ORIGINAL ARTICLE

Association between serum testosterone levels, body mass index (BMI) and insulin in male patients with schizophrenia treated with atypical antipsychotics – olanzapine or risperidone

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Abstract

OBJECTIVE: A sufficient amount of testosterone (T) is essential for adequate sexual functioning but also for cognitive and psychological well-being. Most recent studies have demonstrated that higher BMI and other symptoms of metabolic syndrome are associated with alterations in sex steroid hormone concentrations. Although, neuroleptics are known to cause a significant and sustained weight excess, the relationships between body mass index and the level of testosterone in psychiatric patients have not been thoroughly studied. The main purpose of the present study was to examine the correlations between testosterone, estradiol BMI, and insulin in male patients diagnosed with schizophrenia and treated with olanzapine or risperidone.

METHODS: The study included 78 males diagnosed with schizophrenia according to the DSM-IV diagnostic classification hospitalized in psychiatric inpatient units (42 on risperidone and 36 on olanzapine). The initial and final evaluation of testosterone (T), estradiol, prolactin (PRL) and insulin serum levels were performed at week 3 and 8 after the onset of the new treatment, respectively.

RESULTS: At week 3, the mean serum prolactin was markedly higher, whereas testosterone level was lower in risperidone patients compared to those treated with olanzapine. T level was negatively affected by the studied medication (risperidone), increased prolactin and a higher BMI. At week 8, the mean serum prolactin level was markedly higher in risperidone patients. Higher values of BMI and serum insulin were the most prominent factors independently associated with decreased plasma testosterone levels at that measurement point. Individual changes of T level between week 3 and 8 were positively correlated with the corresponding changes in estradiol levels.

CONCLUSIONS: T serum levels appear to be independently linked with BMI, insulin and prolactin in both investigated neuroleptics. Further research is needed to elucidate the relationship between reproductive hormones and metabolic parameters in patients with schizophrenia under neuroleptic treatment.

INTRODUCTION

Most recent studies have demonstrated that dyslipidemia, diabetes and obesity can be associated with the alterations in sex steroid hormone concentrations (Hu *et al.* 2011). An accumulating body of evidence suggests that visceral fat produces various proinflamatory factors, such as: cytokines, which inhibit testosterone synthesis in the testes by the direct blockage of enzyme action in the testosterone production pathways (Kalinchenko *et al.* 2010; Vermeulen *et al.* 1999; Smits *et al.* 2013). Moreover, insulin has a suppressive effect on testicular steroidogenesis (Pitteloud *et al.* 2005). It has also been suggested that the increase in adipose tissue mass in obesity may result in increased aromatase activity and, thus, lead to the greater conversion of testosterone into estradiol (Page *et al.* 2007). An increase in estradiol concentrations would lead to the suppression of hypothalamic gonadotropin-releasing hormone and pituitary gonadotropin secretion. This might result in the reduction of both testosterone secretion by Leydig cells and spermatogenesis in the seminiferous tubules (Berga *et al.* 2004; Pasquali, 2006) .

Obesity and overweight affect 30–70% of people suffering from schizophrenia. They have a 2.8 to 3.5 increased likelihood of being obese (Coodin, 2001). One of the many reasons why psychiatric patients gain weight and become overweight and obese is the administration of neuroleptics (Dickerson *et al.* 2006; Theisen *et al.* 2001). Weight gain of >7% of pre-illness body weight was reported by 60% of patients; two-thirds of patients attributed weight gain to psychotropic medications (McIntyre *et al.* 2007). In the Paslakis *et al.* study (2012) olanzapine and risperidone were associated with a significant body weight gain as early as at the third week of treatment. Although the majority of neuroleptics are known to cause a significant and sustained weight excess (Alvarez-Jimenesz *et al.* 2008), the relationships between body mass, insulin and the level of testosterone have not been studied.

In this manuscript, we analysed the correlations between plasma testosterone levels (T), body mass index (BMI), serum insulin, prolactin (PRL), and estradiol in patients diagnosed with schizophrenia and treated with olanzapine or risperidone. We selected to carry out our study during the first 8 weeks of treatment, when olanzapine and risperidone-elicited changes in body weight and hormone levels have already become significant (Paslakis *et al.* 2012).

METHODS

Patients

The study included 78 males diagnosed with schizophrenia according to the DSM-IV diagnostic classification and hospitalized in psychiatric inpatient units. All of them met the following inclusion criteria: a) they were free of oral antipsychotic medications for at least 3 weeks before the study and from depot neuroleptics for 3 preceding months, (b) they had no history of chronic somatic diseases, including diabetes (exclusion criterion – fasting plasma glucose level ≥126 mg/dL), (c) they had no medical conditions which might have affected changes in metabolic parameters and no known history of lipid disorders (d) they did not undergo anti-diabetic, hormonal or lipid-lowering therapy or special diets to lower glucose or lipids levels, (e) they had no history of sexual problems, as established on the basis of an interview with individual patients.

We determined the washout time individually for each patient based on the information provided by the subject himself, his family and the psychiatrist responsible for the patient prior to the hospitalization. The patients, who had taken medications known to elevate prolactin serum level, misused the substance and had a significant organic brain disease were excluded.

Following the drug-free period, the study patients received neuroleptic treatment with the doses of risperidone or olanzapine that were adjusted accordingly to achieve the maximal clinical efficacy units (42 – risperidone and 36 – olanzapine). They constituted the initial evaluation groups (third week). After the initiation of treatment, no other psychotropic drugs were administered, except for diazepam (up to a dose of 20 mg/day PO) if a sedative or hypnotic medication was required, and for biperiden (up to 10 mg/day PO) as an anticholinergic compound in the case of emergency of drug-induced acute dystonic reactions or Parkinsonism.

All patients were hospitalized throughout the study. At weeks 8, 28 and 27, patients still continued treatment with risperidone or olanzapine, respectively. These patients constituted the final evaluation groups. The remaining patients dropped out of the study because of the lack of efficacy of the treatment or the need for administering the concomitant medications, not allowed during the study.

Disease characteristics and demographic data were obtained from clinical interview and medical records. The study was approved by the Ethical Committee. Written informed consent was obtained from each subject after a complete description of the study.

Study design

Fasting serum levels of glucose and prolactin were determined in the pre-drug period (baseline) in a local laboratory using standard methodologies to exclude patients with diabetes and hiperprolactinemia.

In risperidone and olanzapine groups the doses averaged 4.7±1.3 mg and 17.8±6.7 mg, at week 3 of treatment respectively, and 4.4±1.6 mg and 16.5±5.8 mg, at week 8 of treatment respectively. The initial and final evaluation of body mass, prolactin (PRL), estradiol, insulin and testosterone (T) serum levels were performed at week 3 and 8 after the onset of the new treatment, respectively. We chose those particular measurement points because olanzapine and risperidone are associ-

ated with a significant body weight gain, insulin and prolactin secretion changes already in the first weeks of treatment (Pasquali 2006; Konarzewska *et al.* 2009).

A single fasting morning blood sample was obtained between 07:00h – 08:00h from all patients who should not have eaten or taken any medications since midnight the previous night. The whole blood was collected and centrifuged to separate the serum. Serum insulin level was measured by radioimmunoassay (INS IRMA) (Starr *et al.* 1978). Prolactin, testosterone, estradiol were determined in the serum using competitive immunoassay with direct chemiluminometric technology (Bayer Health Care). Those assays were carried out by the Department of Endocrinology of the Medical University of Białystok, Poland. In the interpretation of the values of hormone levels we were guided by the reference ranges provided by the assay manufacturers.

Statistical analyses

The effect of the treatment was tested by the analysis of covariance (ANCOVA) with drug and dose (nested within drug, to control for the effect of within-drug dose variation) as the main effects, body mass and the age of patients as covariates, and the respective interaction terms. We used a stepwise approach and retained only significant components in the final models. For this reason, we do not report the effect of dose and interaction terms as they were insignificant at p=0.05.

The within-drug associations were tested with the Pearson product-moment and partial correlation analyses, the latter controlling for the effect of age and/or body mass. Body mass index (BMI) was calculated using the formula: BMI=weight (kg)/[height (m²)].

Both studied medications affect body mass in a similar way (Garyfallos *et al.* 2003), which was also corroborated by the lack of significant interaction between the effect of medication and body mass found in this study. Therefore, apart from the within-drug correlations, we also carried out the correlation analyses across the pooled sample of patients from both study groups. In those analyses, we deliberately did not remove the effect of medication. This enabled us to take advantage of the whole range of between-medication as well as within-medication variation in body mass and related hormonal responses, created by the effect of treatment.

The differences in patients' baseline characteristics between treatment groups were tested by t-test. Within-drug changes in those characteristics between weeks 3 and 8 of the treatment were tested by paired t-test, using initial and final evaluations for individual patients for whom data for both measurement points were available.

Descriptive baseline characteristics are presented as means ± 1 SD, whereas the results of ANCOVA analysis are presented as least square means ± 1 SEM (standard error of the mean). Prior to the statistical analyses, the assumptions of parametric tests were assured (Sokal & Rolf 1995). If not stated otherwise, the significance was tested at p=0.05 and only statistically significant associations are presented and discussed in detail.

RESULTS

Baseline characteristics of study groups

The baseline characteristics of the risperidone and olanzapine treatment groups are presented in Table 1. There were no statistical between-group differences in age, the age at first hospitalization or body mass at the initial and final evaluations. Likewise, baseline measures of fasting serum concentrations of glucose showed no significant differences between the investigated groups.

a) Week 3

Between-drug differences: The analysis of covariance (ANCOVA) comparing risperidone and olanzapine groups revealed a statistically significant effect of drug on T and PRL levels (Table 2). The mean serum T level was lower in risperidone patients than in those treated with olanzapine, whereas PRL levels was markedly higher in the patients treated with risperidone (Table 1). No between-group differences were found in estradiol levels, they were within the normal reference range. ANCOVA also revealed a statistically significant effect of age on insulin, and the effect of body mass on estradiol levels (Table 2).

Testosterone: T levels, in olanzapine-treated patients, were inversely correlated with BMI (r=−0.42, p=0.03, n=26) whereas in risperidone-treated group – with insulin serum levels (r=−0.33, p=0.05, n=35). Across both treatment groups, T was negatively correlated with BMI (r=−0.27, p=0.03, n=62, Figure 1). This correlation remained statistically significant after controlling for the effect of age (partial r=−0.33, p=0.03, n=44). T was also inversely correlated with PRL (r=−0.24, p=0.04, n=72). Correlation between T and PRL remained statistically significant after controlling for the effect of BMI (partial r=−0.45, p=0.004, n=40).

Estradiol: We found a positive correlation between estradiol and BMI in the risperidone group (r=0.51, p=0.001, n=36). Across both treatment groups, serum estradiol level and E/T (estradiol/T) ratio were positively correlated with BMI (r=0.3, p=0.04, n=49; r=0.43, p=0.002, n=49, respectively). These correlations remained statistically significant after controlling for the effect of age (partial r=0.31, p=0.04; n=46; r=0.49, p=0.0005, n=46).

b) Week 8

Between-drug differences: In both studied groups, the body mass of the subjects increased significantly between the third and eighth week of treatment (paired t-test, risperidone group p=0.0002, olanzapine group, p=0.009).

Tab. 1. Baseline demographic and the fasting glucose level (mean ±SD) of subjects entering the study, along with their body mass, BMI, serum levels of prolactin, testosterone, estradiol and insulin at the initial (week 3) and final (week 8) evaluation.

CHARACTERISTICS	OLANZAPINE (n=36)		RISPERIDONE (n=42)		
BASELINE	**Mean**	**SD/SEM**	**Mean**	**SD/SEM**	***p*-value**
Age (years)	33.7	11.4	33.1	10.4	0.82
First hospitalization (years)	25.3	7.1	25.9	8.2	0.76
Fasting glucose (mg/dL)	90.2	10.9	93.8	12.7	0.20
WEEK 3					
Fasting insulin (µIU/L)	9.04	0.6	9.8	0.6	0.37
PRL (ng/ml)	17.64	3.0	40.86	2.6	<0.001
Estradiol (pg/ml)	23.0	2.4	21.2	2.2	0.60
Testosterone (ng/dl)	617.2	33.14	506.6	30.1	<0.02
BMI (kg/m^2)	25.2	0.72	24.3	0.62	0.35
Weight (kg)	79.3	15.0	76.3	13.6	0.38
WEEK 8	**OLANZAPINE (n= 27)**		**RISPERIDONE (n=28)**		
Fasting insulin (µIU/L)	10.0	1.14	10.7	1.0	0.66
PRL (ng/ml)	15.6	3.2	36.4	3.0	<0.0001
Testosterone (ng/dl)	494.6	33.6	448.3	29.6	0.31
Estradiol (pg/ml)	21.8	3.2	23.3	3.0	0.74
BMI (kg/m^2)	26.5	0.87	25.9	0.82	0.67
Weight (kg)	82.4	15.8	79.9	13.6	0.55

Hormone levels at the respective evaluations are presented as the least square means (± SEM) from the ANCOVAs.

Tab. 2. Summary of ANCOVA results of the effect of medication (risperidone vs. olanzapine), age and body mass as covariates on hormone levels at the initial evaluation (week 3).

	Medication effect		Age		Body mass	
	F_{df}	*p*-value	F_{df}	*p*-value	F_{df}	*p*-value
BMI	$0.90_{1,59}$	0.35	$3.32_{1,59}$	0.07	x	
Insulin	$0.83_{1,59}$	0.36	$5.48_{1,59}$	0.02	$2.99_{1,59}$	0.09
PRL	$33.90_{1,63}$	<.0001	$2.62_{1,63}$	0.11	$1.83_{1,63}$	0.18
Testosterone	$6.03_{1,69}$	0.02	$1.01_{1,69}$	0.32	$3.64_{1,69}$	0.06
Estradiol	$0.31_{1,69}$	0.58	$0.08_{1,69}$	0.78	$10.52_{1,69}$	0.002

Tab. 3. Summary of ANCOVA results of the effect of medication (risperidone vs. olanzapine), age and body mass as covariates on hormone levels at the final evaluation (week 8).

	Medication effect		Age		Body mass	
	F_{df}	*p*-value	F_{df}	*p*-value	F_{df}	*p*-value
BMI	$0.46_{1,46}$	0.67	$1.40_{1,46}$	0.24	x	
Insulin	$0.20_{1,40}$	0.66	$3.74_{1,40}$	0.06	$1.48_{1,40}$	0.23
PRL	$22.21_{1,45}$	<.0001	$0.20_{1,45}$	0.66	$0.27_{1,45}$	0.61
Testosterone	$1.05_{1,46}$	0.31	$5.79_{1,46}$	0.02	$18.53_{1,69}$	<.0001
Estradiol	$0.11_{1,48}$	0.74	$1.40_{1,48}$	0.24	$00.00_{1,48}$	0.73

The analysis of covariance (ANCOVA) comparing risperidone and olanzapine groups revealed a statistically significant effect of body mass on T level (Table 3). There were no between-treatment differences in the mean T levels at week 8 (Table 1). The mean serum PRL level was markedly higher in risperidone-treated patients (Table 1). No between-group differences were found in the mean estradiol serum levels, and they were all within the normal reference range (Table 1).

Testosterone: In the risperidone-treated group serum T level was inversely related to BMI (r=−0.56, p=0.003, n=26) and insulin (r=−0.57, p=0.002, n=26).

In both treatment groups pooled together, T was inversely correlated with BMI (r=−0.48, p=0.0008, n=45, Figure 2) as well with insulin serum levels (r=−0.49, p=0.0005, n=45, Figure 3). Those correlations remained statistically significant after controlling for the effect of age (r=−0.52, p=0.0002, n=44; r=−0.48, p=0.005, n= 34, respectively). Nonetheless, no significant correlations were detected between BMI and serum insulin levels, which might suggest that testosterone can be independently related to BMI and insulin. It is supported by a partial correlation analysis which showed that correlations between T and insulin levels remained statistically
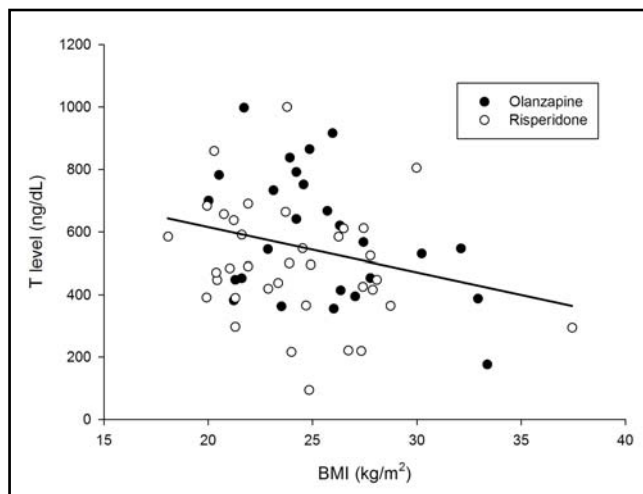
Fig. 1. Correlation between body mass index (BMI) and total serum testosterone level in pooled sample of patients treated with risperidone or olanzapine for 3 weeks (the initial evaluation). Solid line depicts Reduced Major Axis (RMA) regression line.
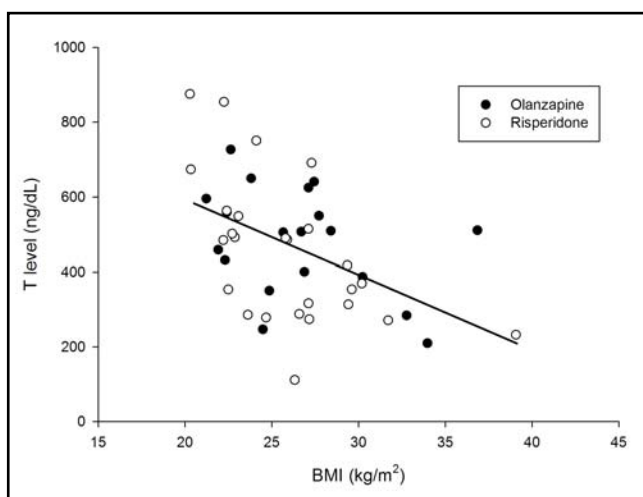

Fig. 2. Correlation between body mass index (BMI) and total serum testosterone level in pooled sample of patients treated with risperidone or olanzapine for 8 weeks (the final evaluation). Solid line depicts Reduced Major Axis (RMA) regression line.
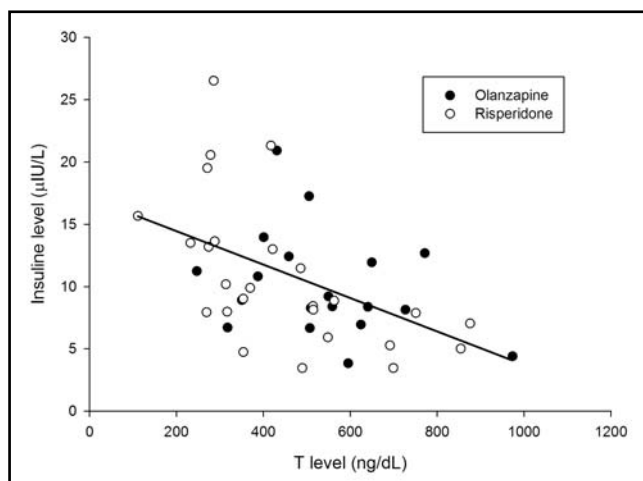

Fig. 3. Correlation between serum levels of total testosterone and insulin in pooled sample of patients treated with risperidone or olanzapine for 8 weeks (the final evaluation). Solid line depicts Reduced Major Axis (RMA) regression line.

significant after controlling for BMI (partial r=−0.48, *p*=0.02, n=25).

Across both treatment groups, individual changes of T level, between the initial and final evaluation, were positively correlated with the corresponding changes in estradiol levels (r=0.28, r=0.04, n=53), but not with the drug-induced increase of BMI (r=−0.05, *p*=0.73, n=44).

Estradiol: No between-treatment differences were found in mean estradiol levels and E/T ratio (Table 1). In both treatment groups analyzed together, E/T ratio and insulin levels were positively correlated (r=0.30, *p*=0.05, n=45), but after controlling for BMI the correlation became insignificant. Drug-induced BMI increase over the treatment time was not correlated with changes in estradiol level (r=−0.06, *p*=0.69, n=45).

DISCUSSION

Antipsychotic drug (AP) therapy, hyperprolactinemia and testosterone

It is well established that typical neuroleptics have pronounced effects on PRL release from the anterior pituitary gland, which explains endocrine side effects – e.g. decreased libido and impotence occurring in a considerable proportion of male schizophrenic patients treated with traditional antipsychotics (Aso *et al.* 1982; Crawford *et al.* 1997; Cutler., 2003; Halbreich *et al.* 2003; Haddad & Wieck 2004; Howes *et al.* 2007). In contrast, the new generation of atypical drugs has variable tendencies to induce hyperprolactinemia (Dickson & Glazer 1999). Olanzapine has been reported to produce little or no clinically significant PRL elevation (Beasley *et al.* 1997; Crawford *et al.* 1997). It has become apparent that risperidone is comparable to typical neuroleptics in its proclivity to raise serum PRL level (Cutler, 2003; Kapur *et al.* 1999; Kinon *et al.* 2003; Kinon *et al.* 2006). If PRL levels are rising, gonadotropin-releasing hormone (GnRhH) and consequently LH and T levels will fall. Only few studies are known to evaluate those hormonal effects in patients using antipsychotics, but those comparing typical neuroleptics have reported conflicting findings related to plasma FSH, LH, and T levels (Fitzgerald *et al.* 2003; Siris *et al.* 1980; Smith *et al.* 2000).

In our study, the mean serum PRL levels at both measurement points were markedly higher in the risperidone group. At the initial evaluation, PRL correlated inversely with T serum level across the treatment groups. The mechanisms responsible for such associations cannot be directly inferred from this study, but several previous findings suggested that T decrease may be related to AP-induced hyperprolactinemia. Low serum testosterone levels have been detected in several hyperprolactinemic conditions in males (Brown *et al.* 1981; Ghadirian*et al.* 1982). A direct effect of prolactin or the AP itself on the hypothalamic neurons controlling gonadotropin secretion has also been postulated

(Legros *et al.* 1975). Rinieris *et al.* (1989) examined testosterone levels in male patients who were treated with haloperidol. The authors found a decrease in testosterone levels only in the patients yielding prolactin levels of 60 ng/mL or higher. Contrary, in the present study, the moderate increase of prolactin levels in male patients treated with risperidone negatively influenced testosterone levels.

BMI

Apart from hyperprolactinemia, a drug-induced weight gain is yet another mechanism involved in the pathogenesis of low T in our study. It seems that higher body mass index is the factor more significantly responsible for T depletion than hyperprolactinemia. T serum level at the initial evaluation proved to be more strongly associated with BMI than with prolactin, whereas, at the final measurement, testosterone was solely dependent on metabolic parameters, such as: body mass index and endogenous insulin level.

Previous studies have shown a negative relationship between total T, free T and increased BMI (Kaufman & Vermeulen 2005; Goncharov *et al.* 2009). Eighteen out of the 20 studies on T levels and 15 of the 16 studies on SHBG (sex hormone binding globulin) levels in general population reported negative relationships between BMI and T. In the 12 studies on free T levels known to us, 10 reported a negative relationship (Kley & Krüskemper 1979; 1994; Pauli *et al.* 2007). The San Antonio Heart Study showed that both total and free T levels inversely correlated with BMI and waist-to-hip ratio (Haffner 1993). Zumoff *et al.* (1990) found that free T levels fall in proportion to total T with increasing BMI and they become subnormal in severely obese men.

Both studied medications affected body mass in a similar way causing significant weight gain. Across the treatment groups, at both measurement points, we found a strong inverse associations between T level and body mass index, which corroborated earlier reports suggesting that body mass can have a negative impact on the key reproductive hormone in human males (Kley & Krüskemper 1979; Giagulli *et al.* 1994, Pauli *et al.* 2008). Interestingly, we found no correlations between the changes in T levels, between two measurement points, and a corresponding BMI change. The lack of the expected negative correlation between increasing BMI and T level in the course of the study treatment may suggest that BMI is not a good predictor of the changes of adiposity over a short period of time.

Testosterone and insulin

In the recent decade, antipsychotic-induced metabolic disturbances in patients suffering from schizophrenia have been widely studied. Most of the second-generation antipsychotics (SGA) are indeed associated with the occurrence or exacerbation of metabolic anomalies. Those effects include impaired glucose tolerance and insulin resistance (Wampers *et al.* 2012). The increase

in body weight and fat tissue is associated with several abnormalities of sex steroid balance. It has been noted that visceral fat cells secrete a large number of cytokines which impair testicular steroidogenesis (Eckel *et al.* 2005; Lyon *et al.* 2003; Trayhurn & Wood 2004). Also insulin has a suppressive effect on T (Pitteloud *et al.* 2005). In contrast, T supplementation therapy of hypogonadism in men has been shown to improve the lipid profile by lowering cholesterol, blood sugar and insulin resistance (Allan *et al.* 2008; Haider *et al.* 2010; Munzer *et al.* 2001; Schroeder *et al.* 2004; Saad *et al.* 2011).

In the study by Tsai *et al.* (2004), T level was correlated with insulin resistance and obesity, denoting an independent effect of insulin resistance on T production. These results are consistent with our study. At eight week of the study treatment, in both groups pooled together, testosterone was inversely correlated with BMI as well with insulin serum levels. Nonetheless, no significant correlations were detected between BMI and serum insulin, which might suggest that T can be independently related to BMI and insulin. This was supported by a partial correlation analysis which showed that correlations between testosterone and insulin levels remained statistically significant after controlling for BMI. This correlation may be mediated through insulin receptors of the Leydig cells decreasing testosterone secretion (Pitteloud *et al.* 2005). It is also possible that fat cells themselves secrete cytokines and other hormones impairing testicular steroidogenesis (Eckel *et al.* 2005; Lyon *et al.* 2003; Trayhurn and Wood, 2004).

Estradiol and testosterone

No between-treatment differences were found at both measurement points in mean estradiol levels which were within the reference range. It is consistent with the results reported by Kinon *et al.* (2003) who found reduced estradiol levels only in patients treated with conventional antipsychotics drugs.

It has been suggested that the increase in adipose tissue mass may result in an increased aromatase activity and, thus, lead to a greater conversion of testosterone into estradiol (Giagulli *et al.* 1994; Schneider *et al.* 1979; Zumoff *et al.* 1981). The majority of articles reported no relationship between estradiol and BMI, including a large population study by Aggerholm *et al.* (2008). However, four studies have found statistically significant positive relationships (Mac Donald *et al.* 2010). According to Williams (2010), obesity, insulin and estradiol itself, all up-regulate the activity of aromatase and effectively reduce T levels and increase the intracellular concentration of estradiol. T and estradiol levels are inversely correlated. However, pathological states like obesity raise unopposed intracellular estrogen levels, and not necessarily lower testosterone levels (Williams, 2010). In our study, in both treatment groups, we found a positive correlation between the increase in estradiol level and a corresponding T level

change. This suggests that during the eighth week of treatment with olanzapine and risperidone one should not expect the depletion of T, but rather a disruption of balance between those two reproductive hormones.

SUMMARY

Our study on the factors affecting T and other reproductive hormones' levels in male schizophrenic patients treated with either olanzapine or risperidone showed that:

1. At week 3 of the treatment, T level was negatively affected by drug-induced hiperprolactinemia and higher BMI.
2. At week 8 of the treatment, higher BMI and serum insulin level were the most prominent factors independently associated with the decreased plasma testosterone levels.

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