunoassay Method with Cobas e411 analyser.

**Reference range of prolactin (ng/mL):** Women (not-pregnant): 4.79-23.3 ng/mL, Men: 4.04-15.2 ng/mL [5].

Blood samples were collected between 10:00 AM and 12:00 Noon as prolactin shows diurnal variation and increases in the early morning at around 08:00 AM. After collection of 12 hour fasting blood sample (5 mL) from patients, serum was separated after centrifugation at 2000 rpm for 3 minutes and further used for measurement of biochemical parameters.

## STATISTICAL ANALYSIS

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 15.0 version and Sci Stat Calc software. The continuous variables of demographic and biochemical parameters were presented as mean±SD (standard deviation). Pearson correlation analysis was carried out to find the association (if any) of the confounding (independent) variables with biochemical parameters (dependent variables). The significance was considered with $p<0.05$.

## RESULTS

A total of 40 MDD patients were studied with a gender distribution of 10 males (25%) and 30 females (75%), age ranging from 21-50 years [Table/Fig-1a,b] with the majority (90%) of the participants belonging to Hindu community. Average ages of MDD male and female subjects were 43.8±5.2 and 40.36±5.96 years, respectively. The study showed significantly higher serum prolactin level in patients than that of controls. Presence of hyperprolactinemia was significantly more in female than that of male population ($\chi^2=0.6349$, $p<0.05$). There is no significant difference in the severity of depression between male and females ($\chi^2=0.14$, $p>0.05$). The measurement of association of risk factor (prolactin) was done using the Odds Ratio, which showed Point Estimate with 95% Confidence Intervals (CI) to be 1.12 (1.03-1.19).

| Age distribution years | Sex distribution (n=40) | |
|---|---|---|
| | Male | Female |
| 21-30 | 0 | 1 |
| 31-40 | 4 | 16 |
| 41-50 | 6 | 13 |

**[Table/Fig-1a]:** Age and sex distribution of study population.

Mann-Whitney U test was used for comparison of Median of prolactin concentration as the values were in nonparametric distribution. Among cases (n=40) median value of prolactin concentration was 19.7 ng/mL (Z=-2.879, p=0.004), where $p<0.005$ is considered to be statistically significant, among controls (n=40) median value of prolactin concentration was 13.6 ng/mL. Mean±SD value of prolactin in cases were 21.05±10.6 ng/mL and in control group were 14.55±4.55 ng/mL.

| Age distribution (years) | Mild | | Moderate | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| 21-30 | 0 | 0 | 0 | 1 |
| 31-40 | 2 | 14 | 2 | 2 |
| 41-50 | 5 | 5 | 1 | 8 |
| Total | 7 | 19 | 3 | 11 |

**[Table/Fig-1b]:** Descriptive data of the study population are shown (No patients in severe scale).

The data obtained from the study showed non-parametric distribution as evidenced by Kolmogorov-Smirnov test (p-value 0.024) and Shapiro wilk test (p-value 0.009) [Table/Fig-2]. [Table/Fig-3] shows comparison of cases according to cut-off prolactin concentration. [Table/Fig-4] shows the relative risk/odds ratio estimation taking 30.075 ng/mL as the 75$^{th}$ percentile of the distribution.

[Table/Fig-5] shows correlation between HAM-D and serum prolactin levels.

| | Kolmogorov-Smirnov[a] | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|
| | Statistic | df | Sig | Statistic | df | Sig |
| Prolactin | 0.150 | 40 | 0.024 | 0.922 | 40 | 0.009 |

**[Table/Fig-2]:** Tests of normality.
a. Lilliefors significance correction; df: Degree of freedom; Sig: Significant

| Sl. No. | Category | HAM-D Score>14 (Moderate depression) | HAM-D Score <14 (Mild depression) | p-value |
|---|---|---|---|---|
| 1 | Prolactin concentration >30.075 ng/mL | 4 | 5 | 0.1689 |
| 2 | Prolactin concentration <30.075 ng/mL | 5 | 26 | |
| 3 | Total | 9 | 31 | |

**[Table/Fig-3]:** Showing comparison of cases according to cut-off prolactin concentration.
(Fisher's-exact test was used as the number of study participants was small)

| | |
|---|---|
| Odds ratio | 4.1600 |
| 95%CI | 0.8181 to 21.1533 |
| Z statistic | 1.718 |
| Significance level | p<0.0858 |

**[Table/Fig-4]:** Relative risk/odds ratio estimation taking 30.075 ng/mL as the 75$^{th}$ percentile of the distribution.

| Parameter | r-value | Level of significance |
|---|---|---|
| HAM-D vs Serum Prolactin | 0.45 | 0.003 |

**[Table/Fig-5]:** Showing significant positive correlation between HAM-D and serum prolactin levels.

## DISCUSSION

Depression is characterised by loss of self-esteem and drive, feelings of sadness, helplessness or worthlessness, and a sense of hopelessness. Stress is characterised by persistent tension, irritability, and a low threshold for becoming upset or frustrated, and an increased tendency to overreact to various stressful conditions [6]. Any one of these components can lead to psychological distress, eventually leading to hyperprolactinemia.

Depression is one of the most commonly occurring psychiatric diseases all over the world. The WHO presents data indicating that depression is currently counted as the fourth most important world health problem. Present study comprised of patients with mild and moderate depression (According to HRSD) who showed similar features of depression such as depressed mood, insomnia, loss of

interest. During detailed history taking, all of these clinical features were observed in most cases, which can be due to stressful condition, ultimately leading to depression. Stress is considered to be the major environmental factor inducing depression, mainly due to hyperactivity of Hypothalamus-Pituitary-Adrenal (HPA) axis. Association of hyperprolactinemia with psychiatric symptoms is well described in the literature [7].

Within brain, prolactin functions as a neuropeptide which has a role in reproduction and stress adaptation. During pregnancy, prolactin level increases which contributes to the variety of behavioral and psychological changes that occur in the new mother. It also promotes neurogenesis and has a role in neuroprotection. Therefore, prolactin level can be used to understand the pathophysiology of depression, since the regulation of its release involves some of the monoamine neurotransmitter systems that have been implicated in the pathophysiology of depression. On the other hand, hyperprolactinemia is always found to be associated to the patients taking antidepressants [8]. Pathological hyperprolactinemia can be caused by prolactinomas [9] as well as conditions like primary hypothyroidism, chronic renal failure and Cushing's disease. There was significant positive correlation found between HAM-D levels and serum prolactin levels [Table/Fig-5]. Thereby, it can also be said in severity of depression that prolactin has a positive predictive value. Unlike the reference studies, present study group patients were not taking any drugs that could alter their serum prolactin levels. They were suffering from depression only, not due to other causes that could cause secondary hyperprolactinemia. But still those patients showed significantly elevated prolactin levels in comparison with control group which could be due to depression alone.

Gender specific differences in hyperprolactinemia have earlier been reported in both the normal population and in patients with non-psychiatric diseases [10,11]. It was also observed that female psychiatric patients had 40% higher prevalence in hyperprolactinemia compared to males [12]. This difference may be due to the ability of oestrogens to raise blood prolactin levels and to enhance the responsiveness of lactotrophic cells of the anterior pituitary to prolactin releasing stimuli [13]. However, some studies have also failed to detect any gender difference in the prevalence of hyperprolactinemia among psychiatric patients [14-16].

Present study results were in concordance with the studies done previously in which women with hyperprolactinemia have been found to be more depressed and anxious than that of controls [17,18]. Investigated psychological aspects of patients with hyperprolactinemia and observed that hyperprolactinemia patients were significantly more hostile, depressed and anxious compared to healthy subjects.

### Limitation(s)

The number of patients included in this study was relatively low because the majority of patients attending tertiary care centre usually, got medication with one other psychotropic drugs from outside. Therefore authors can't conclude that depression leads to hyperprolactinemia and vice versa. Moreover, it was a cross-sectional study, so causality between hyperprolactinemia and depression could not be established.

## CONCLUSION(S)

As drug naive patients with depression show higher prolactin levels than the control population, so serum prolactin level should be measured for patients with depression before prescribing SSRIs. Thus, it may prevent aggravation of already existing hyperprolactinemia in this group of patients.

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