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Hypoprolactinemia and hyperprolactinemia in male schizophrenia patients treated with aripiprazole and risperidone and their relationships with testosterone levels

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Abstract

Aim: Several reports have shown that risperidone increases prolactin concentrations, while aripiprazole decreases prolactin concentrations. The frequency of abnormal prolactin concentrations in patients with schizophrenia receiving these drugs is still unknown. Furthermore, although hyperprolactinemia leads to sexual dysfunction, the relationship between hyperprolactinemia and testosterone, which may be directly related to male sexual function, is not well understood.

Methods: The subjects were 94 male schizophrenia outpatients receiving risperidone or paliperidone (risperidone group) and 83 male schizophrenia outpatients receiving aripiprazole. We measured the serum prolactin and total and free testosterone concentrations. We compared the prolactin and testosterone levels in patients receiving risperidone or paliperidone and patients receiving aripiprazole.

Results: The average serum prolactin concentration was 27.5 ± 13.1 ng/mL for the risperidone group and 3.9 ± 3.5 ng/mL for the aripiprazole group, and the concentrations were significantly different ($P < .001$). Hypoprolactinemia was observed in 75% of the aripiprazole group and hyperprolactinemia in 65% of the risperidone group. A positive correlation between prolactin levels and the risperidone daily dose was found, whereas a negative correlation between prolactin levels and the aripiprazole daily dose was observed. In the risperidone group, total testosterone concentrations were correlated with age, while free testosterone concentrations were inversely correlated with age and prolactin levels.

Conclusion: We found very common hyperprolactinemia and hypoprolactinemia in the risperidone or paliperidone group and aripiprazole group, respectively. Testosterone concentrations were associated with elevated prolactin levels in patients receiving risperidone or paliperidone. Further studies are needed to determine the clinical relevance of abnormal prolactin concentrations in male and female patients with schizophrenia.

KEYWORDS
abnormal prolactin, dopamine antagonist, dopamine partial agonist, hyperprolactinemia, hypoprolactinemia

1 | INTRODUCTION

Sexual dysfunction, which can adversely affect treatment adherence and contributes to poor quality of life, is more common in schizophrenic patients being treated with first- or second-generation antipsychotics.[1] Prolactin is a polypeptide hormone that is involved in over 300 functions, such as the induction and maintenance of milk production, breast enlargement during pregnancy, the inhibition of hypothalamic gonadotropin-releasing hormone, and the maintenance of proper ovarian function and progesterone-secreting structure.[2] As normal range of prolactin was 5-20 ng/ml for male and 5-30 ng/ml for female,[3,4] a serum prolactin concentration more than 20 ng/ml is regarded as the cutoff for hyperprolactinemia and a concentration less than 5 ng/ml as the cutoff of hypoprolactinemia for male. Hyperprolactinemia can lead to various adverse hormonal effects, including sexual dysfunction, gynecomastia, amenorrhea, and galactorrhea.[2]

Dopamine is the most relevant hypothalamic prolactin-inhibiting factor.[5] Dopamine D2 antagonists, such as risperidone, which binds tightly to D2 receptors, are associated with the highest rate of hyperprolatinemia due to their low blood-brain barrier penetration.[6] Hyperprolatinemia is relatively common during antipsychotic treatment, particularly treatment with risperidone in women. Our previous studies showed that prolactin concentrations in women are significantly higher than those in men after risperidone treatment.[7] However, there is little information on the detailed rate of hyperprolactinemia in men.

On the other hand, the D2 partial agonist aripiprazole is considered a prolactin-sparing antipsychotic, and most studies reported lower prolactin concentrations during aripiprazole treatment than during other antipsychotic treatments.[8] Aripiprazole significantly decreases the serum prolactin concentrations at all dosages.[2] Our previous study demonstrated that additional treatment with aripiprazole decreased the prolactin concentration that was elevated with other antipsychotics in a dose-dependent manner but reached a plateau at 6 mg/day.[9] In addition, the serum prolactin concentration in the aripiprazole combination group was lower than that in the nonaripiprazole combination group, regardless of antipsychotic monopharmacy or polypharmacy.[10]

Testosterone, a male reproductive hormone produced in the testes, has been implicated in male-typical sexual behavior. Testosterone levels influence sexual function, such as the loss of libido, impotence, and hypospermatogenesis.[11,12] Prolactin inhibits pulsatile glycoprotein releasing hormone secretion and consequently inhibits the pulsatile release of follicle stimulating hormone, luteinizing hormone, and testosterone.[13] However, there was little information on this association.

Herein, we investigated the association between prolactin abnormalities and dopaminergic agents and the relationship between prolactin and testosterone.

2 | METHODS

The subjects consisted of 177 physically healthy male outpatients who met the criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Version 5. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, Hirosaki University (2017-153), and Dokkyo Medical University (R-34-7J), and all patients gave their written informed consent to participate in the study.

Out of 177 patients, 93 males were outpatients receiving risperidone (n = 14) or paliperidone (n = 79), and 83 males were outpatients receiving aripiprazole. The inclusion criteria were the male schizophrenia patients treated with monotherapy of risperidone, paliperidone, or aripiprazole. The exclusion criteria were the patient treated

TABLE 1 Characteristics of male subjects receiving risperidone and aripiprazole

	Risperidone	Paliperidone	Risperidone group	Aripiprazole group
	n = 14	n = 79	n = 93	n = 83
Age (yo)	36.7 (11.0)	43.3 (11.7)	42.3 (11.8)	36.9 (10.2)**
Dose (ng/ml)	4.2 (2.7)	8.4 (2.9)	4.2 (1.7)	13.2 (8.8)
Prolactin (ng/ml)	27.5 (16.3)	27.5 (12.7)	27.5 (13.2)	3.9 (3.5)***
Total testosterone (ng/ml)	4.0 (1.5)	4.3 (1.8)[a]	4.2 (1.7)	5.1 (2.3)**
Free testosterone (pg/ml)	9.7 (1.0)	7.5 (2.7)	7.8 (2.6)	11.4 (4.6)***

Note: Data show mean (standard deviation).

[a]$P < .01$ compared with risperidone.

**$P < .01$.; ***$P < .001$ compared with risperidone group.

with other doperminergic agents and patients less than 20 years and older than 75 years. The patients must have received the same antipsychotic treatment for more than 3 consecutive months. The means and SDs of age are given in Table 1. No other drugs were given, except biperiden 4 mg to 40 patients, flunitrazepam 1-4 mg to 68 patients, and sennoside 12-48 mg to 32 patients. No depot antipsychotics were administered before the study. Blood samples for the quantification of the levels of prolactin and total and free testosterone were obtained between 8 AM and 12 PM.

Serum prolactin concentrations were measured by enzyme immunoassay (IMX Prolactin Dinapack, Dainabot Ltd.). Serum testosterone was measured by electrochemiluminescence immunoassay (ECLIA) (Roche Testosterone II Cobas), and free testosterone was measured by radioimmunoassay (RIA) (DPC Coat-A-Count kit, Diagnostic Products Corporation).

We analyzed risperidone and paliperidone as the risperidone group because they have the same pharmacological profile and the same effect on prolactin (Table 1). Daily dose of paliperidone was calculated as twice as daily dose of risperidone; 2 mg of paliperidone was equivalent as 1mg of risperidone. Drug differences based on age, prolactin concentration, and testosterone concentration were analyzed using *t* tests. Simple (Pearson) correlation analyses were used to examine the associations of the prolactin concentration with age and drug dosage and of the total and free testosterone concentrations with age, drug dosage, and prolactin concentration. Multiple regression analyses were performed to examine the associations of the total and free testosterone concentrations with age, the prolactin level, and the daily dose of each drug. A *P* value less than 0.05 was regarded as statistically significant. All analyses were performed using SPSS 25.0J for Windows (SPSS Japan Inc).

3 | RESULTS

There was no difference in prolactin levels between the risperidone-treated groups. The average serum prolactin concentration was 27.5 ± 13.1 ng/ml in the risperidone group and 3.9 ± 3.5 ng/ml in the aripiprazole group (Table 1), and the concentrations were significantly different ($P < .001$). We set more a serum prolactin concentration more than 20 ng/ml as the cutoff for hyperprolactinemia and a concentration less than 5 ng/ml as the cutoff of hypoprolactinemia.[2,3] The frequency of patients with serum prolactin concentrations less than 5 ng/ml was 0 of 94 (0%) in the risperidone group, whereas it was 62 of 83 (75%) in the aripiprazole group. The frequency of patients with serum prolactin concentrations greater than 20 ng/ml was 61 of 94 (65%) in the risperidone group, whereas it was 0 of 83 (0%) in the aripiprazole group. A positive correlation between the prolactin level and the risperidone daily dose was found, whereas a negative correlation between the prolactin level and the aripiprazole daily dose was observed (Figure 1 and Table 2).

The average serum total and free testosterone concentrations were 4.2 ± 1.7 ng/ml and 7.8 ± 2.6 pg/ml in the risperidone group

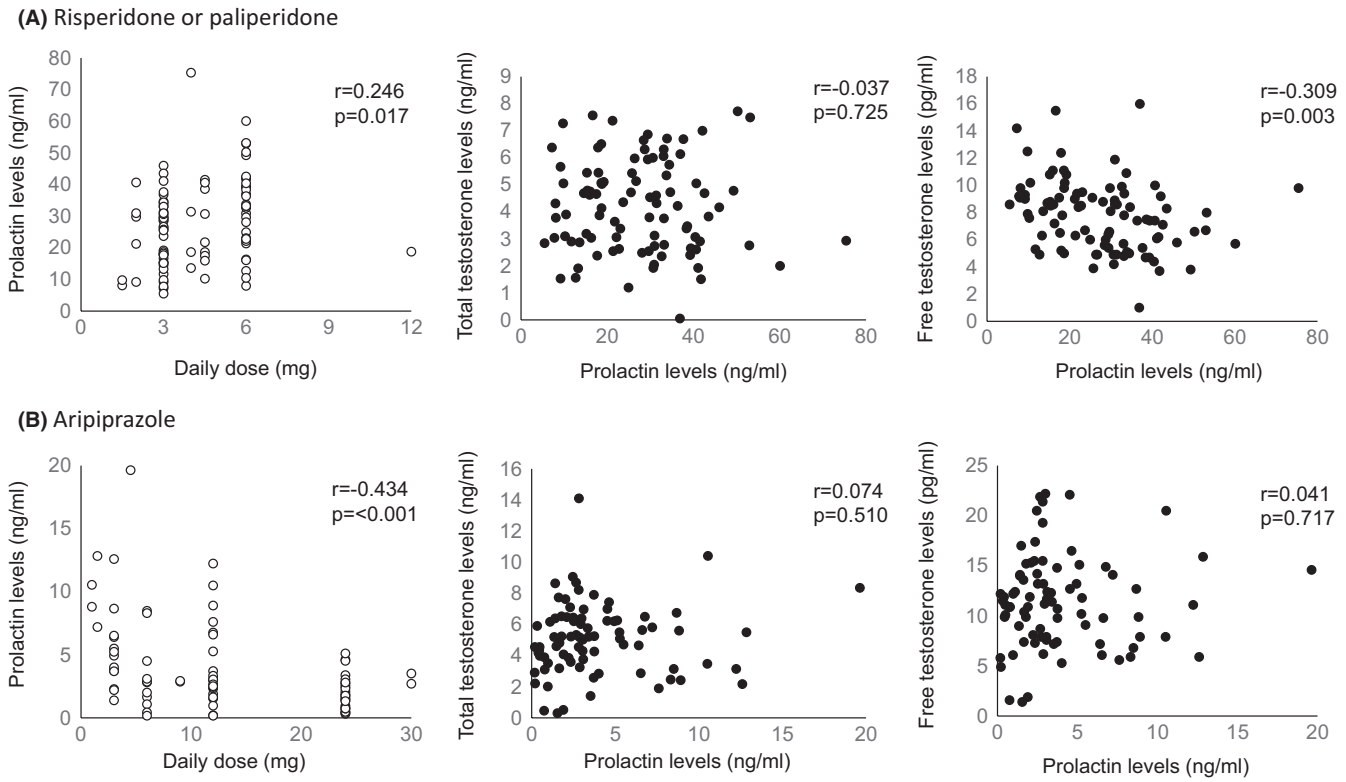

FIGURE 1 Correlations between daily doses and prolactin levels (left hands), prolactin levels and total testosterone (middle-hand), and prolactin levels and free testosterone (right hands). Upper figures indicate correlations in risperidone and paliperidone group, and lower figures indicate correlations in aripiprazole group

TABLE 2 Simple and multiple regression analyses between prolactin and age and dose in male patients receiving risperidone and aripiprazole

	Risperidone		Aripiprazole	
	r	beta	r	beta
Age (yo)	−0.165	−0.091	0.092	0.007
Dose (ng/ml)	0.246*	0.215[a]	−0.434***	−0.433***
R		0.260*		0.435***

Abbreviations: Beta, partial regression coefficients; R, Multiple correlation coefficients.

[a]$P = .051$.

*$P < .05$.; ***$P < .001$.

TABLE 3 Simple and multiple regression analyses between total testosterone and age, dose, and prolactin in male patients receiving risperidone and aripiprazole

	Risperidone		Aripiprazole	
	r	beta	r	beta
Age (yo)	0.460***	0.429***	−0.121	−0.145
Dose (ng/ml)	−0.253*	−0.121	−0.090	−0.099
Prolactin (ng/ml)	−0.037	0.064	0.074	0.044
R		0.475***		0.172

Abbreviations: beta; Partial regression coefficients; R, Multiple correlation coefficients.

*$P < .05$.; ***$P < .001$.

and 5.1 ± 2.3 ng/ml and 11.4 ± 4.6 pg/ml in the aripiprazole group (Table 1), respectively; both differences were significant ($P < .01$) (Table 1). In the risperidone group, the total testosterone concentration was correlated with age, while the free testosterone concentration was inversely correlated with age and prolactin levels (Figure 1 and Table 3,4). In the aripiprazole group, no correlations were found among testosterone concentrations, age, daily dose, and prolactin levels (Figure 1 and Table 3,4).

4 | DISCUSSION

The results of this study showed that no hypoprolactinemia was found in the risperidone group, whereas hypoprolactinemia was observed in 75% of the aripiprazole group. The frequency of patients with serum prolactin concentrations greater than 20 ng/ml was 61 of 94 (65%) in the risperidone group, whereas it was 0 of 83 (0%) in the aripiprazole group. Prolactin concentrations were correlated with the dosage of dopamine antagonist and inversely correlated with the dosage of dopamine partial agonist. Therefore, the prolactin concentration can be controlled by the dose reduction of dopaminergic agents. These findings were in line with previous studies showing positive correlations between 9-hydroxyrisperidone concentrations and prolactin[14] and inverse correlation between aripiprazole concentrations and prolactin,[15] and it may be natural that prolactin

TABLE 4 Simple and multiple regression analyses between free testosterone and age, dose, and prolactin in male patients receiving risperidone and aripiprazole

	Risperidone		Aripiprazole	
	r	beta	r	beta
Age (yo)	−0.341**	−0.423***	−0.196	−0.206
Dose (ng/ml)	−0.010	−0.067	−0.010	−0.030
Prolactin (ng/ml)	−0.309**	−0.362***	0.041	0.047
R		0.507***		0.207

Abbreviations: beta; Partial correlation coefficients; R, Multiple correlation coefficients.

**$P < .01$.; ***$P < .001$.

secretion is directly influenced by drug concentrations of dopaminergic agents because the pituitary gland is outside the blood-brain barrier.

A previous study suggested that the incidence of hypoprolactinemia was 44.0% (11/25), including 7 patients who received aripiprazole and other antipsychotics, and there was no significant correlation between the prolactin levels and dose of aripiprazole used in the 18 patients who had taken aripiprazole alone.[16] However, our study found a significant correlation between the aripiprazole dose and the prolactin concentration. The former was a preliminary study with a small number of subjects (n = 18). Although no direct relationship between hypoprolactinemia and clinical relecvance has been determined, patients in the lowest prolactin quartile showed a higher risk of metabolic syndrome ($P < .05$), arteriogenic erectile dysfunction ($P < .05$), and premature ejaculation ($P < .05$) in a consecutive series of 2531 male patients attending the outpatient clinic for sexual dysfunction.[4] Therefore, hypoprolactinemia is, to some extent, clinically relevant. Taken together with the high frequency of hypoprolactinemia in patients taking aripiprazole, further studies are needed to determine the relevance in the clinical setting.

Testosterone binds strongly to sex hormone binding globulin (SHBG), and the measurement of free testosterone may be more appropriate than measuring the total serum testosterone, according to the free hormone theory.[17] There is general agreement that approximately 44% of circulating testosterone is strongly bound to SHBG, 54% is loosely bound to albumin, and 2% is present as a free hormone.[18] Serum SHBG increases with age and often affects the proportion of testosterone in each fraction. The Japanese clinical guidelines for late-onset hypogonadism (LOH) (Japanese Society of Urology and Japanese Society of Men's Health) define the diagnostic criteria for LOH as the simultaneous presence of reproducibly low serum free testosterone (free testosterone <8.5 pg/ml) and three sexual symptoms (erectile dysfunction and reduced frequencies of sexual thoughts and morning erections). In this study, the prevalence of low levels of free testosterone was significantly higher in the risperidone group than in the aripiprazole group, with 57% of patients receiving risperidone having free testosterone levels less than 8.5 pg/ml and 29% of patients receiving aripiprazole having free testosterone less than 8.5 pg/ml. This is may be explained by much

higher prolactin concentration in patients receiving risperidone in patients receiving aripiprazole and the free testosterone concentration inversely correlated with prolactin levels in only the risperidone group. On the other hand, no difference was found in the prevalence of low total testosterone levels (less than 2.31 ng/ml) between the risperidone group (11%) and aripiprazole group (9%). The discrepancy between free testosterone and total testosterone may be explained by the characteristics of SHBG, the level of which fluctuates with physiological conditions are altered by natural hormones and synthetic steroids. Interindividual differences in plasma SHBG levels and activity are also influenced by polymorphisms within the structural and regulatory regions of the SHBG gene.[19]

This study had several notable limitations. First, this study had a cross-sectional design. We did not obtain the degree of hypoprolactinemia because we had no baseline prolactin data before aripiprazole therapy. The possibility that some patients would have had hypoprolactinemia without antipsychotics, including aripiprazole, cannot be excluded. In addition, we did not examine pituitary function tests or brain imaging. Second, we did not evaluate the symptoms of sexual function; hence, we could not determine the effect of hypoprolactinemia induced by aripiprazole treatment on sexual function, although sexual dysfunction in schizophrenia is thought to be caused by abnormal prolactin. In addition, approximately 30%-40% of healthy subjects complain of some sexual dysfunction. Third, we did not measure the drug concentrations. There is interindividual variability between doses and drug concentrations, probably because of interindividual variability in the activity of the enzymes catalyzing drug metabolism, particularly CYP2D6, by which risperidone and aripiprazole are metabolized. Stronger correlations among prolactin, testosterone, and drug concentrations might have been obtained in this study if the drug concentrations were included in the analyses. Last, measuring the serum free testosterone concentration with analogue immunoassays has been widely criticized due to the lack of accuracy and the variability in results with fluctuating SHBG concentrations. An alternative is to calculate the free testosterone using equations based on the law of mass action. Otherwise, the levels of free testosterone could have been calculated from the total testosterone, SHBG, and albumin concentrations using a simple formula.

5 | CONCLUSIONS

In conclusion, we found very common hyperprolactinemia and hypoprolactinemia in the risperidone group and aripiprazole group, respectively. Testosterone concentrations were associated with elevated prolactin levels in patients receiving risperidone, but in patients receiving aripiprazole, there was no tendency of such associations.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

NYF and MT designed the study and wrote the initial draft of the manuscript. NYF, and MT, SY, and MS took samples and obtained patients' informed consents. KS contributed to the analysis and interpretation of data, and NS assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, Hirosaki University, and Dokkyo Medical University (reference number:R-27-6J, R-34-7J), and all patients gave their written informed consent to participate in the study.

INFORMED CONSENT

All participants provided their written informed consent. Public availability of raw data was not planned in the research protocol approved by an Institution Reviewer Board. We did not obtain informed consent of the public availability.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Not available.

ANIMAL STUDIES

Not available.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy and ethical restrictions.

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