

Hormone Profile in Acute Psychotic Disorders: A Cross-Sectional Comparison of Serum Hormone Concentrations in Treated and Untreated Male Patients with Schizophrenia

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ABSTRACT

Background: Antipsychotic drugs for the treatment of schizophrenia provide effective treatment of psychotic symptoms but might lead to neuroendocrine abnormalities.

Objective: The aim of this study was to assess hypothalamic-pituitary-gonadal (HPG) axis function by comparing serum hormone profiles of newly admitted patients with psychotic disorders who were receiving antipsychotic drugs with those who were antipsychotic–drug-free during the preceding 6 months.

Methods: Adult male patients admitted during a 1-year period (December 1999 to December 2000) to 1 of 2 Brazilian public psychiatric inpatient units that provide care for severely ill patients were eligible for this cross-sectional study if they had a diagnosis of schizophrenia based on the criteria given in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, and a score >24 on the Brief Psychiatric Rating Scale. On the morning after admission, serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), prolactin, free testosterone (FT), and total testosterone (TT) were determined. A commercial laboratory provided the normal serum hormone concentrations of healthy Brazilian men in the same age range as that of the study patients.

Results: Sixty-three adult male patients, aged 18 to 55, were included in the study. Forty-eight (76.2%) patients (mean [SD] age, 30.6 [8.9] years) were receiving antipsychotic drugs (treated). Fifteen (23.8%) patients (mean [SD] age, 36.5 [9.8] years) were antipsychotic–drug-free for 6 months before admission

(untreated). The only significant between-group difference was for disease duration (treated, 7.6 [8.1] years vs untreated, 12.3 [9.7] years; $P = 0.044$). Treated patients were more likely to have higher dispersed serum hormone concentrations than the untreated patients. Serum concentration of FSH was numerically higher in the treated patients than in the untreated patients, although the difference was not statistically significant. Compared with the control group (1436 men and women for prolactin; 226 men for LH; 207 for FSH; 128 for TT; 128 for FT; and 128 for SHBG), patients in the treated group had significantly different mean [SD] serum concentrations of all hormones (treated vs control: prolactin, 24.3 [23.7] $\mu\text{g/L}$ vs 6.8 [0.12] $\mu\text{g/L}$, $P < 0.001$; LH, 4.9 [3.4] U/L vs 3.3 [0.13] U/L, $P = 0.001$; FSH, 4.4 [3.9] U/L vs 3.0 [0.06] U/L, $P = 0.025$; TT, 17.5 [7.8] nmol/L vs 20.1 [1.64] nmol/L, $P = 0.004$; FT, 0.056 [0.08] nmol/L vs 0.06 [0.003] nmol/L, $P < 0.001$; and SHBG, 33.3 [18.9] nmol/L vs 48.4 [1.45] nmol/L, $P = 0.002$). Compared with the control group, patients in the untreated group had significantly different mean (SD) serum concentrations of all hormones except FSH and TT (untreated vs control: prolactin, 19.9 [12.8] $\mu\text{g/L}$ vs 6.8 [0.12] $\mu\text{g/L}$, $P = 0.001$; LH, 6.0 [1.9] U/L vs 3.3 [0.13] U/L, $P = 0.002$; FT, 0.08 [0.04] nmol/L vs 0.06 [0.003] nmol/L, $P = 0.001$; and SHBG, 26.6 [11.6] nmol/L vs 48.4 [1.45] nmol/L, $P < 0.001$). No differences were found between the TT distribution curve of the control group and that of the untreated patients.

Conclusion: This study supports further investigation of a potential difference in the HPG axis among treated and untreated patients with schizophrenia and those who do not have that condition. (*Curr Ther Res Clin Exp.* 2006;67: 350–363) Copyright © 2006 Excerpta Medica, Inc.

Key words: prolactin, hormone profile, schizophrenia, psychotic disorders, antipsychotics.

INTRODUCTION

The onset of schizophrenia at the beginning of or during the reproductive years suggests that the disorder might be associated with cerebral and physiologic changes that begin in adolescence. In a study performed by Van Cauter et al,¹ plasma levels of prolactin, growth hormone, corticotropin, and cortisol were measured at 15-minute intervals for 24 hours in 9 unmedicated schizophrenic male patients and in 9 age-matched normal male subjects. Various abnormalities were found in response to neuroendocrine challenges, such as the dexamethasone suppression test. In the schizophrenic patients, the authors observed an almost 3-fold sleep-related increase in prolactin concentrations associated with intensified frequency of nocturnal prolactin pulses. This increased stimulatory effect of sleep on prolactin secretion became evident immediately after sleep onset. In addition, the normal inhibition of cortisol secretion during early sleep was absent in the patients with schizophrenia.

A study by Gil-Ad et al² reported abnormal growth hormone response to luteinizing hormone-releasing hormone (LHRH) and to thyrotropin-releasing

hormone in adolescents with schizophrenia but not in adults with that condition. The authors suggested that such responses were the result of the interaction of developmental changes with the disease processes or the lower gonadotropin and testosterone concentrations seen in antipsychotic–drug-free patients with schizophrenia.

It has been suggested that serum prolactin concentrations increase in drug-naive male and female patients with schizophrenia.³ In a study by Garver,⁴ slightly higher prolactin concentrations were observed in untreated patients with acute schizophrenia than in treated patients with chronic schizophrenia or healthy individuals. Stress has also been associated with transient increases in prolactin and cortisol concentrations.^{5,6} Higher prolactin and cortisol concentrations, in turn, might be attributable to the stimulatory effect of serotonergic pathways.⁷

Schizophrenia is a chronic disorder that requires long-term treatment with antipsychotic drugs.⁸ Dopaminergic receptors can be found in cerebral pathways, such as the nigrostriatal, tuberoinfundibular, mesolimbic, and mesocortical systems.⁹ Blockade of dopamine receptors in the tuberoinfundibular system stimulates prolactin release in lactotroph cells. Prolactin secretion is under (the influence of) tonic dopaminergic inhibition, which, in turn, is self-regulated by negative feedback. Typical antipsychotic drugs such as haloperidol have been associated with dose-dependent increases in prolactin secretion,^{10,11} probably due to their primary effect on the pituitary gland,^{12,13} which results in the suppression of sex hormones.^{14,15}

Twenty-nine stable patients meeting criteria for schizophrenia or schizoaffective disorder were included in an open-label study performed by Kirkpatrick et al¹⁶ that evaluated prolactin secretion before and after abrupt withdrawal of a neuroleptic drug. The findings suggested that basal prolactin concentrations were significantly lower on postwithdrawal days 3, 4, and 5 than on subsequent days. The authors hypothesized that this rebound effect is a result of the changes that chronic neuroleptic administration produces in the dopaminergic receptors of the tuberoinfundibular system. The study by Markianos et al¹⁷ assessed prolactin responses to IM haloperidol 5 mg in the drug-free state and after 1 month of treatment with neuroleptics in 14 adult schizophrenic male patients who had never had drug treatment and in 20 adult schizophrenic male patients who had discontinued neuroleptic treatment for 2 months to 1 year. The results indicated that after discontinuation of neuroleptic drugs, the hypothalamic-pituitary dopamine receptors may remain sensitive for a long time.

Limited studies investigating hormone concentrations in patients with schizophrenia have produced inconsistent results.^{18–20} Patients with schizophrenia might display a variety of hormone profiles.

Changes in hormone concentrations can affect mood, cognition, and behavior and can be the reason for sexual dysfunction and other clinical symptoms. An understanding of these mechanisms is necessary to improve clinical outcomes.

The aim of this study was to assess hypothalamic-pituitary-gonadal (HPG) axis function by comparing serum hormone concentrations from newly admitted male patients who were receiving antipsychotic drug treatment for psychotic disorders with patients who were antipsychotic-drug-free for the preceding 6 months.

PATIENTS AND METHODS

This cross-sectional study was conducted in 2 acute care public psychiatric inpatient units in Brazil—the Pax Clínica Psiquiátrica (Goiânia) and the Clínica Santa Monica (Salvador). The local ethics committees and the ethics committee of the Federal University of São Paulo approved the study. The study was performed in accordance to the Declaration of Helsinki.²¹ All participating patients (or their legal guardians) provided informed written consent.

All consecutive male patients aged 18 to 55 years admitted during a 1-year period (December 1999 to December 2000) who received a diagnosis of schizophrenia or related disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,²² and scored >24 on the Brief Psychiatric Rating Scale²³ were eligible for the trial. We did not include women in the study, because the concentrations of gonadal hormones would have been affected by menstrual cycle phases, pregnancy and childbearing, and menopause. The study comprised newly admitted patients that were treated or untreated. Treated patients were those receiving treatment with antipsychotic drugs; untreated patients were those who had not received any antipsychotic drug for the previous 6 months.

The participants' charts were reviewed to collect data regarding their disorder history. Patients were assessed on admission by attending physicians using the Positive and Negative Syndrome Scale (PANSS).²⁴ On the morning after admission, blood samples were collected to determine serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), prolactin, free testosterone (FT), and total testosterone (TT). Biochemical analyses of all hormones, with the exception of FT, were performed using a Wallac-Delfia 1234/1296 fluorometer (Perkin-Elmer Life Sciences Inc., Boston, Massachusetts). FT was measured by radioisotopic analysis using a Packard-Cobra II auto-gamma counter (Perkin-Elmer Life Sciences Inc.).

Gauss curves were used for displaying the distribution of the serum hormone concentrations of the treated and untreated patients compared with normal concentrations. These normal values were determined by analyzing blood samples taken from healthy controls and were provided by a commercial laboratory (Laboratório Fleury, São Paulo, Brazil). In addition to radioisotopic analysis, the normal FT concentration was also calculated using the serum concentrations of TT and SHBG. The normal serum concentrations of FSH, LH, and prolactin were determined using values obtained from samples sub-

mitted to the laboratory by patients during a 30-day period; samples from patients enrolled in clinical studies, those receiving any drugs, and ill patients were excluded.

Statistical Analysis

The demographic and clinical data for the 2 patient groups were compared using the Fisher exact test. Descriptive statistics such as mean and standard deviation were used for describing the hormone data.

The nonparametric Mann-Whitney test was used for comparing the 2 independent groups of sampled data, making no assumptions about the distribution of the data. *P* values were obtained to compare hormone concentrations between the 2 patient groups.²⁵ The Kolmogorov-Smirnov test was used for testing the equality of distributions of hormone levels of the 2 patient groups compared with the control groups.²⁶ Statistical significance was set at *P* < 0.05 for the analysis.

RESULTS

Sixty-three male patients (mean [SD] age, 32.9 [9.5] years; range, 18–55 years) were included in the study. At admission, 76.2% (48) of the patients were receiving treatment with typical antipsychotic drugs (treated group); 15.9% (10) of these were concomitantly using an antidepressant. Fifteen (23.8%) patients had not received any antipsychotic or other psychotropic drug (untreated group) for ≥6 months before admission. The mean (SD) PANSS score for positive symptoms for the entire study population was 23.3 (5.9), and the mean (SD) score for negative symptoms was 25.4 (5.8); the mean (SD) total PANSS score for the study population was 101.2 (23.1). The mean (SD) disease duration was 11.4 (9.0) years.

The only statistically significant differences in demographic characteristics between the 2 groups was the disease duration, which was significantly longer in the untreated group than in the treated group (12.3 [9.7] years vs 7.6 [8.1] years; *P* = 0.044) (Table I).

Control groups were derived from men in the same age range (18–55 years) as the study patients who were determined to be healthy and not receiving

Table I. Demographic and clinical characteristics of treated and untreated male patients with schizophrenia (N = 63).

Characteristic	Patients		<i>P</i>
	Treated (n = 48)	Untreated (n = 15)	
Age, mean (SD), y	30.6 (8.9)	36.5 (9.8)	0.064
Duration of disease, mean (SD), y	7.6 (8.1)	12.3 (9.7)	0.044

antipsychotic drugs based on their responses to a questionnaire. SHBG and testosterone data were obtained by measuring samples obtained from 128 Brazilian men employed by the laboratory. Serum FSH concentration was based on samples from 226 men; LH, 207 men; and prolactin, 1436 men and women.

Table II shows the mean serum concentrations of prolactin, LH, FSH, TT, FT, and SHBG for the treated group, the untreated group, and the control groups. The treated group had significantly different serum concentrations of all hormones studied compared with the control groups (treated vs control: prolactin, 24.3 [23.7] µg/L vs 6.8 [0.12] µg/L, $P < 0.001$; LH, 4.9 [3.4] U/L vs 3.3 [0.13] U/L, $P = 0.001$; FSH, 4.4 [3.9] U/L vs 3.0 [0.06] U/L, $P = 0.025$; TT, 17.5 [7.8] nmol/L vs 20.1 [1.64] nmol/L, $P = 0.004$; FT, 0.056 [0.08] nmol/L vs 0.06 [0.003] nmol/L, $P < 0.001$; and SHBG, 33.3 [18.9] nmol/L vs 48.4 [1.45] nmol/L, $P = 0.002$). The untreated group had significantly different mean (SD) values for all hormones except FSH and TT (untreated vs control: prolactin, 19.9 [12.8] µg/L vs 6.8 [0.12] µg/L, $P = 0.001$; LH, 6.0 [1.9] U/L vs 3.3 [0.13] U/L, $P = 0.002$; FT, 0.08 [0.04] nmol/L vs 0.06 [0.003] nmol/L, $P = 0.001$; and SHBG, 26.6 [11.6] nmol/L vs 48.4 [1.45] nmol/L, $P < 0.001$). Serum prolactin concentrations were significantly higher in both the treated group ($P < 0.001$) and the untreated group ($P = 0.001$) when compared with the control group. There was no significant difference in prolactin concentration between the treated and the untreated group.

In treated patients, although the values of LH concentration (**Figure 1**) (relative dispersion [D] = 0.2568; critical value of D = 0.2349) and FSH concentration (**Figure 2**) (D = 0.4471; critical value of D = 0.2358) were within the normal range, they were shifted slightly to the right and had greater dispersion compared with untreated patients.

No differences were found between the TT distribution curve of the controls and that of untreated patients (**Figure 3**). The distribution curve of FT for the treated patients was shifted to the left, meaning that those patients had lower values than the controls (D = 0.6622; critical value of D = 0.2152).

Unfortunately, male-only prolactin curves were unavailable for the control group. However, patients in the treated and untreated groups had higher serum prolactin concentrations than the values obtained from the mixed-gender group of healthy controls.

DISCUSSION

Our results suggest that serum prolactin concentrations did not differ between untreated patients and treated patients. Several authors²⁷⁻³⁰ have reported normal or decreased serum prolactin concentrations in drug-naïve acute schizophrenic patients, as well as decreased prolactin concentrations in patients with chronic schizophrenia without ventricular dilatation. However, elevated serum prolactin concentrations have been reported after stress.^{5,6,31} Therefore, given that our study population had acute psychotic symptoms at admission, the stress response might be responsible for the increased serum prolactin concen-

Table II. Mean (SD) serum concentrations of prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), and sex hormone-binding globulin (SHBG) for male patients who were receiving antipsychotic drug treatment (treated group), not receiving drug treatment (untreated group), and healthy controls (control group).

Hormone	Group			<i>p</i>		
	Control	Treated	Untreated	Treated vs Untreated	Treated vs Control	Untreated vs Control
Prolactin, µg/L	6.8 (0.12)	24.3 (23.7)	19.9 (12.8)	0.831	<0.001	0.001
LH, U/L	3.3 (0.13)	4.9 (3.4)	6.0 (1.9)	0.412	0.001	0.002
FSH, U/L	3.0 (0.06)	4.4 (3.9)	3.1 (1.9)	0.558	0.025	0.615
TT, nmol/L	20.1 (1.64)	17.5 (7.8)	21.5 (5.5)	0.143	0.004	0.638
FT, nmol/L	0.06 (0.003)	0.056 (0.08)	0.08 (0.04)	0.052	<0.001	0.001
SHBG, nmol/L	48.4 (1.45)	33.3 (18.9)	26.6 (11.6)	0.980	0.002	<0.001

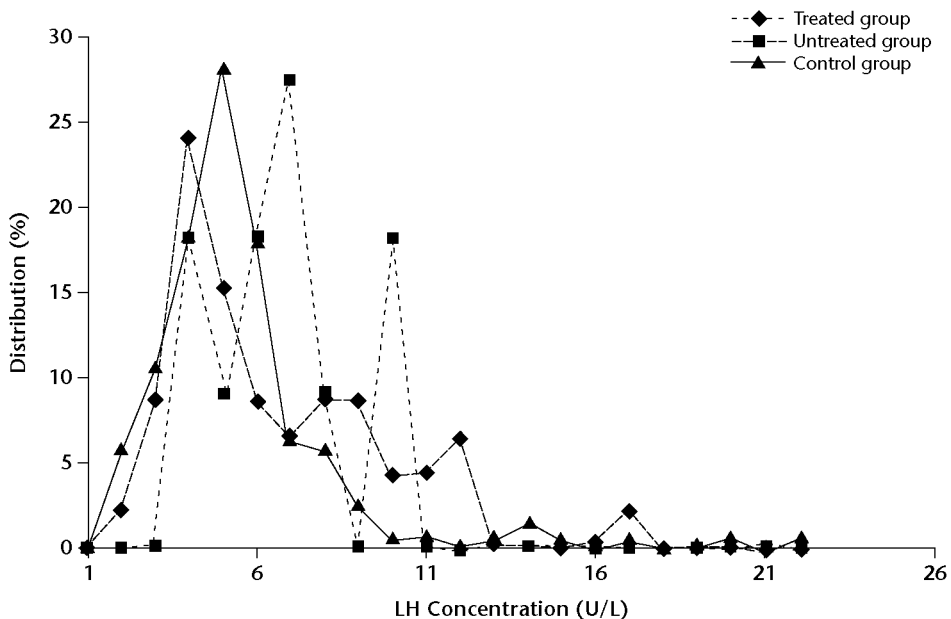


Figure 1. Luteinizing hormone (LH) distribution curves for psychotic male patients receiving drug treatment (treated group), psychotic male patients not receiving drug treatment (untreated group), and healthy male controls (control group).

trations observed. On the other hand, in patients with a long history of illness who have undergone several previous treatments, the potential exists for the hypothalamic-pituitary dopamine receptors to remain sensitized for a long time after discontinuation of neuroleptic drugs.¹⁷

Due to a lack of data (MEDLINE search; key terms: *curve, normal distribution, hormone, drug-free, schizophrenia*) on normal distributions of serum hormone concentrations in antipsychotic-drug-free patients with psychotic disorders, we compared the distribution curves of both treated and untreated patients with those of the control groups. We found that only the untreated patients had dispersion of hormone concentrations similar to that of the control groups. This supports the hypothesis made by Meltzer³² that such drugs can alter hormone concentrations. However, these results might be misleading, because the curves of our matched controls might be different from those of a wider population of healthy individuals.

Serum concentrations of LH and FSH in treated patients suggested discrete shifts to values higher than those measured in the controls. This might be related to the slightly lower testosterone concentrations found in patients receiving antipsychotic treatment, because LH is responsible for the release of testosterone. When testosterone levels are low, the pituitary gland releases LH, leading to increased production of testosterone in the testicles.³³

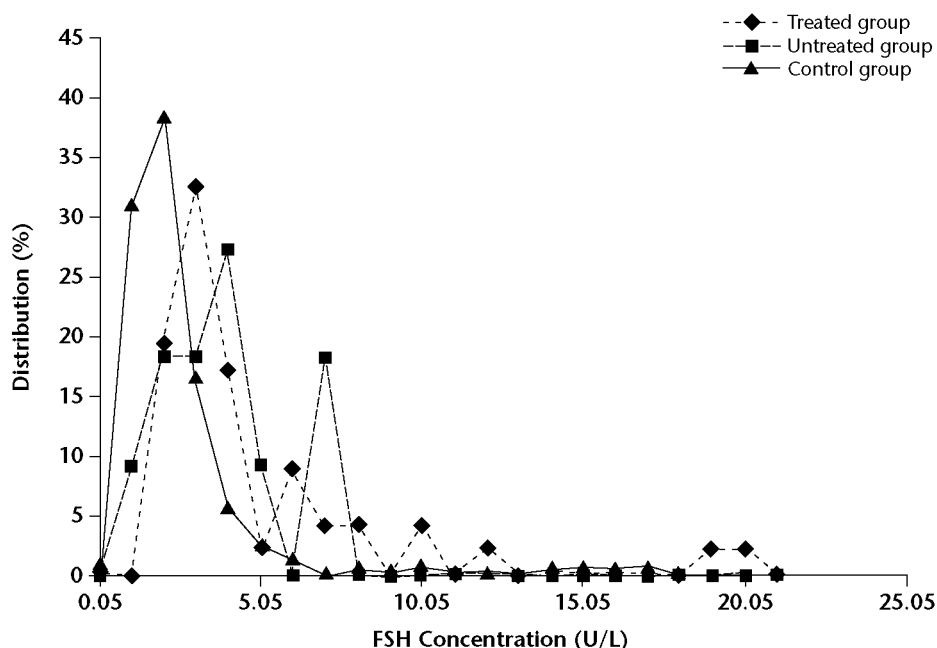


Figure 2. Follicle-stimulating hormone (FSH) distribution curves for psychotic male patients receiving drug treatment (treated group), psychotic male patients not receiving drug treatment (untreated group), and healthy male controls (control group).

Stress-related hormones influence reproductive function at 3 sites on the HPG axis: in the central nervous system, by inhibiting LHRH secretion; in the pituitary gland, by interfering with the LHRH-induced release of LH; and in the gonads, by altering the stimulating effect of gonadotropins on the secretion of sex steroids.³⁴ Humans exposed to acute stress respond with a small and often short-lived increase in plasma LH and testosterone concentrations.³⁵ The specific importance of endogenous testosterone is not fully understood, although it might be speculated that testosterone initiates recuperation.³⁶

Serum concentrations of FSH and TT in untreated patients were comparable to those of the controls, indicating that these hormones might normalize more rapidly than the other hormones after treatment is discontinued. This might also indicate that the other hormones are altered by the disease itself, or that FSH and TT concentrations changed in the untreated patients under stress, reaching more normal concentrations, while the treated patients reacted differently or in a less pronounced way to stress. The concentration of FT, which is the proportion of testosterone that is biologically active, was decreased in treated and untreated patients.

Analysis of the hormone distribution curves suggested that treated patients had greater dispersion than the healthy controls and the untreated patients.

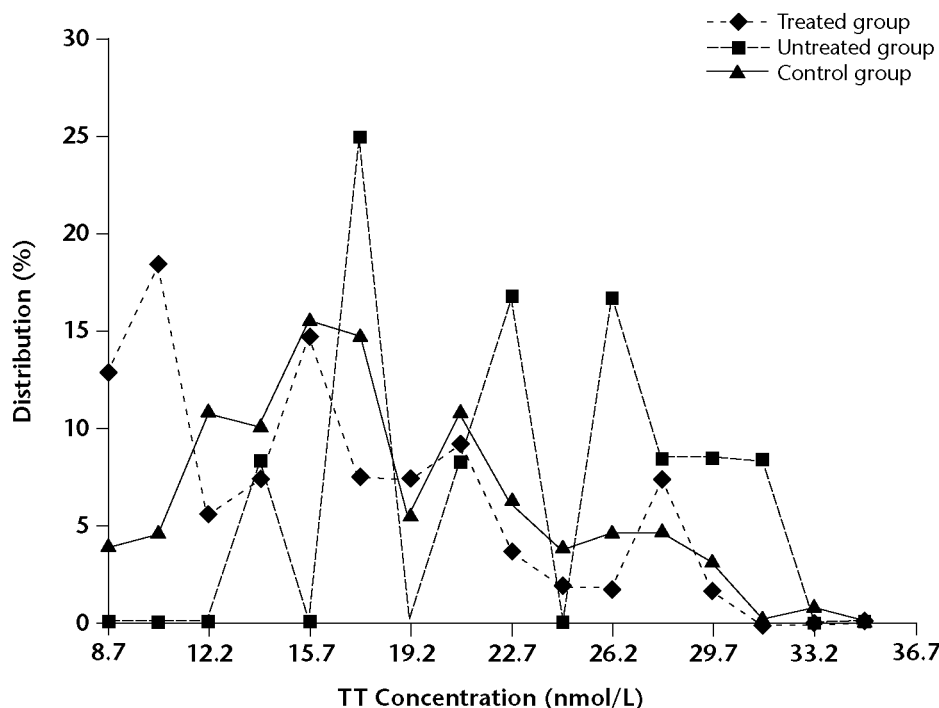


Figure 3. Total testosterone (TT) distribution curves for psychotic male patients receiving drug treatment (treated group), psychotic male patients not receiving drug treatment (untreated group), and healthy male controls (control group).

This might be explained by the fact that treated patients respond erratically to antipsychotic drugs, with great interindividual variation. Variations in response might also be the result of differences in regimen compliance.

Findings regarding prolactin concentrations represent another important result of this study. We observed significantly higher serum prolactin concentrations in untreated patients than in the control groups. Therefore, our findings did not corroborate the view that a shift from prolactin-enhancing antipsychotic drugs to nonprolactin-enhancing atypical drugs is associated with normalizing prolactin concentrations. Based on our findings, patients who have undergone long-term treatment with antipsychotic drugs might experience a lower increase in prolactin concentrations over time, leading to lower levels overall. Another consideration is that in the acute period of a psychotic disorder, treated patients and untreated patients might have similar prolactin concentrations because cortisol interferes with the prolactin concentration. Thus prolactin concentrations in treated and untreated patients might reflect a non-specific response to stress.

The clinical consequences of these findings need to be explored further. An interval of time would be required before adopting any drug treatment involv-

ing the hormonal system, since the concentration of cortisol and other involved hormones are altered during this acute period of the disease.

There are some limitations to our analyses. Although statistically significant differences in serum hormone concentrations were not found between the 2 study groups, this might have been due to the small sample size (type 2 error). It is important to point out that our antipsychotic–drug-free patients were not drug-naïve. Therefore, we were unable to determine whether there was a carry-over effect associated with a drug that was not specific to psychotic symptoms. Because we measured hormone levels during acute episodes of psychotic disorders, the hormone changes might be associated with stress or to residual effects of the drug. In addition, the serum hormone concentration distribution curves of patients were compared with those of the controls. The serum hormone concentration distribution curves of drug-naïve patients, which might be different, were not assessed in our analyses. Future studies would need to replicate these findings with a much larger sample size and would also benefit by inclusion of a matched control sample. Despite the methodologic limitations, we feel that the findings of this study are meaningful for understanding the hormonal physiology and pathophysiology of patients with schizophrenia, as well as its clinical consequences.

CONCLUSIONS

In this cross-sectional study of patients with acute psychotic disorders, we observed that serum prolactin concentrations were significantly higher in patients who were receiving antipsychotic drugs and in antipsychotic–drug-free patients than in healthy controls, although we found no difference between the 2 groups of patients. Despite the fact that concentrations of other hormones were within normal ranges in both treated and untreated patients, there was greater dispersion in the serum hormone concentration distribution curves of patients receiving antipsychotic drugs than those of untreated patients. This study supports further investigation of a potential difference in the HPG axis between patients with schizophrenia and those who do not have that condition.

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