e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(2); 323-333

Original Research Article

A Study of Association between Serum Testosterone Levels and Clinical Aspects of Schizophrenia

Mamta Singh[1], Gora Dadheech[2], Shikha Mathur[3], R. K. Solanki[4]

[1]Assistant Professor, Department of Biochemistry, S.M.S. Medical College, Jaipur, Rajasthan

[2]Assistant Professor, Department of Biochemistry, Dr. S.N. Medical College, Jodhpur, Rajasthan

[3]Professor, Department of Physiology, MGUMST, Jaipur, Rajasthan

[4]Professor, Department of Psychiatry, Rajasthan University of Health Sciences, Jaipur, Rajasthan

Received: 29-11-2022 / Revised: 30-12-2022 / Accepted: 30-01-2023

Corresponding author: Dr. Mamta Singh

Conflict of interest: Nil

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 & 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 withother 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 either lower level of testosterone may have a role in presentation of negative symptoms in schizophrenia or 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.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative

(http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

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 family plus financial costs to society are very high and not to be underestimated [3].

A criterion based method is currently used to diagnose schizophrenia, which includes both positive (like hallucinations and delusions) and negative (like volition and alogia) symptoms [4,5]. In schizophrenia, negative symptoms are more important and have a greater impact on functioning and quality of life than positive symptoms. It has been reported that an individual's clinical presentations and expressions of schizophrenia symptoms differ noticeably by gender. Males with schizophrenia have worse premorbid performance, more intense negative symptoms, and worse outcomes than females [6-9]. Even in the premorbid stage of the condition, patients with predominant negative symptoms show signs of sexual apathy or psychosexual immaturity [10]. Since various factors, including genetics, biological, cultural, and environmental, may contribute to these stark sex differences, the precise neurobiological basis for them is not fully understood [11,12].

Evidence, however, suggests that sex steroidal hormones played a crucial part in the development and propagation of these discrepancies in multiple dimensions and the start of disease in reproductive age [8,9,13]. Sex steroids are strong neurodevelopmental hormones that are also pivotal for the neuroprotection and neuromodulation of the mature brain [14]. According to animal research, sex hormones throughout adolescence modify the brain's substantia-nigra-dopamine pathway, making those who are predisposed to psychosis more vulnerable to the emergence of psychopathology [15].

Male sexual hormone testosterone is responsible for typical male traits including impulsivity and sensation seeking. It works through non-genomic mechanisms that affect electrical excitability, synaptic function, morphological characteristics, and neuron-glia connections, as well as through genomic systems that regulate the synthesis, release, and metabolism of several neuropeptides and neurotransmitters [16]. Additionally, it has been discovered to affect a number of neurotransmission systems, including serotonergic, dopaminergic, glutamatergic, and GABAergic, all of which are thought to be crucial in the pathophysiology of schizophrenia [13]. According to functional imaging studies, optimum testosterone levels in the bloodstream are necessary for men with schizophrenia to improve neuronal processing in their cognitive and affective circuits [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 sex steroid 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 schizophrenia patients 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 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 has 30 items on three subscales: 16 items to cover general psychopathology (i.e., uncooperativeness and guilt), 7 items for positive symptoms (like hallucinations and delusions) and 7 items for negative symptoms (i.e., blunted affect). A seven-point scale is used to grade each item.

The general psychopathology scale varied from 16 to 112. The positive and negative symptom subscales ranged from 7 to 49. Score in total is 210. Each scale has a comparatively high level of dependability, with strong internal consistency and inter-rater reliability. Validity was determined by factor analytic validation of the subscales and association with other symptom severity measures [18].

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): On the basis of interviewers' observations, it is used to evaluate the mental status of schizophrenia patients (according to the severity- absent, mild, moderate, and severe). The items are (a) depressed mood (how he has been feeling over the past two weeks), (b) hopelessness (how do you picture the future), (c) self-depreciation, (d) guilty ideas of reference, (e) pathological guilt, (f) morning depression, (g) suicide (h) early awakening and (i)

observed depression [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 were 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 samples 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 participantsage 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	
	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)

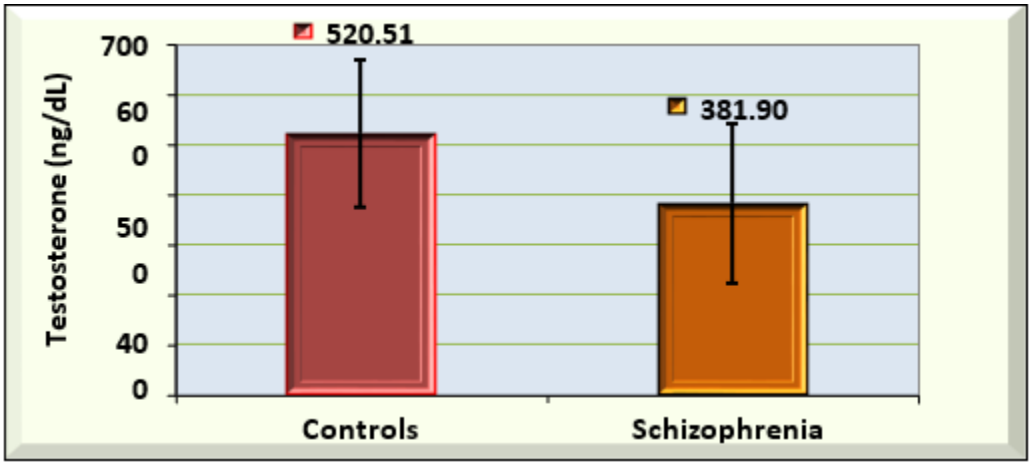

Figure 1: Comparison of serum testosterone levels in healthy subjects andschizophrenia patients

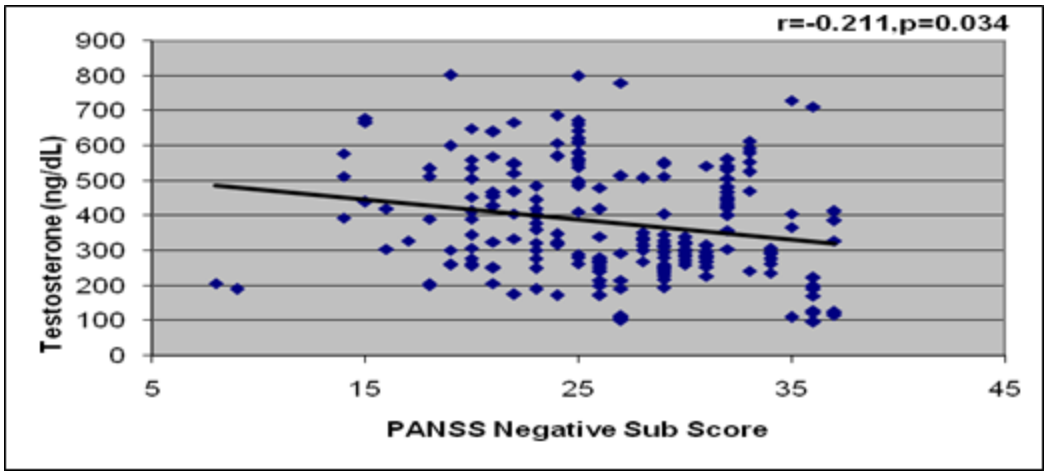

Figure 2: Correlation of serum testosterone with PANSS negativescores

Discussion

The current study revealed that serum testosterone levels were found significantly lower in male patients with schizophrenia compared to age-matched healthy persons (Table-1). In addition, there was observed an inverse correlation between testosterone and the severity of the 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 [4,5,15,23-26].

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 was also detected between negative subscale scores of PANSS and testosterone only in patients with predominant negative symptoms [5].

Goyal RO *et al* suggested that neuroactive steroids like testosterone and its synthetic derivatives may have an adjunctive role in reversing or slowing the progression of negative symptoms in schizophrenia and reported lower testosterone levels in schizophrenic patients with predominantly negative symptoms than predominantly positive symptoms [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* [28] and Van Rijin S *et al* [29], no differences in testosterone levels were found in adult male schizophrenia 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.

Testosterone action in the brain can directly be mediated by androgen receptor, or indirectly through the estrogen receptor. Through non-genomic and genomic processes, it modifies the effects of different neurotransmitters and neuropeptides [33,34]. It is a positive modulator of the glutamatergic system and a functional antagonist of the 5-HT3 receptor. The psychopathology of schizophrenia may be influenced by low testosterone levels, which may lead to excessive serotonergic activity and poor GABAergic functioning [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 [36,37,38]. The modulation of hippocampal neuroplasticity, augmentation of neurotrophin expression, neurogenesis, and neuroregeneration, as well as protection against apoptosis and beta-amyloid toxicity, have all been demonstrated to be influenced positively by testosterone in several neurodegenerative illnesses [39]. Overall, our results show that testosterone can reduce the negative symptoms of schizophrenia by 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 sothe 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

In this study, two important findings were observed. The first finding was that schizophrenia patients had considerably lower levels of testosterone than controls in the same age group and BMI. The second finding was that, in male patients with schizophrenia, testosterone levels were inversely correlated with the intensity of the negative symptoms. Therefore, based on our findings, it is necessary to assess the hormone levels in male schizophrenia patients who exhibit a predominance of negative symptoms. This is because these patients have a higher risk of osteoporosis and cardiovascular co-morbidities due to lower levels of sex hormones which is a cause for concern. In the near future, testosterone-targeting therapy approaches might be helpful in reducing the negative symptoms of disease.

References

1. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM_IV-TR, American Psychiatric Association; 2000.
2. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018 Oct;17(3):341-356.
3. Carr Vaughan J, Neil Amanda L, Halpin Sean A, Holmes Scott, Lewin Terry J. Costs of schizophrenia and other psychoses in urban Australia: findings from the Low Prevalence (Psychotic) Disorders Study. Australian & New

Zealand Journal of Psychiatry. 2002; 37(1):31–40.
4. Shirayama Y, Hashimoto K, Suzuki Y, Higuchi T. Correlation of plasma neurosteroid levels to the severity of negative symptoms in male patients with schizophrenia. Schizophr Res.2002; 58:69–74.
5. Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr Res.2006; 84:405–410.
6. Cotton SM, Lambert M, Schimmelmann BG, Foley DL, Morley KI, Mc Gorry PD, *et al*. Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. Schizophr Res. 2009;114(1-3):17–24.
7. Beratis S, Gabriel J, Hoidas S. Age at onset in subtypes of schizophrenic disorders. Schizophrenia Bull. 1994; 20(2):287–296.
8. Goldstein Jill M, Link Bruce G. Gender and the expression of schizophrenia. J Psychiatry Research. 1988;22(2):141–155.
9. Goldstein JM. Gender and schizophrenia: an introduction and synthesis of findings. Schizophrenia Bull. 1990; 16:179-183.
10. Tharoor H, Kaliappan A, Gopal S. Sexual dysfunctions in schizophrenia: Professionals and patients' perspectives. Indian J Psychiatry. 2015 Jan-Mar; 57(1): 85-87.
11. Hafner H. Gender differences in schizophrenia. Psychoneuro-endocrinology. 2003; 28:17- 54.
12. Rossler W, Hengartner MP, Ajdacic-Gross V, *et al*. Sex differences in sub-clinical psychosis-Results from a community study over 30 years. SchizophreniaResearch. 2012; 139:176–182.
13. Lodha P and Karia S. Testosterone and schizophrenia: A clinical review. Ann Indian Psychiatry. 2019; 3: 92-96.
14. McEwen BS and Milner TA. Understanding the broad influence of sex hormones and sex differences in the brain. J Neurosci Res. 2017; 95:24–39.
15. Sisek-Sperm M, Krizaj A, Jukic V, Milosevic M, Petrovic Z, Herceg M.Testosterone levelsand clinical features of schizophrenia with emphasis on negative symptoms and aggression.Nord J Psychiatry. 2014; 69(2):1-8.
16. Genazzani AR *et al*. Endocrinology of Menopausal Transition and Its Brain Implications CNS Spectr. 2005 Jun;10(6):449-57.
17. Vercammen A, Skilleter AJ, Lenroot R, Catts SV, Weickert CS, Weickert TW. Testosterone is inversely related to brain activity during emotional inhibition in schizophrenia. PLoS One. 2013;8(10): e77496.
18. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull. 1987; 13:261–276.
19. Inada T. Evaluation and diagnosis of drug-induced extrapyramidal symptoms: commentaryon the DIEPSS and guide to its usage. 1996 Japanese, Tokyo Seiwa Publishers.
20. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophrenia Research. 1990; 3:247–251.
21. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004 Jan 10;363(9403):157-63.
22. Lindamer LA, Bailey A, Hawthorne W, Folsom DP, Gilmer TP and Garcia P *et al*. Genderdifferences in characteristics and

service use of public mental health patients with schizophrenia. Psychiatry Serv., 2003; 54:1407-1409.
23. Hashim HM and Negm MG. Dehydroepiandrosterone sulfate and testosterone levelscorrelate with negative symptoms in male patients with schizophrenia. Egypt J of Psychiatry 2012; 33:181-5.
24. Ko YH, Jung SW, Joe SH, Lee CH, Jung HG, Jung IK, Kim SH and Lee MS. Association between serum testosterone levels and the severity of negative symptoms in male patientswith chronic schizophrenia. Psychoneuro-endocrinology. 2007; 32: 385-391.
25. Smith JB, Rosen J, Colbert A. Low serum testosterone in outpatient psychiatry clinics: Addressing challenges to the screening and treatment of hypogonadism. Sex Med Rev. 2018; 6:69-76.
26. Kaneda Y. Possible relationship between testosterone and comorbid major depressive episode in male patients with schizophrenia treated with typical antipsychotic medications. Clin Neuropharmacol. 2003; 26:291–293.
27. Goyal RO, Sagar R, Ammini AC, Khurana ML and Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann NY Acad Sci. 2004; 1032: 291-294.
28. Strous RD, Maayan R, Kaminsky M, Blumensohn R, Weizman A and Spivak B. DHEA and DHEA-S levels in hospitalized adolescents with first-episode schizophrenia and conduct disorder: A comparison study. European Neuropsychopharmacology.2009; 19: 499-503.
29. Van Rijn S, Aleman A, de Sonneville L, Sprong M, Ziermans T, Schothorst P, *et al.* Neuroendocrine markers of high risk for psychosis: Salivary testosterone in adolescent boys with prodromal symptoms. Psychol Med. 2011; 41:1815-22.
30. Cleare AJ, O'Keane V, Miell JP. Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in chronic fatigue syndrome. Psychoneuroendocrinology. 2004; 29: 724–732.
31. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab. 2009 Mar; 94(3):907-13.
32. Kelly DM and Jones TH. Testosterone and obesity. Obes Rev. 2015 Jul;16(7):581-606.
33. Białek M, Zaremba P, Borowicz KK, Czuczwar SJ. Neuroprotective role of testosterone inthe nervous system. Pol J Pharmacol. 2004; 56:509–518.
34. Colciago A, Bonalume V, Melfi V and Magnaghi V. Genomic and Non-genomic Action ofNeurosteroids in the Peripheral Nervous System. Frontier Neuroscience.2020; 14:796-808.
35. Hayashi T and Su-TP. Sigma-1 receptor ligands: Potential in the treatment of neuropsychiatric disorders. CNS Drugs. 2004; 18(5): 269-84.
36. de Jonge JC, Vinkers CH, Hulshoff Pol HE, Marsman A. GABAergic Mechanisms in Schizophrenia: Linking Postmortem and *In Vivo* Studies. Front Psychiatry. 2017 Aug 11; 8:118.
37. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry. 2020; 19:15–33.
38. Maki-Marttunen V, Andreassen OA, Espeseth T. The role of norepinephrine in the pathophysiology of schizophrenia. Neuroscience and Behavioral Reviews. 2020;118: 298-314.

39. Siddiqui AN, Siddiqui N, Khan RA, Kalam A, Jabir NR, Kamal MA, *et al.* Neuroprotective role of steroidal sex hormones: An overview. CNS Neurosci Ther 2016; 22:342-50.