A randomized, double-blind, placebo-controlled trial of metformin treatment for weight gain associated with initiation of risperidone in children and adolescents

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ABSTRACT

الأهداف: تقييم أثر العلاج بعقار متفورمين على زيادة الوزن المحفزة (BWG) بعقار ريسبيريدون لدى المرضى.

الطريقة: أُجريت دراسة عشوائية مجهولة الطرفين، محكومة بعقار وهمي استمرت لمدة 12 أسبوعا خلال الفترة مابين أكتوبر 2006م وحتى أكتوبر 2007م، في مركز استشارات الأمراض النفسية لدى الأطفال والمراهقين في جامعة أصفهان للعلوم الطبية – إيران. تم تسجيل 49 مريض في الدراسة، شخصت حالاتهم على أنها انفصام الشخصية. أعطي عقار متفورمين (500mg BID)، أو العقار الوهمي مع عقار ريسبيريدون (6mg) لجميع المرضى. تم قياس الوزن والطول ومؤشر كتلة الجسم (BMI)، وذلك في العلاج، وبعد أربعة أسابيع، وبعد اثني عشر أسبوعا من الدراسة. قيمت التغيرات في الوزن، ومؤشر كتلة الجسم باستخدام تحليل التغير في القياسات المتكررة.

النتائج: تم استبعاد 17 مريضا من الدراسة. أظهر تحليل التغير في القياسات المتكررة وجود فروقات ذات دلالة بين الوزن، ومؤشر كتلة الجسم (BMI)، في مجموعة المتفورمين ($p<0.001$ $p<0.015$)، ومجموعة العقار الوهمي ($p<0.013$ $p<0.005$).

خاتمة: لم يظهر العلاج بعقار متفورمين أثرا ذا دلالة على التحكم بوزن الجسم للمرضى بعد 12 أسبوعا.

Objective: To evaluate the effect of metformin treatment on the risperidone-induced body weight gain in patients.

Methods: In a 12-weeks, double-blind, placebo controlled, randomized trial between October 2006 and October 2007 which was conducted in the Child and Adolescent Psychiatric Consultation Center of Isfahan University of Medical Sciences, 49 patients were entered the study with schizophrenia diagnosis. Then metformin (500 mg bid) or placebo was administrated with risperidone (6 mg) for the patients. Weight, height, and body mass index (BMI) were measured at the beginning, at 4 weeks, and at 12 weeks of the study. Changes in weight and BMI were evaluated by using repeated measures analysis of variance.

Results: Seventeen patients were excluded from the study. Repeated measure analysis of variances showed a significant difference between weight and BMI in both metformin ($p<0.001$, $p<0.015$) and placebo group ($p<0.013$, $p<0.005$).

Conclusion: Metformin treatment did not show a significant effect to control the body weight of patients after 12 weeks.

Saudi Med J 2008; Vol. 29 (8): 1130-1134

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Received 25th February 2008. Accepted 30th June 2008.

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Second-generation, or atypical, antipsychotic medications have been widely used to psychiatric problems in both children and adolescents.[1,2] This is due to their ability to control many symptoms associated with positive symptoms, negative symptoms and cognition in schizophrenia. These properties are associated with lower rate of extrapyramidal side effects and tardive dyskinesia that has been observed with the use of "typical" antipsychotics.[3] On the other hand, a marked increase in body weight has been shown by the administration of these agents,[4,5] which is more pronounced in younger adults and children.[6,7] Thus, patients on these drugs may be more prone to cardiovascular disease, insulin resistance, metabolic

syndrome and other complications of obesity.[8-11] Aside from medical complications, gain weight was also an emotionally distressing side effect that contributes to no adherence with antipsychotic treatment.[12] Patients who gained weight associated with the use of antipsychotic had a reduced quality of life, poor self esteem, and decreased vitality.[12,13] Risperidone is a combined dopamine D2 and serotonin 5HT2A receptor antagonist, which is used largely for both acute and maintenance therapy for schizophrenia.[3] Like other atypical antipsychotics it may lead to weight gain. In a meta-analysis evaluating 10 weeks of therapy with risperidone, the mean increase in weight was 2.10 kg.[14] Also, in a double-blind study of schizophrenic and schizoaffective patients mean weight gain after one year of risperidone therapy was 2.3 kg.[15] In addition, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study of chronic schizophrenic patients showed that weight gain associated with risperidone was 0.43 ± 0.49 kg after 18 months.[16] Although risperidone increases the body weight of a group of patients but in comparison with olanzapine and clozapine, it seems to have a lower risk of inducing type 2 diabetes mellitus and metabolic syndrome.[8] Patients need to be assisted to control their body weight. Limited evidence exists that nizatidine (an H2 hista¬mine receptor blocker), amantadine (a N-methyl-D-aspartate receptor antagonist), reboxetine (a noradrenergic antidepressant) sibutramine (a noradrenergic and serotonergic reuptake blocker) and topiramate (an anticonvulsant) induce a moderate degree of weight loss in the short-term in atypical antipsychotic-treated patients.[17] However, the efficacy of these pharmacological treatments is inconclusive due to the limited number of randomized clinical trials (RCT) and small sample size in most studies.[17,18] Metformin, an antidiabetic agent, has been shown to decrease body weight in overweight and obese diabetic and nondiabetic individuals;[19] however, there are a few controversial evidences about the possible role of metformin in reducing weight gain associated with antipsychotics. Thus, we conducted a 12-week double-blind, placebo-controlled trial study, adding metformin or placebo to the medication regimens of schizophrenia subjects taking risperidone.

Methods. This 12-weeks, double-blind, placebo-controlled, randomized trial was conducted in the Child and Adolescent Psychiatric Consultation Center of Isfahan University of medical sciences between October 2006 and October 2007. The patients were selected among who admitted at this center and needed to take antipsychotics with the diagnosis of schizophrenia or schizoaffective disorder. The study was approved by the Human Ethics Committee of Isfahan University of Medical Sciences. All participants and their families received a full explanation of the nature of the study and were required to sign an agreement form. After providing written informed consent, each subject underwent a diagnostic evaluation by a psychiatrist using the Structured Clinical Interview for a text revision of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV TR).[1] Patients were included in the study if they met the following criteria: agreed to participate in the study and sign the informed consent form, age <20 years, taking risperidone (2-6 mg per day as their responses to treatment) as therapeutic agent, creatinine level less than 1.4 mg/dl, and normal liver function tests. Subjects were excluded from the study if they were unable to provide informed consent, had been treated with antipsychotics before, had current substance abuse or significant medical illness (including hepatic disease, renal disease), had untreated hypertension, had a history of intolerance of metformin, were receiving treatment with agents that induce weight loss, had a history of glaucoma, had heart disease or an abnormal electrocardiogram, had a history of asthma, being treated with a combination of antipsychotics, or were being treated with antimigraine agents containing serotonin agonists. The patient's profile, weight, height, drug history, and past medical history were recorded by a resident of psychiatry. After completing baseline assessments, the subjects were randomly assigned to metformin and placebo. Each subject was given a one week supply of 500 mg metformin tablets or identical-appearing placebo tablets and instructed to take the tablets in the morning. After one week, the dose was increased to 2 tablets, one in the morning and one at the night. The subjects were called each week to follow up and check the side effects of the drugs. Then the anthropometric characteristics of each patient including weight, height, and BMI were recorded 4 weeks and 12 weeks of the beginning of the study. Safety laboratory tests, including Fasting blood glucose, complete blood count, creatinine, prolactin level, and liver function tests, based on the standard hematological and clinical chemistry values, were performed at baseline, week 4, and week 12.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11.5. All statistical tests were 2-tailed, and significance was determined as $p<0.05$. Student's t test was used to compare the data between 2 groups. For outcome measures, including body weight, height, and body mass index (BMI), we analyzed the change from baseline by using a repeated-measures analysis of covariance, controlling for baseline.

Results. We recruited 49 patients for this study. Of these, 17 were excluded due to incomplete use of drugs or side effects of the drugs. Two of these patients have experienced diarrhea at the second week. One of them was in metformin group and one in the placebo group. Three patients had nausea and vomiting in metformin group, which were excluded from the study too. Forty-seven patients have suffered from schizophrenia and 2 from schizoaffective disorder. But the schizoaffective patients were excluded from the study due to side effects. Finally, 32 patients remained with equal numbers at metformin and placebo groups. The demographic characteristics of the patients in both groups are shown in **Table 1**. The mean age of metformin group was 2.32 years greater than the placebo group; but the statistical analysis did not show any significant difference (p=0.71, t=1.873). The side effects of metformin at the end of the study were nausea (25%), bloating (18.75%), vomiting (6.25%), diarrhea (6.25%), and enuresis (6.25%). The mean ± standard deviations (SD) of height, weight, and BMI in both groups are listed in **Table 2**. The mean weight, height, and BMI of metformin group at the baseline were 5.37 kg, 13.53 cm, 0.41 kg/m^2, greater than the placebo group; but these differences were not statistically significant (p<0.382, t=0.887), (p<0.081, t=1.805), and (p=0.758, t=0.311). While the subjects given placebo, continued to gain weight and increase in BMI over 12 weeks with a rate of 0.183 kg per a week, the weight and mean BMI of the subjects treated with metformin showed a decrease over the first 4 weeks, and an increase over the next 8 weeks. Repeated measure analysis of covariance showed a significant difference between weight and BMI in both metformin (p<0.001, F=6.234 and p<0.015, F=5.801) and placebo group (p<0.013, F= 7.439 and p<0.005, F=8.135). Although the mean differences of BMI and weight between the beginning of the study and 4 weeks of the study were significantly higher in placebo group than metformin group (p<0.013, p<0.026); these differences were not significant at the 12 weeks of the study (p<0.099, p<0.147). Range, median, and mean ± standard deviation of weight gain in placebo and metformin group between the beginning of the study and 4 weeks of the study, beginning of the study and week 12, and week 4 and 12 weeks of the study were shown in **Table 3**. The weight, height, and BMI of metformin and placebo group remained insignificant at the 4-week (p<0.475, t=0.723), (p<0.085, t=1.782), and (p<0.891, t=0.138) and 12 weeks ((p<0.541, t=0.619), (p<0.086, t=1.778), and (p<0.885, t=0.146)) of the study. The percentage of weight gain between the beginning of the study and 12 weeks of the study was higher in placebo group (mean ± standard deviation: 6.42 ± 4.04, median: 5.34, and range: 12.77) than in the metformin group (mean ± standard deviation: 2.7 ± 1.58, median: 2.56, and range: 7.66), (p<0.006). Six patients of placebo group

Table 1 - Demographic characteristics of patients.

Group	Mean age	Standard deviation	Boys %	Girls %
Metformin	11.25	2.46	68.75	31.25
Placebo	8.93	4.28	62.5	37.5

Table 2 - Weight, height, and body mass index of patients at the beginning, 4 weeks, and 12 weeks of the study.

Group and time of evaluation	Weight (kg)	Height(cm)	BMI (kg/m^2)
Metformin			
Beginning of the study	35.2 ± 12.94	139.56 ± 18.65	17.42 ± 2.75
4 weeks of the study	35.03 ± 12.96	139.56 ± 18.65	17.33 ± 2.71
12 weeks of the study	36.03 ± 12.81	139.56 ± 18.65	17.9 ± 2.63
Placebo			
Beginning of the study	29.83 ± 20.04	125.84 ± 24	17.01 ± 4.42
4 weeks of the study	30.68 ± 20.24	126.03 ± 23.97	7.51 ± 4.32
12 weeks of the study	32.03 ± 22.45	126.09 ± 23.87	18.11 ± 4.97

Table 3 - Range, median, and mean ± standard deviation of weight gain in placebo and metformin group.

Group/time	Mean (kg)± Standard deviation	Median (kg)	Range(kg)
Metformin group			
Beginning of the study and week 4	-0.18 ± 0.08	-0.2	0.4
Beginning of the study and week 12	0.81 ± 0.33	0.8	1.8
4 weeks of the study and week 12	1 ± 0.32	1.0	1.7
Placebo group			
Beginning of the study and week 4	0.85 ± 0.53	0.9	2.6
Beginning of the study and week 12	2.2 ± 2.54	1.2	9.3
4 weeks of the study and week 12	1.35 ± 2.4	0.3	7.9

have had ≥7% weight gain in contrast with one patient in metformin group (p<0.033, odds ratio=0.11).

Discussion. Our study found that metformin did not show significant benefit over the 12 weeks. But many previous studies have shown different results. Chen et al[20] in 2007 discovered that metformin was effective to decrease body weight over 8 weeks in patients who took olanzapine.[20] Although Klein et al[1] also demonstrated that 12 weeks treatment with metformin was effective in controlling the body weight, which is different with our methodology. They have examined patients who have had a significant weight gain (at least 7% or 10%) but in our study the prophylactic effects of metformin was considered. Peuskens[15] and Babtista et al[21,22] discovered different results in this matter. In 2006, they found that metformin did not prevent olanzapine-induced body weight gain.[21] In 2007, they concluded a different result and showed the beneficial effects of metformin in body weight gain and carbohydrate metabolism control.[15] In 2008, they discovered that metformin plus sibutramine is as effective as metformin to control the body weight induced by olanzapine.[22] Ozenoglu et al[23] and Dibben et al[24] showed 2 cases of olanzapine induced weight gain which was responsive to metformin treatment. Despite the statistical analysis no significant results was observed between the 2 groups with the weight and BMI, the percentage of weight gain was higher among placebo group than metformin. Of these 6 patients of placebo group, a significant weight gain (7-10%) in contrast with one patient from the metformin group was observed. This result has cleared the way that, although metformin was not effective to control the body weight, it can prevent excessive weight gain. Wu et al[25] in 2008 examined the effectiveness of metformin to prevent body weight gain and cleared that mMetformin was effective and safe in attenuating olanzapine-induced weight gain. Also, they have shown that fewer patients increased their baseline weight by more than 7% when they have taken metformin.[25] In the present study, the sample size was not enough to demonstrate the effectiveness of metformin. It might be possible that risperidone, clozapine, and olanzapine have different mechanisms in relation to weight gain. Previous study recommended a hierarchy in the magnitude of BWG that may induce by using diverse agents, being very high for clozapine and olanzapine; high for quetiapine, zotepin, chlorpromazine, and thioridazine; moderate for risperidone and sertindole; and low for ziprasidone, amisulpiride, haloperidol, fluphenazine, pimozide, and molindone.[26] In the other hand the patients of this study were children and they were in their growth age. Thus increase in their body weight should be considered. Also higher doses of metformin were administrated in other studies; and the patients have taken part in dietary management and life style modification sessions.[1] The results of the present study have revealed that metformin was effective over the 4 weeks of the study. It is suggestible that metformin can control the body weight in short term. This result has been confirmed with previous studies. In our study, we selected patients started on risperidone while in other studies they selected patients who received the antipsychotic agents for a long time before they entered the study.[1,20] Therefore, the short term body weight gain in our study is not because of risperidone side effect. Medications for weight control have been widely used with or without trying to modify the life style. But psychiatric patients are less likely to succeed with life style interventions alone than are those without mental illness.[1] However Wu et al[27] in 2008 have shown that metformin or life style modification alone can control the body weight gain induced by antipsychotics; but they have concluded that their combination is more effective in this patients. Although the effects of risperidone on metabolic disturbance are less than olanzapine and clozapine,[28] we did not check the possible effects of metformin on metabolic problems that could be induced with risperidone. In the present study, metformin did not worsen psychotic symptoms or side effects associated with risperidone. Further research is warranted to determine if metformin would result in significant weight loss in a trial with a larger sample size or longer follow-up duration in risperidone-treated patients. It is also important to explore other effective intervention strategies to deal with other antipsychotic associated weight gain and metabolic problems.

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