Original Article

Factors Influencing Blood Prolactin Levels in Patients with Schizophrenia under Risperidone Treatment

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Abstract

Objectives: Risperidone, a dopamine and serotonin antagonist or a second-generation (atypical) antipsychotic drug, is commonly prescribed for various psychiatric disorders, including schizophrenia, bipolar disorder, and autism spectrum disorders. While effective, risperidone often leads to hyperprolactinemia, impacting about 40%–80% of patients. In this study, we intended to examine the prevalence of hyperprolactinemia in Taiwanese patients with schizophrenia who received risperidone medication and to analyze potential links between prolactin blood levels and clinical variables. **Methods:** Patients with schizophrenia receiving risperidone monotherapy were included in this cross-sectional study. Blood levels of prolactin and metabolic parameters were measured. **Results:** A total of 176 participants diagnosed with schizophrenia, including 87 women and 89 men, were enrolled in our study. The prevalence of hyperprolactinemia and metabolic syndrome was 75.6% and 31.8%, respectively. Patients with hyperprolactinemia showed significantly higher insulin blood levels ($p < 0.05$) and significantly higher homeostasis model assessment for insulin resistance (HOMA-IR) indexes ($p < 0.05$) than those without hyperprolactinemia. The results of multivariate linear regression analysis showed that female sex ($p = 0.001$), HOMA-IR index ($p < 0.01$), and risperidone daily dosage ($p < 0.05$) were significantly associated with prolactin blood level. **Conclusion:** This study adds to the existing knowledge concerning risperidone-induced hyperprolactinemia in Taiwanese patients with schizophrenia. Hyperprolactinemia and metabolic syndrome are prevalent in patients with schizophrenia treated with risperidone. Clinicians are advised to be aware of these problems and monitor them regularly with their patients who receive treatment with risperidone.

Key words: serotonin and dopamine antagonist, insulin resistance, metabolic homeostasis, Taiwan
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Introduction

Risperidone is a dopamine and serotonin antagonist as defined in a neuroscience-based nomenclature system (www.NbN3.org). It is a second-generation (atypical) antipsychotic drug that primarily exerts its pharmacological effects through dopamine D_2 and 5-HT_{2A} receptor antagonism [1]. Risperidone is widely prescribed for treating various psychiatric disorders, including schizophrenia, bipolar disorder, and specific behavioral disturbances associated with autism spectrum disorders [2]. While it has proven effective in managing the symptoms of these conditions, risperidone is also linked to remarkable side effects, notably its impact on elevated prolactin blood levels. Dopamine acts as a prolactin-inhibiting factor on dopamine D_2 receptors, whereas serotonin stimulates prolactin secretion. Several studies have consistently reported that the administration of risperidone for the treatment of schizophrenia is associated with elevated prolactin blood levels. This elevated prolactin level is often accompanied by a notable incidence of prolactin-related symptoms.

Prolactin, primarily associated with lactation, also plays a vital rôle in the body [3]. Hyperprolactinemia is defined as an increase in the blood level of prolactin beyond normal values, which vary depending on the assay technique used. The maximum cutoff values range from 15 to 25 ng/mL in women

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and 15 to 20 ng/mL in men. Health professionals often fail to detect antipsychotic-induced hyperprolactinemia symptoms. There are several reasons, including the nature of the symptoms and the attitudes of both patients and health professionals. Nonadherence to antipsychotic treatment is common with prolactin-related side effects. Hyperprolactinemia manifests differently in genders: menstrual irregularities and hirsutism in female patients, or gynecomastia and oligospermia in male patients [4]. Both genders have shared symptoms of hyperprolactinemia, such as galactorrhea, infertility, and sexual dysfunction [5]. Furthermore, long-term health consequences of hyperprolactinemia include weight gain, reduced bone density, osteoporosis, fractures [6], and an elevated risk of breast cancer [7].

The prevalence of risperidone-induced hyperprolactinemia is estimated at 40%–80% [8, 9]. In many studies, investigators have tried have tried to identify specific factors influencing the prolactin response to antipsychotic medication [1]. It is repeatedly found that prolactin responses to antipsychotic drugs are more in female patients than in male patients [10, 11]. This gender difference can be explained by the ability of estrogen to elevate prolactin blood levels and enhance responsiveness to prolactin-releasing stimuli [12, 13]. In addition, prolactin elevations due to risperidone medication tend to be dose-related [14, 15]. An increased dosage of risperidone is likely to result in heightened dopamine D_2 blockade, consequently leading to elevated blood levels of prolactin. Several studies have also investigated the interplay between age and the tendency of antipsychotics to raise prolactin levels, uncovering diverse patterns and implications. Notably, female patients of reproductive age exhibit greater susceptibility to the prolactin-elevating effects induced by risperidone [8, 9].

Earlier investigations involving Taiwanese individuals with schizophrenia have consistently shown elevated prolactin levels attributable to risperidone [16-18]. But these studies are limited due to their relatively small sample sizes. Notably, some Taiwanese studies indicated that the patients in risperidone long-acting injection group exhibit lower prolactin blood levels compared to those in the oral risperidone group [19, 20]. In contrast, another study has found no differences between the patients in risperidone long-acting injection group and those in the oral risperidone group [21]. Consequently, the evidence regarding the beneficial effect of risperidone long-acting injection over oral risperidone on prolactin blood levels remains inconclusive.

In this study, we intended to examine the prevalence of hyperprolactinemia in Taiwanese patients with schizophrenia who received risperidone medication. We also attempted to analyze the potential links between prolactin blood levels, clinical variables, and laboratory variables.

Methods

Study participants

The Joint Institutional Review Board of Taipei Medical University approved this cross-sectional study protocol (protocol number = N202107011 and date of approval = August 11, 2021), requiring to obtain informed consent signed by study participants. After providing a detailed study description, we obtained written informed consent from the participants. The study took place from August 2021 to August 2023.

In this study, we included patients aged 20–65 years and with schizophrenia diagnosed according to *the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. They needed to have received risperidone monotherapy at the same dose for the previous six months. Doses of 25, 50, or 75 mg of risperidone long-acting injection every two weeks were bioequivalent to daily oral doses of 2, 4, or 6 mg of oral risperidone, respectively.

Assessments

All study participants participated in clinical interviews, received anthropometrical parameter assessments, and provided fasting blood samples. A trained study nurse interviewed patients to collect demographic and psychiatric information. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).

Blood samples were obtained in the morning after overnight fasting. Blood was stored at −80°C before testing. Blood levels of prolactin were measured using electrochemiluminescence immunoassays. Hyperprolactinemia was considered when the prolactin blood level exceeded 20 ng/mL in women and 15 ng/mL in men, in accordance with laboratory procedures. Enzymatic colorimetric assays were used to measure fasting blood levels of glucose, high-density lipoprotein cholesterol (HDL-C), and triglycerides. Blood insulin levels were measured using an electrochemiluminescence immunoassay kit. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) as follows: (fasting glucose [mmol/L] × fasting insulin [mU/L]/22.5) [22].

In this study, we used the modified Adult Treatment Panel III criteria for Asians to evaluate participants for metabolic syndrome [23]. A diagnosis of metabolic syndrome required three or more of the following five criteria: (a) abdominal obesity (waist circumference of ≥ 90 cm in men and ≥ 80 cm in women), (b) fasting hypertriglyceridemia (≥ 150 mg/dL); (c) low fasting HDL-C levels (< 40 mg/dL in men and < 50 mg/dL in women), (d) high blood pressure (≥ 130/ ≥ 85 mmHg) or current treatment with antihypertensive medication, and (e) high fasting blood levels of plasma glucose (≥ 100 mg/dL) or current treatment with antidiabetic medication.

Statistical analysis

The variables were compared using the Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. We used Pearson's correlation method to analyze the correlations between variables and prolactin blood levels. A multivariate linear regression model with a selection of clinically relevant variables related to prolactin level was used. All continuous variables that were entered in the regression were logarithmically transformed to normalize data, while categorical variables were recoded into sets of distinct binary variables.

With the Statistical Package for the Social Science software version 19 for Windows (SPSS Inc., Chicago, Illinois, USA), we analyzed all study variables. The differences between groups were considered significant if *p*-values were smaller than 0.05.

Results

A total of 176 participants diagnosed with schizophrenia, including 87 women and 89 men, were enrolled in our study. The participants' mean age was 44.4 ± 11.9 years, and the mean risperidone dose was 4.0 ± 1.5 mg/day. The mean prolactin level was 56.7 ± 53.8 ng/mL. The overall prevalence of metabolic syndrome was 31.8%.

Table 1 summarizes the participants' demographic, clinical, and laboratory data with and without hyperprolactinemia. Notably, 75.6% of the participants were diagnosed with hyperprolactinemia. Participants with hyperprolactinemia showed significantly higher insulin levels ($p < 0.05$) and HOMA-IR indexes ($p < 0.05$) than those without hyperprolactinemia.

Table 2 presents the demographic, clinical, and laboratory data stratified by sex. Male participants showed significantly lower prolactin blood levels ($p < 0.001$), BMIs ($p < 0.05$), and HDL-C blood levels ($p < 0.05$), alongside significantly higher diastolic blood pressure values ($p < 0.05$) and triglyceride blood levels ($p < 0.01$). But there was no significant difference in the prevalence of hyperprolactinemia between genders.

Pearson's correlation method was used to analyze the correlations between variables and prolactin blood levels. Prolactin blood level had significantly positive correlations with risperidone dose ($r = 0.188$, $p < 0.05$), insulin level ($r = 0.229$, $p < 0.01$), and HOMA-IR index ($r = 0.160$, $p < 0.05$). Subsequently, we did further correlation analyses to explore the impact of the interplay between sex and age on prolactin blood levels. But no significant correlations were observed between age and prolactin blood levels in either male or female patients.

A multivariate linear regression model was used to identify variables associated with prolactin blood levels (Table 3). The selection of variables of interest was based on correlation results, with risperidone dose, blood insulin level, and HOMA-IR index chosen. In addition, considering findings from previous studies, sex and age were also included as variables of interest. The assumptions of homogeneity of variance and linearity of data were met, the residuals were about normally distributed, and the collinearity statistics exhibited acceptable results, with variance inflation factor scores under 5 for each predictor. As shown in Table 3, female sex (B = 0.496 (B means beta coefficient), $p = 0.001$), HOMA-IR index (B = 0.216, $p < 0.01$), and risperidone dose (B = 0.320, $p < 0.05$) were significantly associated with prolactin blood level. The results of the regression showed that the overall model containing all the above-mentioned variables was significant with F (3; 172) = 8.921, adjusted R^2 of 0.135, $p < 0.001$.

Discussion

The study provided valuable information about the impact of risperidone on prolactin blood levels and its association with clinical variables in Taiwanese patients with schizophrenia. The finding showed a high prevalence of hyperprolactinemia (75.6%) in patients receiving risperidone. This result aligns with previous findings, demonstrating the propensity of risperidone to elevate prolactin blood levels significantly.

One noteworthy correlation in this study was the positive relationship between risperidone dose and blood prolactin levels. As shown in Table 3, the result of the multiple

Table 1. Demographic, clinical, and laboratory characteristics of study subjects by hyperprolactinemia

	Hyperprolactinemia present (n = 133)	Hyperprolactinemia absent (n = 43)
Demographic parameters		
Sex (male/female)	66/67	23/20
Age (years)	44.7 ± 12.5	43.5 ± 9.7
Duration of illness (years)	18.5 ± 10.3	17.2 ± 10.4
BMI	26.9 ± 11.1	24.9 ± 4.4
Waist circumference (cm)	89.1 ± 14.6	89.5 ± 13.4
SBP (mmHg)	119.0 ± 16.0	123.1 ± 18.0
DBP (mmHg)	76.2 ± 11.4	76.1 ± 14.5
Clinical parameter		
Risperidone dosage (mg/day)	4.1 ± 1.6	3.7 ± 1.5
Laboratory parameters		
Blood glucose level (mg/dL)	103.6 ± 75.6	88.5 ± 17.4
Blood insulin level (μU/mL)	12.9 ± 14.0*	8.4 ± 5.0
HOMA-IR	3.9 ± 6.3*	2.0 ± 1.6
Blood triglycerides level (mg/dL)	133.3 ± 75.8	152.3 ± 119.6
Blood HDL-C level (mg/dL)	51.3 ± 16.2	49.6 ± 17.4
Metabolic syndrome (%)	30.8	34.9

*$p < 0.05$ significantly differently between groups using t-test.
BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; SBP, systolic blood pressure

Table 2. Comparison of demographic, clinical, and laboratory characteristics of study subjects by sex

	Male patients (n = 89)	Female patients (n = 87)
Demographic parameters		
Age (years)	43.7 ± 11.2	45.2 ± 12.6
Duration of illness (years)	17.6 ± 9.7	18.8 ± 10.9
BMI	24.5 ± 4.1*	28.3 ± 13.3
Waist circumference (cm)	89.0 ± 11.4	89.3 ± 16.8
SBP (mmHg)	120.2 ± 14.7	119.9 ± 18.3
DBP (mmHg)	78.2 ± 12.4*	74.1 ± 11.7
Clinical parameters		
Risperidone dose	3.8 ± 1.6	4.1 ± 1.5
Metabolic syndrome (%)	30.3	33.3
Laboratory parameters		
Prolactin blood level (ng/mL)	40.3 ± 39.3***	73.5 ± 81.2
Hyperprolactinemia (%)	74.2	77.0
Glucose blood level (mg/dL)	102.9 ± 89.3	96.8 ± 28.7
Insulin blood level (μU/mL)	10.6 ± 10.5	13.0 ± 14.3
HOMA-IR	3.2 ± 5.7	3.7 ± 5.4
Triglyceride blood level (mg/dL)	155.9 ± 108.6**	119.5 ± 56.5
HDL-C blood level (mg/dL)	46.3 ± 15.8***	55.6 ± 15.9

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ significantly different between groups using t-test.
BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; SBP, systolic blood pressure

Table 3. Multiple linear regression analysis with prolactin blood levels as dependent variable

	B (95% CI)	t
Female sex	0.496 (0.212–0.781)	3.444***
HOMA-IR	0.216 (0.074–0.358)	3.004**
Dosage (mg/day)	0.320 (0.012–0.627)	2.050*
Blood insulin level	0.134 (−0.539–0.807)	0.393
Age	0.053 (−0.443–0.549)	0.212

*$p < 0.05$; **$p < 0.01$; ***$p = 0.001$
B, regression coefficient; CI, confidence interval; HOMA-IR, homeostasis model assessment for insulin resistance

linear regression analysis showed that higher risperidone caused significantly higher blood prolactin levels ($p < 0.05$). Risperidone leads to a higher increase in blood prolactin levels than other second-generation antipsychotics due to high dopamine D_2 receptor affinity and an incomplete crossing of the blood–brain barrier. Higher doses of risperidone are generally associated with greater blockade of the dopamine D_2 receptors. This blockade of dopamine transmission leads to the loss of inhibitory control over dopaminergic prolactin in lactotrophic cells in the anterior lobe of the pituitary. This finding is consistent with existing literature, emphasizing the dose-dependent nature of risperidone-induced hyperprolactinemia [15, 24].

We found that blood insulin levels ($p < 0.05$) and insulin resistance (as indicated by the HOMA-IR index) ($p < 0.05$) were significantly correlated with prolactin blood levels. The significance of the correlation of HOMA-IR with prolactin blood level was still maintained ($p < 0.01$) in multiple linear regression analysis, although the significance of blood insulin level was lost in this study (Table 3). This correlation between insulin variables and blood prolactin level means that potential underlying metabolic mechanisms contribute to risperidone-induced hyperprolactinemia [25]. The effects of prolactin on metabolism are the result of its pleiotropic action reflected by the presence of the prolactin receptors in the main metabolic organs, including the pancreas, liver, adipose tissue, muscle, intestine, and hypothalamus [25]. Recent study findings have supported that prolactin levels within or above the reference range may be differently related to metabolic homeostasis [26, 27]. Clinical data have shown an association of hyperprolactinemia with an increased prevalence of obesity and metabolic disorders such as dyslipidemia, glucose intolerance, and insulin resistance. But the establishment of a cutoff value for prolactin blood levels as a marker for metabolic diseases creates a practical problem rooted in the variability and prolactin secretion, the susceptibility of prolactin secretion to external stimuli, the impact of medication, and intraindividual variation. While the exact mechanisms remain to be elucidated, this association emphasizes the importance of considering metabolic factors in understanding the complexities of antipsychotic-induced hormonal dysregulation.

In this study, gender disparities in prolactin blood levels were also highlighted. As shown in Table 2, female patients were found to have significantly higher prolactin levels compared to male patients ($p < 0.001$). This significance was further shown ($p = 0.001$) in multiple linear regression analysis (Table 3). This observation is consistent with previous study findings, emphasizing the gender-specific impact of antipsychotics on prolactin secretion [11, 28]. This might be partly due to higher base levels of prolactin and higher vulnerability to hyperprolactinemia in response to antipsychotic drugs in female patients. Such gender-related variations are crucial in tailoring treatment approaches.

In our study, we found that the prevalence of metabolic syndrome was 31.8% of our study patients. This finding is consistent with previous epidemiological studies reporting about one-third of Taiwanese patients with schizophrenia or schizoaffective disorder having metabolic syndrome [29]. Huang et al. [29] have also proposed a notable association between females and the presence of metabolic syndrome.

In the present study (Table 2), we found that compared to female patients, male patients showed significantly higher diastolic blood pressure values ($p < 0.05$) and significantly higher triglyceride levels ($p < 0.01$), but male patients had significantly lower BMI ($p < 0.05$) and significantly lower HDL-C ($p < 0.001$) levels. But, despite these gender-specific variations in metabolic parameters, we did not observe a significant gender difference in the occurrence of metabolic syndrome in our study (Table 2). Montgomery et al. [9] reviewed data from electronic databases to ascertain the prevalence and effects of hyperprolactinemia in hospitalized

patients with schizophrenia who were being treated with first- and second-generation antipsychotics. Their findings suggest that age does not exert a discernible influence on the prevalence of prolactin elevation in male patients, but that a decrease in prolactin blood levels with age is identified in female patients [9]. In the current study, we observed no significant correlations between prolactin blood levels and age in either male or female patients. Nonetheless, additional studies are warranted to look deeper into the potential impact of age on prolactin blood levels and to enrich our understanding of these dynamics.

A potential therapeutic approach for managing risperidone-induced hyperprolactinemia involves changing from the oral form to the long-acting injectable form of risperidone. Bai et al. [19] documented a decrease in prolactin blood levels following the switch from oral risperidone to risperidone long-acting injection. But, another study presented conflicting results [21]. Due to a limited sample size (only seven participants receiving risperidone long-acting injection), we did not compare prolactin blood levels between the two groups of patients with different drug administration routes. Consequently, additional research is essential to clarify the effects of diverse administration routes of antipsychotics on prolactin blood levels, and to offer a more comprehensive understanding of this complex relationship.

Study limitations

The readers are warned not to overinterpret the study findings because this study has four limitations:

- The cross-sectional design restricts the establishment of causal relationships between variables. Longitudinal studies could provide a more comprehensive understanding of the dynamic changes in prolactin levels over time and their correlation with metabolic profiles.
- Participants with schizophrenia in this study were clinically stable. The results cannot be generalized to patients in other illness stages.
- All participants in this study received risperidone monotherapy. The results cannot be generalized to other antipsychotic drugs.
- The exact days in the female patients' menstrual cycles when the blood tests were performed were not recorded in our study.

With those limitations in this study, we suggest that further studies addressing those four limitations are needed to strengthen and duplicate the study findings.

Summary

Our study findings add to the existing knowledge concerning risperidone-induced hyperprolactinemia in Taiwanese patients with schizophrenia. Prolactin blood level was positively correlated with risperidone dose, blood insulin level, and insulin resistance index. Female patients had higher prolactin blood levels than that of male patients. Prolactin levels and metabolic parameters in risperidone-treated patients with schizophrenia should be monitored regularly.

Data Availability Statement

Original study data used in this study can be shared if contact with the corresponding author is made.

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Conflicts of Interest

Mong-Liang Lu, a domestic advisory board member of *the Taiwanese Journal of Psychiatry* (Taipei), had no rôle in the peer review process or decision to publish this article. All authors of this article declared no conflicts of interest in writing this paper.

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