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The Short-Term Effects of Risperidone-Induced Hyperprolactinemia on Lipid Metabolism in Drug-Naïve Children and Adolescents

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Objective The present cross-sectional study was designed to assess the risk of elevated prolactin levels and other hormonal or metabolic changes in children and adolescents taking risperidone.

Methods Twenty-five children and adolescents [aged 7−18 years, 12.1±3.3 years (mean±SD); 19 boys and 6 girls] who had been taking risperidone for at least 3 months were enrolled. The following blood parameters were measured: serum levels of prolactin, thyroid hormones, alanine transaminase (ALT), sex hormones, lipids.

Results The median risperidone dosage was 1.55 mg/day (SD 1.14 mg/day, range 0.25−4.00 mg/day). The prolactin level (33.65± 16.71 ng/mL, range 5.8−68.3 ng/mL) was higher than normal, and was elevated (≥15 ng/mL in male, ≥23.3 ng/mL in female) in about 84% of the patients. The dosage of risperidone was positively correlated with serum prolactin level (r=0.767, p<0.001). The TG/HDL ratio was higher in the group with higher prolactin levels (i.e., ≥30 ng/mL), and hence might be a useful marker of insulin resistance.

Conclusion In young patients taking risperidone, a high serum prolactin level may influence lipid metabolism, even when cholesterol levels are within the normal range. Further investigation is needed around this issue. Serum prolactin assessment is recommended for children and adolescents taking risperidone. **Psychiatry Investig 2015;12(1):55-60**

Key Words Risperidone, Hyperprolactinemia, Prolactin, Antipsychotics, Lipid.

INTRODUCTION

Hyperprolactinemia is reportedly associated with abnormal carbohydrate and lipid metabolism.[1] Decreased glucose tolerance, hyperinsulinemia, increased lipid synthesis, and increased food intake have been demonstrated in patients with hyperprolactinemia, and hence long-term hyperprolactinemia is often accompanied by weight gain in humans.[2,3] In particular, sustained elevation of prolactin, caused by either antipsychotic drugs or prolactinomas, leads to increased weight, which can be ameliorated by normalization of serum prolactin.[4-6] In addition, there is increasing evidence that prolactin plays a role in whole-body insulin sensitivity by stimulating insulin release and regulating adipokine release.

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Risperidone has been used widely in children and adolescents with tic disorders, attention deficit/hyperactivity disorder (ADHD), conduct disorders, and psychotic disorders,[7] and has the potential to increase plasma prolactin levels, which can induce a range of short- and long-term adverse effects.[8] The short-term adverse effects include galactorrhea, gynecomastia, menstrual irregularities, and sexual dysfunction.[9] The reported long-term adverse effects are loss of bone density, weight gain, and tumors.[10] However, among these adverse effects, the relationship between antipsychotic-induced hyperprolactinemia and weight gain or metabolic changes remains unclear, given that prolactin-sparing antipsychotics, including quetiapine, olanzapine, and clozapine can also induce weight gain without hyperprolactinemia.

The present study was designed to determine the relationship between hyperprolactinemia and metabolic changes in children and adolescents taking risperidone, by examining prolactin levels and metabolic profiles, such as weight, body mass index (BMI), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG). While there have been many studies of short- and long-term antipsychotic-induced hyperprolactinemia, to the best of our

knowledge, this is the first study of antipsychotic-induced hyperprolactinemia and metabolic changes in drug-naïve children and adolescents.

METHODS

Subjects

Twenty-five children and adolescents aged between 7 and 18 years who had been taking risperidone for at least 3 months were recruited from outpatient child psychiatric clinics. The protocol was approved by the institutional review board (Inje University). The parents provided written informed consent for their children to participate in the study, and the children assented to their participation. Basic data were obtained, including age, gender, height and weight, medication and dosage, adverse effects history, other medications being taken, family medical history, and diagnoses. Patients were excluded from participation if they had been taking other antipsychotics, or were taking any medication or had any physical condition that could affect prolactin and hormonal levels. This was the first visit to the psychiatric clinic for all of the included patients, and so none of them had a history of antipsychotic treatment before the study. Concomitant treatment with antidepressants, anticholinergics, and benzodiazepines was allowed. Diagnoses were established by the child and adolescent psychiatrist who was treating the patient, according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria.

Procedure

Blood was collected by standard venipuncture. A range of common adverse effects was assessed through questioning the patients and their parents. The following parameters were measured: weight, height, BMI (kg/m^2), and plasma levels of glucose, triglycerides (TG), total cholesterol, HDL, prolactin, thyroid hormones [free thyroxine (T4), triiodothyronine, bound T4, and thyroid-stimulating hormone], alanine transaminase, and the sex hormones [luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, estrogen, and estradiol in girls; testosterone and free testosterone in boys].

Table 1. Subject characteristics

	All (N=25)	Range	Males (N=19)	Females (N=6)	Reference range
Characteristic					
Age (years)	12.12±3.35	7–18			
Height (cm)	149.5±16.8	121.3–176	148.18±18.76	154.05±7.82	
Weight (kg)	48.7±17.1	23.9–88	47.54±18.51	52.56±12.77	
BMI (kg/m^2)	20.9±3.5	15.3–28.9	20.69±3.45	21.89±4.03	
Dosage of risperidone (mg)	1.52±1.16	0.25–4	1.51±1.16	1.54±1.28	
Serum profile					
Prolactin (ng/mL)	33.65±16.71	5.8–68.3	35.42±16.93	28.05±16.07	4.0–15.2 ng/mL (male) 4.0–23.3 ng/mL (female)
Glucose (mg/dL)	97.08±13.58	80–149	97.84±14.93	94.67±8.57	70–110 mg/dL
ALT (IU/L)	28±48.32	9–249	30.78±55.54	19.67±11.84	<40 IU/L
Total cholesterol (mg/dL)	173.2±28.61	121–257	172.74±26.77	174.67±36.69	130–240 mg/dL
HDL (mg/dL)	53.54±11.28	35–86	53.50±10.68	53.67±14.05	30–80 mg/dL
TG (mg/dL)	123.96±69.54	48–302	115.58±62.66	150.50±89.25	30–200 mg/dL
T3 (ng/mL)	1.26±0.27	0.73–1.74	1.32±0.27	1.07±0.17	0.80–2.00 ng/mL
T4 (μg/dL)	7.71±1.52	4.6–10.8	7.96±1.50	6.91±1.41	5.1–14.1 μg/dL
TSH (μIU/mL)	2.98±2.06	0.45–7.49	3.14±2.13	2.48±1.91	0.27–4.20 μIU/mL
LH (mIU/mL)	2.66±2.92	0.1–11.3	2.04±2.18	4.65±4.20	
FSH (mIU/mL)	2.85±1.68	0.4–7.6	2.48±1.40	4.01±2.10	
Free testosterone (ng/dL)		0.08–13.8	3.48±4.06		
Testosterone (ng/dL)		25–490.5	138.65±174.26		
Estrogen (pg/mL)		33.3–268		170.86±98.94	
Progesterone (ng/mL)		0.1–0.4		0.24±0.09	
Estradiol (pg/mL)		5–84.2		44.33±28.59	

BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone, TG: triglycerides, HDL: high-density lipoprotein, TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxin, ALT: alanine aminotransferase

Statistical methods

SAS 9.3 (SAS Institute, Cary, NC, USA) and SALT 2.5 were used for all statistical analyses. Descriptive statistics were used to describe the demographics, clinical measures, and laboratory values. Quantitative data are expressed as mean±SD values. Group comparisons were made using independent-samples t-test, and Pearson's correlation analysis was used for correlation analysis. For all statistical analyses, the level of statistical significance was set at $p<0.05$ (two-tailed).

RESULTS

In total, 25 patients (aged 12.1±3.3 years, 19 boys and 6 girls) were enrolled in the study. The results are listed in Table 1 and summarized in Table 2 and 3. Most of the patients were diagnosed with ADHD, a tic disorder, major depression, bipolar disorder, disruptive behavior disorder, psychotic disorder, or mental retardation. The most common diagnoses were tic disorder (n=10, 40%) and mood disorders (depression and bipolar disorder; n=11, 44%), while six patients (24%) had an anxiety disorder and six (24%) had ADHD.

Ten subjects (40%) were taking risperidone monotherapy. Among the remainder, the concomitant medications comprised selective serotonin reuptake inhibitors (36%), valproic acid (20%), benzodiazepine (16%), methylphenidate (12%), and benztropine (8%).

The median risperidone dosage was 1.55 mg/day (SD=1.14 mg/day, range 0.25−4 mg/day). The prolactin level (33.65± 16.71 ng/mL, range 5.8−68.3 ng/mL) was higher than normal, with hyperprolactinemia (>15.2 ng/mL in male, >23.3ng/

Table 2. Diagnoses and concomitant medication for each of the participants

Patient number	Gender	Age	Diagnosis	Dosage of risperidone (per day)	Concomitant medication
1	M	8	Tic Ds, Anxiety Ds	1 mg	None
2	M	14	Psychotic Ds, Depression	3 mg	Benztropine
3	M	13	ADHD, ODD	1 mg	Methylphenidate
4	M	9	ADHD, Bipolar Ds	1 mg	None
5	M	15	OCD	1 mg	Fluoxetine, Lorazepam, Propranolol
6	F	12	ADHD, Tic Ds	1.5 mg	None
7	F	13	Psychotic Ds	0.25 mg	None
8	F	13	Psychotic Ds, Depression	4 mg	None
9	F	15	Anxiety Ds, Depression	1.5 mg	Sertraline
10	M	9	ADHD, Tic Ds	1.5 mg	Atomoxetine
11	F	11	Tic Ds, Anxiety Ds	1 mg	Fluoxetine
12	M	9	ADHD, MR	1 mg	Methylphenidate
13	M	17	MR, Bipolar Ds	1 mg	Valproic acid, Escitalopram
14	M	17	Bipolar Ds	4 mg	Lamotrigine, Escitalopram, Clonazepam, Trazodone, Benztropine
15	M	10	Tic Ds, Anxiety Ds	0.25 mg	Sertraline (25 mg)
16	M	13	Psychotic Ds, Depression, Anxiety Ds	3 mg	Escitalopram (20 mg), Lorazepam (2 mg)
17	M	8	ADHD, Bipolar Ds	1 mg	Methylphenidate, Valproic acid
18	F	18	Bipolar Ds	1 mg	Valproic acid, Escitalopram
19	M	15	Bipolar Ds	2 mg	Valproic acid
20	M	8	Tic Ds	2 mg	None
21	M	18	Bipolar Ds, Panic Ds	4 mg	Sertraline, Clonazepam, Alprazolam, Benztropine, Propranolol
22	M	10	Tic Ds	0.5 mg	None
23	M	7	Tic Ds	1 mg	None
24	M	11	Tic Ds	1 mg	None
25	M	10	Tic Ds	0.5 mg	None

M: male, F: female, ADHD: attention-deficit hyperactivity disorder, OCD: obsessive compulsive disorder, ODD: oppositional defiant disorder, Ds: disorder, MR: mental retardation

mL in female) found in 84% of the patients. The prolactin level was higher than 30 and 50 ng/mL in 15 (60%) and 4 (16%) of these patients, respectively. None of the children presented clinical signs of hyperprolactinemia.

The dosage of risperidone was significantly correlated with prolactin level after adjusting for age and BMI ($p<0.001$, $r=0.813$). This prolactin elevation was not correlated with age, sex, glucose, thyroid hormones, sex hormones, or lipid profiles. However, the TG/HDL ratio was significantly associated with risperidone dosage ($r=0.570$, $p=0.004$) (Figure 1). In addition, there was a tendency for prolactin to increase with the TG/HDL ratio ($r=0.391$, $p=0.059$) (Figure 2).

The TG/HDL ratio was higher in the group of patients with particularly high prolactin levels (i.e., ≥30 ng/mL) after adjusting for age and BMI ($p=0.028$) (Figure 3, Table 4).

Table 3. List of diagnoses and concomitant medications

Diagnosis	N (%)
ADHD	6 (24)
Tic Ds.	10 (40)
Depression	4 (16)
Bipolar Ds.	7 (28)
Anxiety Ds.	6 (24)
ODD	1 (4)
Psychotic Ds.	4 (16)
MR	2 (8)
Concomitant medication	
SSRIs	9 (36)
Benzodiazepine	4 (16)
Methylphenidate	3 (12)
Atomoxetine	1 (4)
Valproic acid	5 (20)
Benztropine	2 (8)

ADHD: attention-deficit hyperactivity disorder, ODD: oppositional defiant disorder, MR: mental retardation, SSRIs: selective serotonin reuptake inhibitors

DISCUSSION

This cross-sectional study investigated the relationship between risperidone and hormonal or metabolic changes. Hyperprolactinemia was observed in 84% of the participants, consistent with previously reported prevalence rates of hyperprolactinemia (range 45−100%).[11,12] Furthermore, we found a dose-dependent effect of risperidone on prolactin levels, as noted previously.[12] None of the children in our study reported adverse effects related to hyperprolactinemia, although one study found that 25% of subjects experienced sexual side effects.[13] However, Johnsen and colleagues found no correlation (Pearson) between prolactin levels and symptoms, and some of their patients did not report any symptoms despite the presence of hyperprolactinemia.[14]

The changes in prolactin observed in young patients are generally consistent with data obtained in adults. However, this effect may be more pronounced in postpubertal children and adolescents than in adults as a consequence of the age-related decrease in dopamine receptors. Data from children with

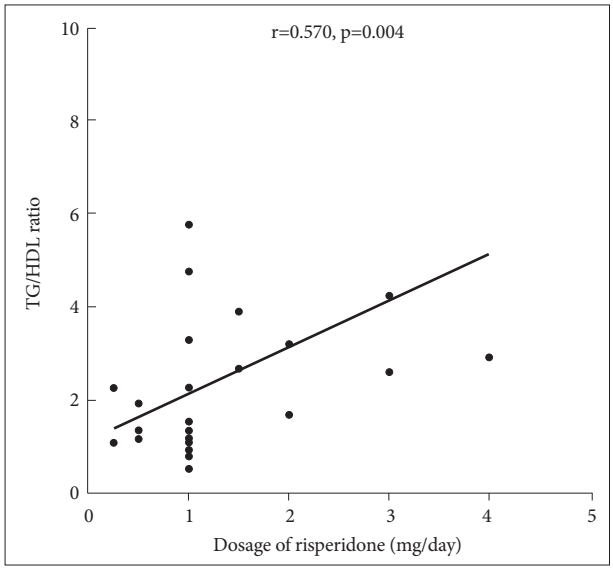

Figure 1. Relationship between risperidone dose and TG/HDL ratio. TG: triglyceride, HDL: high-density lipoprotein.

Table 4. Differences in lipid profile according to prolactin level (ANCOVA after adjusting for age and BMI)

Lipid profile	Group 1 PRL <30 ng/mL (N=10)	Group 2 PRL ≥30 ng/mL (N=15)	p
Prolactin (ng/mL)	17.86±8.08	44.18±11.82	<0.001
Dosage of risperidone (mg/day)	0.75±0.40	2.03±1.23	0.005
Total cholesterol (mg/dL)	172.6±41.30	173.60±17.50	0.903
TG (mg/dL)	81.20±30.86	152.47±74.17	0.084
HDL (mg/dL)	58.90±11.63	49.71±9.65	0.028
TG/HDL ratio	1.45±0.67	3.40±2.03	0.017

PRL: prolactin

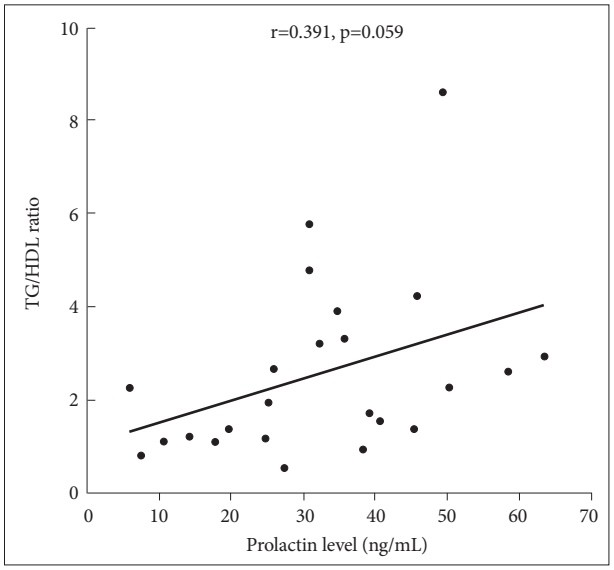

Figure 2. Relationship between prolactin level and TG/HDL ratio. TG: triglyceride, HDL: high-density lipoprotein.

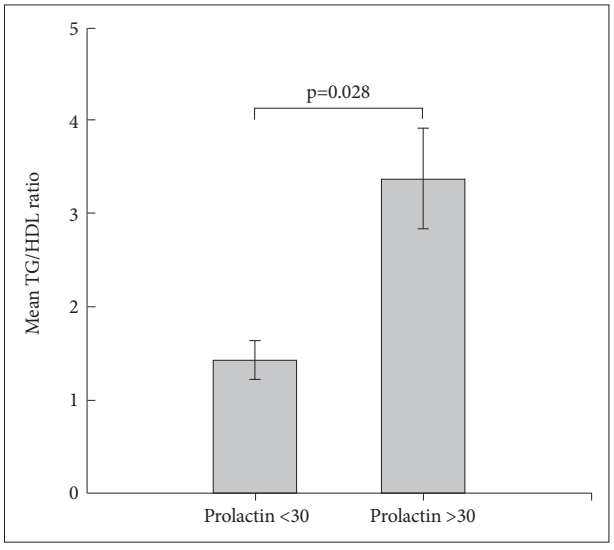

Figure 3. TG/HDL ratio according to low and high prolactin levels (dichotomized at prolactin level 30 ng/mL). TG: triglyceride, HDL: high-density lipoprotein.

hyperprolactinemia suggest that growth arrest, osteopenia, and delayed pubertal development occur as a result of enduring high levels of prolactin although some researchers have found no relationship between prolactin levels and age.[15,16] In addition, the adolescent patients with hyperprolactinemia had more severe bone loss problem than the adult patients. In spite of treatment with dopaminergic agents, the bone mass in the adolescent patients were not restored to normal levels.[17] Young women including female adolescents have greater prolactin response to atypical or typical antipsychotics than prepubertal girls or males.[18] Female hormones such as estrogen increase prolactin synthesis and intensify prolactin response to atypical or typical antipsychotics.[13,19]

Hyperlipidemia has been reported during treatment with atypical antipsychotics. In the present study, serum TG, total cholesterol, and HDL remained within the normal range in most patients. However, those patients with higher prolactin levels exhibited elevated TG/HDL ratios. Hyperprolactinemia has been reported to be associated with abnormalities of carbohydrate and lipid metabolism.[1] Reduced glucose tolerance and hyperinsulinemia have been demonstrated in patients with hyperprolactinemia.[2,3] The simple calculated measure of TG/HDL ratio has been identified as a predictor of insulin resistance and cardiovascular disease, and may also be a useful marker of atherogenic lipoprotein profile,[4,20] enabling clinicians to identify patients who may be at higher risk of metabolic disturbances.[20]

It has been shown that prolactin levels are positively correlated with glucose level measured using the oral glucose tolerance test.[11] However, our findings showed no correlation between prolactin and glucose. Prolactin affects metabolic homeostasis by regulating key enzymes and transporters that are associated with glucose and lipid metabolism in several target organs.[1,21]

Hyperprolactinemia occurs as a result of blockade of the D2 receptor in the anterior lobe of the pituitary in the tuberoinfundibular dopamine system. This can lead to a reduction in gonadotropin production.[22] However, our results did not show any significant relationship between short-term risperidone treatment and sex hormones. However, it has been reported that chronic treatment with antipsychotic drugs decreases plasma levels of testosterone due to hyperprolactinemia.[23] This discrepancy appears to be due to the treatment duration.

The findings of the present study are not consistent with previous reports of the effects of risperidone treatment. In some studies the blood concentrations of LH, FSH, and testosterone did not differ significantly between before and during risperidone administration, and there was no delay in progression through Tanner staging.[24,25] Transient increases in prolactin were not correlated with growth or sexual maturation.[26] These results show that blocking of both dopamine and serotonin receptors does not influence the pituitary-gonadal axis, but considerably increases prolactin release.[27] Other studies have found that treatment with risperidone can be associated with disturbances in reproductive hormones (testosterone) and gonadotropins (FSH).[28] Prolactin inhibits the release of gonadotropin-releasing hormone (GnRH) in the hypothalamus. GnRH stimulates the release of LH and FSH from the anterior pituitary gland. The positive feedback of estradiol on LH secretion in women is also blocked. Consequently, estrogen levels in women and testosterone levels in men are suppressed. Thus, controversy persists around this particular is-

sue. Several factors limit the ability to generalize the results of this study. First, we could not control for concomitant medication. Second, blood samples were drawn across the day (9AM−3PM), and with some patients in a nonfasting state. Thus, the known diurnal influences and effects of meals on prolactin levels may have affected the results. Third, the sample was relatively small. Moreover, this was a cross-sectional study, and so baseline values were not obtained. However, this is the first study to examine the relationship between hyperprolactinemia and the TG/HDL ratio. Future long-term cohort studies should evaluate the effect of hyperprolactinemia on lipid metabolism.

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