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A study of association between serum testosterone levels and clinical aspects of schizophrenia

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Abstract
Background: Sex disparities in schizophrenia especially in negative symptoms may be related to the action of sex steroid hormones.
Objective: The purpose of this study was to analyze relationship of serum testosterone levels with respect to clinical psychopathology laying emphasis on negative symptoms in male patients with schizophrenia.
Material and Methods: The study population consisted of two hundred male schizophrenia patients and fifty- age matched healthy individuals. Sociodemographic data and history of illness were noted in semi-structured proforma. Clinical psychopathology was assessed by Positive and Negative Syndrome Scale (PANSS). Drug Induced Extrapyramidal Symptoms Scale (DIEPSS) and Calgary Depression Scale for Schizophrenia (CDSS) were also used to exclude the effects of extrapyramidal symptoms and depression. Serum testosterone level was measured by chemiluminescence method. Data were analyzed by chi square test (x^2) and *z*-test. Pearson's correlation analysis was used for association of testosterone level with PANSS sub-scale scores.
Results: Mean testosterone level was significantly lower in schizophrenia patients (381.90±158.29; $p = 0.001$) as compared to healthy subjects (520.51±145.94). A significant inverse association was detected between PANSS negative sub scale scores and testosterone levels ($r = -0.211$, $p = 0.034$). There was no correlation with other PANSS sub scale items (i.e., positive symptoms, general psychopathology and total scores), age of onset and disease duration.
Conclusion: The present study indicates that lower level of testosterone may have a role in presentation of negative symptoms in schizophrenia, and the pathophysiological processes of disease affected the testosterone levels. Therefore, clinicians are advised to monitor levels of testosterone in patients with predominant negative symptoms of schizophrenia and enquire about sexual dysfunction and infertility. Lower level of sex steroids is a point of concern as these patients are at high risk of osteoporosis and cardiovascular co-morbidities. In near future therapeutic strategies targeting testosterone could be useful in ameliorating the negative symptoms of disease.

Keywords: Schizophrenia, testosterone, PANSS, negative symptoms

Introduction
Schizophrenia is a common psychiatric illness which causes profound impact on patients, their caregivers and community. It commences in late adolescence or early adulthood and causes lifelong impairment in occupational and social functioning [1]. Moreover, majority of patients with disease do not recover completely with currently available neuroleptic medications and develop adverse outcomes that further worsen their quality of life [2]. Therefore, burden of disease for the patient and their family plus financial costs to the society are very high and not to be underestimated [3].
Currently diagnosis of schizophrenia is done using criterion-based systems, including positive (e.g. hallucinations and delusions) and negative (e.g. a volition and alogia) symptoms [4, 5]. Negative symptoms play an important role in schizophrenia and contribute more to impairment quality of life and poor functioning than positive symptoms. There has been found a marked sex disparity in clinical presentation/expression of symptoms of schizophrenia in patients. Males with schizophrenia experience more severe negative symptoms, worse premorbid functioning and less favorable outcome than females [6-9]. Sexual apathy or psychosexual immaturity is observed even in premorbid state of the disease in predominant negative symptom patients [10].

The exact neurobiological basis for these pronounced sex disparities is not well understood, as several factors like genetics, biological, cultural and environmental may underline these differences [11, 12].

However, evidences support that these disparities in various dimensions, and onset of disease in reproductive age suggests the pivotal role of sex steroidal hormones in the unfolding and clinical presentation of this disorder [8, 9, 13]. Sex steroids are potent neurodevelopmental hormones that also play important role in the neuromodulation and neuroprotection of the mature brain [14]. Animal studies have suggested that during adolescence sex steroids alter substantia-nigra-dopamine pathway in the brain, and increase vulnerability to the development of psychopathology in individuals susceptible to psychosis [15].

Testosterone is a male reproductive hormone, responsible for male typical behaviors including impulsivity and sensation seeking. It acts through genomic mechanisms, modulating synthesis, release and metabolism of many neuropeptides and neurotransmitters, and through non-genomic mechanisms, influencing electrical excitability, synaptic function, morphological features and neuron-glia interactions [16]. It is also found to influence various neurotransmission systems i.e., serotonergic, dopaminergic, glutamatergic and GABAergic that are said to play an important role in the pathophysiology of schizophrenia [13]. Evidence from functional imaging studies indicates that optimal circulating levels of testosterone are required to benefit neural processing in cognitive and affective circuitry in men with schizophrenia [17].

Previous studies that have evaluated the serum levels of testosterone in schizophrenia and its contribution in psychopathology and pharmacotherapeutic interventions, have not shown consistent results. Although evidence suggests that measurement could be a useful biological marker for severity of negative symptoms in schizophrenia patients and more research about role of reproductive hormones in psychopathology of the disorder may result in more effective prevention and treatment strategies. The present study aimed to evaluate the serum levels of testosterone in schizophrenic patient and compare it with healthy subjects and to find out its association with symptom severity.

Material and Methods

Participants

This cross-sectional, comparative study was conducted in the Department of Biochemistry, in association with the Department of Psychiatry, SMS Medical College and Attached Hospitals, Jaipur, India. Study protocol was approved by the Ethics Committee of the Institute. After taking necessary permission two hundred male patients with schizophrenia were enrolled in this study. The clinical diagnosis of schizophrenia was made by a trained Psychiatrist, using ICD-11 criteria (International Classification of Mental Disorders-11). All the patients were on stable doses of antipsychotics at the time of examination. Fifty healthy subjects, who were never diagnosed for any psychiatric illness nor were on any type of treatment and reported no family history of mental disorders were used as controls. An informed and written consent was obtained from all participants after explaining the purpose and forthcoming procedure of the study. Patients were screened with a specially designed screening proforma, which encompasses the entire inclusion and exclusion criteria with the yes/no options. They all had no abnormal medical findings as evidenced by assessment of medical histories and physical examinations and no other physical or chronic medical illness, substance abuse (including anabolic steroids), or substance dependence in the past 06 months. Participants with a BMI less than 20 kg/m^2 or more than 30 kg/m^2, those with drug- induced extrapyramidal symptoms, and depression patients were excluded. Symptom severity/Psychopathology was assessed by the two competent Psychiatrists using "Positive and Negative Syndrome Scale" (PANSS) on the same day of blood collection.

Instruments of the study

Positive and Negative Syndrome Scale (PANSS)

This scale includes 30 items on three subscales: Seven items covering positive symptoms (e. g. hallucinations and delusions), seven covering negative symptoms (e.g. blunted affect) and 16 covering general psychopathology (e.g. guilt, uncooperativeness). Each item is scored on a seven point scale.

The positive and negative symptom subscales ranged from 7 to 49 and general psychopathology scale ranged from 16 to 112. Total score is 210. Reliability for each scale is fairly high, with excellent internal consistency and inter-rater reliability. Validity was based on correlation with other symptom severity measures and factor analytic validation of the subscales [18].

The Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS)

This scale consists of 8 individual items and one global item i.e., overall severity. It is used to assess treatment- emergent extra pyramidal symptoms. The items include (1) Gait (2) Bradykinesia (3) Sialorrhea (increased salivation) (4) muscle rigidity (5) Tremor (6) Akathisia (7) Dystonia and (8) Dyskinesia. The severity of each item was rated from 0 (normal) to 4 (severe) [19].

Calgary Depression Scale for Schizophrenia (CDSS)

It is used to assess the mood state of schizophrenia patients on the basis of interviewers' observations (according to the severity- absent, mild, moderate, and severe). The items are- (a) depression (his mood over the last 2 weeks), (b) hopelessness (how do you see the future), (c) self-depreciation, (d) guilty ideas of reference, (e) pathological guilt, (f) morning depression, (g) observed depression, (h) early awakening, and (i) suicide [20].

Body Mass Index

Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Patients were categorized as – (a) underweight - (i.e., BMI < 18.5 kg/m^2); (b) normal- (i.e., between 18.5–24.9 kg/m^2); (c) overweight-(i.e., 25.0 to 29.9 kg/m^2); (d) obese-(i.e., ≥ 30 kg/m^2) according to the WHO classification [21].

Collection and Analysis of Blood Samples

Five milliliters of blood was drawn between 8.30 to 9.30 a.m. from cubital vein of each subject by using aseptic technique for estimation of serum testosterone and routine investigations. In this way possible changes induced by circadian variation or by previous meals were minimized.

Blood samples were allowed to clot at room temperature and serum was separated by centrifugation at 1300-1800 rpm for 10 minutes and stored at -20°C. Chemiluminescence analysis was performed to measure the serum level of testosterone (Advia Centaur XP Immunoassay System, Siemens Healthcare, Germany) by using commercially available reagents. The procedure given in the manuals, accompanying the kits, were strictly followed.

Statistical Analysis

All the statistical analyses were done with statistical package for the social science (SPSS Inc., Chicago, Illinois, USA) version 15 of Microsoft Windows. Data were statistically described in terms of frequencies, percentage and mean±standard deviation (SD). For sociodemographic variables Pearson`s chi-square (x^2) test was used to compare between the groups. Comparison of the quantitative variables between the study groups was performed using the *z*-test. Correlation between serum testosterone and clinical variables i.e., PANSS Items (i.e positive symptoms, negative symptoms, general psychopathology and total scores), age of onset, duration of illness, number of hospitalizations etc. were calculated using the Pearson's Correlation Coefficient (*r*). Statistical significance was set at two-tailed $p<0.05$.

Results

The socio-demographic characteristics of the study groups are presented in Table-1. Only male patients were included in the study to make sample somewhat homogenous, because there is substantial evidence that males with schizophrenia suffer a more severe form of the illness and a more malignant course than females [22]. We did not restrict the participants age range (between 18 to 60 years) to include patients with different age at onset and duration of illness, so that the complete spectrum could be covered possibly.

In both the groups, most subjects were educated up to middle, unemployed, married, monthly income up to Rs.6000/-, from nuclear extended family, and of rural background. The schizophrenia group and healthy subject group were comparable on socio-demographic variables because of selection criteria. The mean age of schizophrenia patients and healthy subjects was 31.76±8.19 (20-58 years) and 34.50±9.24 (18-57 years) years respectively. Statistically there was no difference in age of the participants in both groups ($p>0.05$). Body Mass Index (BMI) of all the participants (26.12±3.57 v/s 27.12±2.98) was between the range of 20 to 30 kg/m^2 and comparable.

Table-2 shows the clinical characteristics of schizophrenic patients. Mean values of the PANSS score were as follows: total scores 99.43±11.06; positive subscale scores 25.12±6.07; negative subscale scores 26.32±5.87 and general psychopathology scores 47.97±7.90. Mean age at onset of illness was 23.53±5.49 years (range 16 to 38 years) and total duration of illness was 8.23±5.90 years (range 2 to 35 years) and number of hospitalizations in years was 3.20±1.68 years.

Mean serum testosterone values (381.90±158.29 ng/mL) were significantly lower in schizophrenia patients ($z=5.90$; $p<0.001$) than matched healthy control subjects (520.51±145.94 ng/mL) as shown in Table-1 and Figure-1.

Table-3 represents the correlation between clinical psychopathology as evaluated by PANSS scale with serum testosterone levels. In study population a significant inverse correlation (r=- 0.211, p=0.034) was observed between PANSS negative subscale scores with serum testosterone levels (Table: 3 and Figure: 2). There was no association with other items of PANSS scale (i.e., positive symptoms, general psychopathology and total scores), age of onset and total duration of disease.

Table 1: Socio-demographic and biochemical characteristics of study participants

Variables	Schizophrenia Patients	Healthy Subjects	'z'value / x^2 (df)	Significance
Age (years) (Mean ± SD)	31.76±8.19 (20-58)	34.5±9.24 (18-57)	1.89	0.06 (NS)
BMI (kg/m^2) (Mean ± SD)	26.12±3.57 (22-30)	27.12±2.98 (21-29)	0.692	0.488(NS)
Testosterone (ng/dL) (Mean ± SD)	520.51±145.94 (238.0-712.0)	381.90±158.29 (96.2-802.1)	5.90	0.001*(S)
Education (N %)				
Uneducated	14 (07%)	03 (06%)	0.608 (3)	0.895(NS)
Up to middle	77 (38.5%)	17 (34%)		
Middle to Sr. Sec	69 (34.5%)	18 (36%)		
Graduate to post. Grad	40 (20%)	12 (24%)		
Occupation (N %)				
Unemployed	72 (36%)	09 (18%)	7.63 (4)	0.106 (NS)
Farmer/workers	61 (30.5%)	24 (48%)		
Professional	52 (26%)	13 (26%)		
Businessmen	08 (04%)	02 (04%)		
Retired person	07 (3.5%)	02 (04%)		
Monthly Income (N %)				
Up to 6000	110 (55%)	28 (56%)	0.048(2)	0.976(NS)
6001 to 15000	51 (25.5%)	12 (24%)		
>15000	39 (19.5%)	10 (20%)		
Marital Status (N %)				
Single	67 (33.5%)	16 (32%)	0.254 (2)	0.881(NS)
Married	109 (54.5%)	29 (58%)		
Widower/divorced/separated	24 (12%)	05 (10%)		
Family Type (N %)				
Nuclear	64 (32%)	14 (28%)	0.443(2)	0.801(NS)

Nuclear extended	106 (53%)	27 (54%)		
Joint/others	30 (15%)	09 (18%)		
Locality (N %)				
Urban	24 (12%)	7 (14%)	0.147 (1)	0.701(NS)
Rural	176 (88%)	43 (86%)		

Table 2: Clinical characteristics of patients

Variables	Schizophrenia Patients
PANSS Scores	
Total PANSS Scores	99.43±11.06(65-126)
Positive Sub Scale Scores (TP)	25.12±6.07(11-39)
Negative Sub Scale Scores (TN)	26.32±5.87(8-42)
General Psychopathology (TGP)	47.97±7.90(26-66)
Age of onset (years)	23.53±5.49(16-38)
Duration of illness (years)	8.23±5.90(2-35)
Number of hospitalizations (years)	3.20±1.68
DIEPSS	0.9±1.1
CDSS	3.2±2.8

Table 3: Correlation of serum testosterone with clinical psychopathology

Variables	Serum Testosterone	
Pearson Correlation Coefficient (*r*)		***P*-Value**
PANSS Scores		
Total Positive Symptom Scores (TP)	0.134	0.182 (NS)
Total Negative Symptom Scores (TN)	-0.211	**0.034***(S)
Total General Psychopathology Scores (TGP)	-0.173	0.084 (NS)
Total PANSS Scores	-0.162	0.106 (NS)
Age of onset (years)	-0.012	0.900 (NS)
Total duration of illness (years)	-0.163	0.107 (NS)

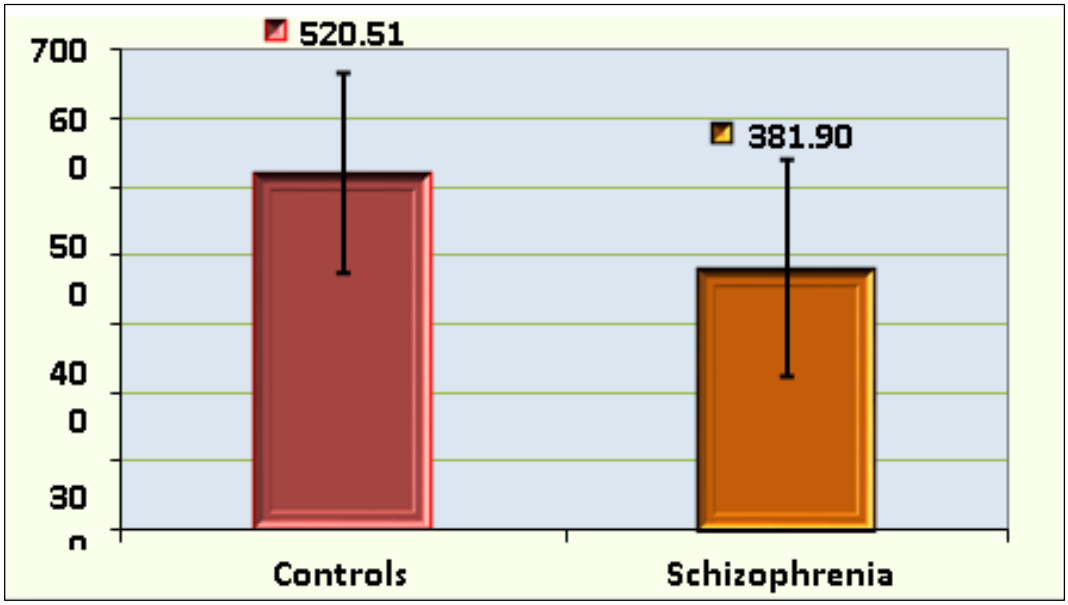

Fig 1: Comparison of serum testosterone levels in healthy subjects and schizophrenia patients

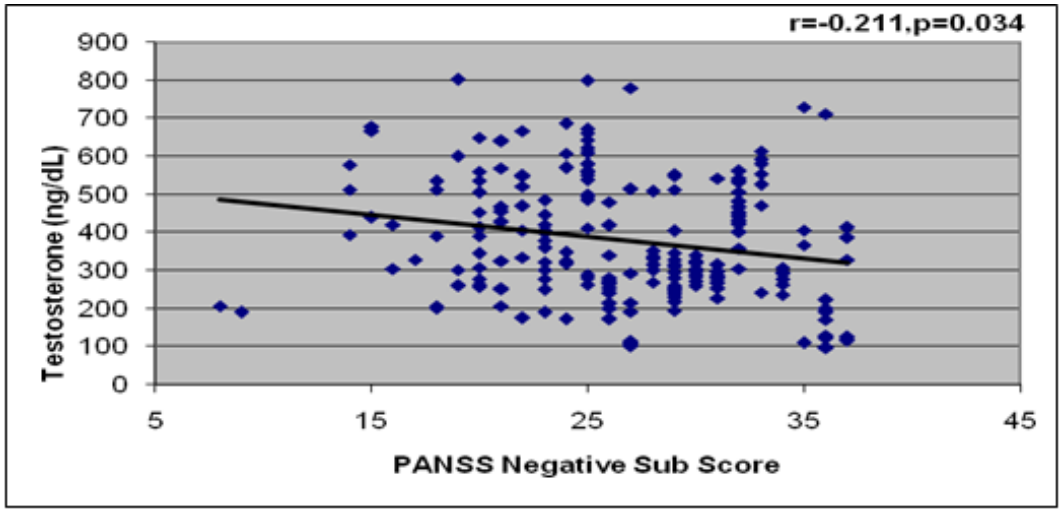

Fig 2: Correlation of serum testosterone with PANSS negative scores

Discussion

The present study showed that serum levels of testosterone were significantly lower in schizophrenic male patients than age-matched healthy subjects (Table-1). Moreover, there was an inverse correlation between testosterone and severity of negative symptoms (Table-3).

Our findings suggest that testosterone or in broad terms dysfunction of hypothalamic- pituitary- gonadotropin-axis could mediate clinical aspects (i.e., negative symptoms) of

the disorder. This is in line with some previous studies reporting the relationship between gonadal sex hormones and severity of symptoms even though the studies are somewhat different [4, 5, 15, 23, 24-26].

A decrease in serum testosterone levels in schizophrenia patients has also been reported by Hashim HM *et al*, [23], who found significantly lower testosterone levels (3.88±1.6 v/s 5.80±1.5; t=5.98, $p<0.001$) in a group of 50 male patients with chronic schizophrenia and its inverse correlation with PANSS negative subscale scores. In another cross-sectional study plasma levels of testosterone in the patients with predominant and non-predominant negative symptoms were found significantly lower than those in normal controls. A significant inverse association were also detected between negative subscale scores of PANSS and testosterone only in patients with predominant negative symptoms [5].

In a comparative pilot study, Goyal RO *et al*, reported lower testosterone levels in schizophrenic patients with predominantly negative symptoms than predominantly positive symptoms and suggested that neuroactive steroids such as testosterone and its synthetic derivatives may have an adjunctive role in reversing or slowing the progression of negative symptoms in schizophrenia [27].

So, similar to our study all the above cited studies favor that lower testosterone levels or abnormalities in HPG axis may have role in clinical expression of the disease. However, in few studies by other authors like Strous RD *et al* (2004) [28], and Van Rijin S, *et al.* (2011) [29], no differences in testosterone levels were found in adult male patients when compared to controls. The inconsistencies in findings of the studies may be due to sample sizes, wide clinical variability, medications, differences in the age, and duration of illness of the patients [30]. Many factors affect serum testosterone levels like age, diurnal variation and adiposity [31, 32]. In the present study, to reduce the effects of these factors, we recruited healthy subjects with similar age ranges, collected blood samples between 8:30 and 9:30 a.m., and excluded patients who were obese, that is, those with a BMI of over 30 kg/m^2 in this study.

In brain testosterone action may be mediated directly via the androgen receptor or indirectly via estrogen receptor. It modulates the action of various neurotransmitters and neuropeptides through non-genomic and genomic mechanisms [33, 34]. It is a functional antagonist of 5- HT3 receptor while positive modulator of glutamatergic system. Decreased concentration of testosterone may contribute to excessive serotonergic action and deficit in GABAergic functioning, which may be involved in the psychopathology of schizophrenia [35].

There are evidences suggesting that the limited availability of neurotransmitters, such as serotonin, dopamine and norepinephrine, along with dysregulation of glutamatergic system might form the pathophysiological basis for negative symptoms of schizophrenia [36-38]. Testosterone has also been found to have neuroprotective effects in some neurodegenerative diseases, as it assists the regulation of hippocampal neuroplasticity, enhancement of neurotrophin expression, neurogenesis, neuroregeneration, and provides protection against apoptosis and beta-amyloid toxicity [39]. Overall our finding indicates that lower level of testosterone can affect the negative symptoms of schizophrenia via neuroprotection.

This study had few limitations. Firstly, we did not measure other related hormone levels, such as the gonadotropin releasing hormone (GnRH), luteinizing hormone (LH) and prolactin (PRL) and thus we did not identify their associations with testosterone levels. Secondly, all the patients were on antipsychotic medications; therefore, it is recommended that in future studies, drug naive subjects should be studied in order to exclude the effect of those drugs on the level of serum testosterone. Finally, the study design is cross-sectional so the direction of causality cannot be determined. However, this study indicates that testosterone may play an important role in the severity of negative symptoms in male patients with schizophrenia.

Conclusion

Two important observations were found in this study. First observation was that significantly lower level of testosterone was found in schizophrenia patients as compared to controls of the same age group and BMI. Second observation was that testosterone levels were inversely associated with the severity of negative symptoms in male patients with schizophrenia. So, our findings suggest that there is a need to determine the hormone levels in male schizophrenic patients with predominantly negative symptoms. Lower level of sex steroids is a point of concern as these patients are at increased risk for osteoporosis and cardiovascular co-morbidities. In near future, therapeutic strategies targeting testosterone could be useful in the ameliorating the negative symptoms of disease.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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