Treatment of depression in type 2 diabetes with Fluoxetine or Citalopram?

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ABSTRACT

الأهداف: عمل مقارنة بين العقارين فلوكسيتين وسيتالوبرام من ناحية تأثيرهما المُضاد للاكتئاب، بالإضافة إلى دراسة مدى فعاليتهما في التحكم بمستويات سكر الدم لدى المرضى المصابين بالسكري من النمط الثاني.

الطريقة: أُجريت هذه الدراسة العشوائية المُقارنة في قسم السكري للأبحاث بجامعة كرمنشاه للعلوم الطبية، كرمنشاه، إيران وذلك خلال الفترة من سبتمبر 2006م إلى أكتوبر 2007م. شملت هذه الدراسة 40 مريضاً مُصاباً بالسكري من النمط الثاني، كما أنهم يعانون من الاكتئاب الشديد وقد تم تقسيمهم عشوائياً إلى مجموعتين (20 مريضاً في كل مجموعة). لقد تلقت المجموعة الأولى 40 مليغرام لكل ديسيلتر من الفلوكسيتين، فيما تلقت المجموعة الثانية نفس الجرعة ولكن من عقار السيتالوبرام. لقد قمنا بإعادة تقييم حالة المرضى بعد مرور 12 أسبوعاً من العلاج وذلك لاختبار درجة حدة الاكتئاب ووضع مرض السكري. اعتمدنا مقياس بيك للاكتئاب ومقابلة المريض مع الطبيب النفسي من أجل تقييم درجة حدة الاكتئاب ومتابعة حالة المرضى. وتم الحصول على نتائج تحليل مستويات الهيموغلوبين الغليكوزيلاتي، ومستويات سكر الدم أثناء الصيام وذلك من أجل مراقبة المؤشر الجلاسيمي.

النتائج: أشارت النتائج إلى ظهور تحسن ملحوظ في درجة حدة الاكتئاب، ومستويات سكر الدم أثناء الصيام، ومستويات الهيموغلوبين الغليكوزيلاتي لدى المرضى في كلي المجموعتين وذلك بعد مرور 12 أسبوعاً من العلاج. ولم يكن هناك اختلافاً واضحاً بين المجموعتين فيما يخص تحسن حالة الاكتئاب ومرض السكري.

خاتمة: أثبتت الدراسة مدى فعالية عقاري الفلوكسيتين والسيتالوبرام في التقليل من حدة الاكتئاب لدى المرضى المصابين بالسكري من النمط الثاني ولكن من دون التأثير سلباً على مستوى سكر الدم.

Objectives: Comparing the antidepressant effects of Citalopram with Fluoxetine and their effect on glycemic control in diabetic patients.

Methods: Forty patients attending the Diabetes Research Center in Kermanshah University of Medical Sciences, Kermanshah, Iran from September 2006 to October 2007 with type II diabetes and suffering from major depression were randomly assigned to 2 groups (n=20 per group) in a randomized controlled trial method. They received up to 40mg/d of Fluoxetine or Citalopram. Twelve weeks after treatment, patients were reassessed in terms of severity of depression and diabetic status. The Beck Depression Inventory (BDI) and psychiatric interview were used to measure the severity of depression and follow up the patients. Glycosylated hemoglobin (HbA1c) levels and fasting blood sugar (FBS) was obtained to monitor glycemic control.

Results: After the 12-week treatment, both groups showed significant improvement in severity of depression, FBS, and HbA1c. There were no significant differences between the 2 groups in terms of improvement in depression and diabetic status.

Conclusion: Fluoxetine and Citalopram can effectively reduce the severity of depression in diabetic patients without an adverse effect on glycemic control.

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Major depression is highly prevalent among diabetic patients[1] and it has been reported in 15-20% of type 1 or 2 diabetics.[2] Depression may influence adherence to medication and reduce compliance with the diabetic regimen.[3] It has also been associated with poor control of blood sugar,[4] and may lead to increased risk for micro and macro vascular complications.[1-3] However, there are controversial reports on the effect of different antidepressants in diabetic patients. Some studies support depression screening and its treatment as a routine component of diabetic care.[5] It was shown that concurrent use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in depressed patients have been associated with increased risk of developing diabetes type 2.[4] Also, Nortriptyline (a TCA drug) markedly reduced depression symptoms in diabetic patients in comparison with placebo, but at the same time deteriorated glycemic control.[6] Despite the adverse effects with Fluoxetine in 10-15% of patients, studies have shown that it reduces depression symptoms[2] as well as the need for antiglycemic medications.[7,8] According to a report from Keslsey,[9] in diabetic neuropathy, Sertraline, Citalopram, and probably Venlafaxine are the drugs of choice. There are some claims of the advantages of Citalopram in depressed patients who suffer from diabetes,[9] possibly because Citalopram has a little effect on hepatic cytochrome P450 enzymes and therefore it reduces drug-drug interactions.[9] The purpose of this study is to compare the antidepressant effects of Citalopram and Fluoxetine in patients with co-morbid depression and diabetes, and also the effect of these drugs on glycemic control and diabetic status.

Methods. This randomized clinical trial was conducted at the Diabetes Research Center in Kermanshah University of Medical Sciences, Kermanshah, Iran between September 2006 and October 2007, and included diabetic patients screened for major depression with a Beck's Depression Inventory (BDI) score of ≥14. To confirm the diagnosis of major depression, we used a structural clinical interview diagnosis (SCID) using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria administered by a psychiatrist. Forty-seven volunteers (35-67 years old) who met the inclusion criteria were randomly assigned to 2 groups using a computer generated randomization list. Assuming differences of 3 in mean of BDI among the 2 groups with standard deviation of 3.5, we planned to recruit 22 people in each group. From the total of 47 patients, 7 patients did not return for follow up because of drugs side effects (6 cases in the Fluoxetine group and one in the Citalopram group) and therefore were excluded (**Figure 1**). An informed consent form was obtained from all patients, and the ethical committee of Kermanshah University of Medical Sciences approved this study.

For the study, the following were excluded: patients with a history of previous treatment for depression,

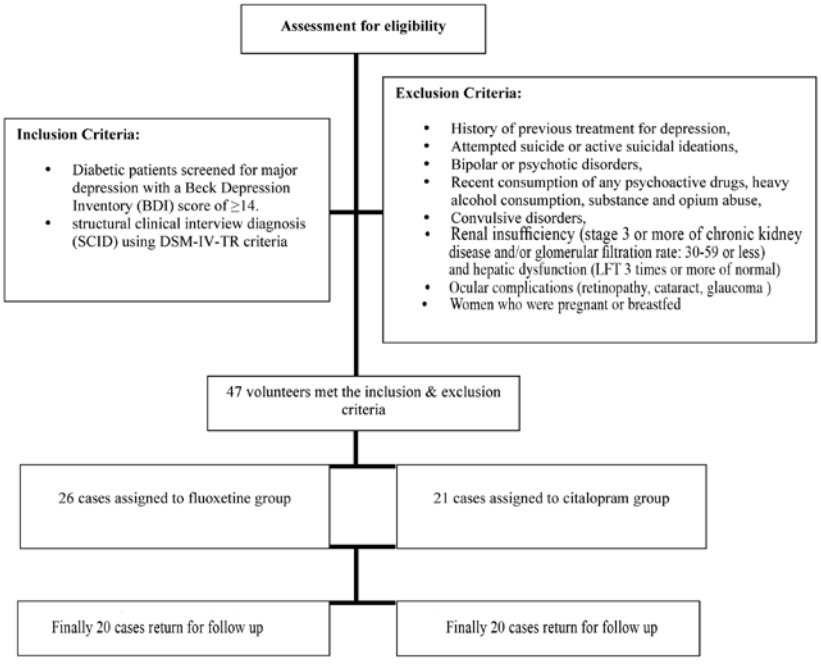

Figure 1 - Case selection protocol.

attempted suicide or active suicidal ideations, bipolar or psychotic disorders, recent consumption of psychoactive drugs, heavy alcohol consumption, substance and opium abuse, patients with convulsive disorders, those with renal insufficiency (stage 3 or more of chronic kidney disease and/or glomerular filtration rate: 30-59 or less) and hepatic dysfunction (liver function test 3 times or more of normal), ocular complications (retinopathy, cataract, glaucoma) and women who were pregnant or breastfeeding. The severity of symptoms was measured by the BDI-II test.[2] This test includes 21 items scoring 0 to 3 for each item. The severity of depression is classified into 4 categories: 0-13 for "minimal depression," 14-19 for "mild depression," 20-28 for "moderate depression," and 29-63 for "severe depression." In addition, a SCID based on DSM-IV-TR criteria was used to assess depression. The psychologist who "assessed the depression with BDI" and the person who "monitored" the patients, and the psychiatrist who performed the professional interviews to assess severity of depression was blinded to the allocation of patients to groups. Fasting blood sugar (FBS) and glycosylated hemoglobin (HbA1c) were assessed for all participants before and 12 weeks after the treatment. All blood samples for checking the HbA1c were examined in the Vijeh Clinic's Laboratory in Kermanshah University of Medical Sciences by using the ion exchange method with normal ranges of 6.5-8%. There was no change in diabetic medications of patients during the study. Those who monitored the patients' diabetic status were blinded to the group in which patients were included. Lipid profile including triglycerides and low-density lipoproteins (LDL) and FBS requested for each patient were measured. All patients were educated regarding hypoglycemic symptoms. Body mass index (BMI) was measured in all patients and those with BMI>30 were considered obese.

The 12 weeks treatment period began with the baseline visit and subsequent visits at weeks 4, 8, and 12. Fluoxetine and Citalopram dosing began at 20 mg/d in the morning and increased to a maximum of 40 mg/d based on the clinical evaluations. The evaluation of diabetes status of patients was continued in the Diabetes Center. To control the blood sugar of participants, they were treated with either insulin or Metformin and Glibenclamide. Patients were not allowed to take any other psychoactive drugs. If there were an indication for another drug, we excluded them from the study. At the beginning of the follow-up period, 7 patients refused to take anti-depressant medications and therefore were excluded from the study. From this 7, 6 had been assigned to the Fluoxetine group (**Figure 1**).

Differences in the demographic and clinical characteristics of the subjects were determined using Fisher's exact test, Chi-square, and independent t-tests with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 15. The Chi-square and Fisher's exact tests were used to examine differences in the percentages of patients in each study group achieving significant improvement in depression, which were determined by 50% improvement in BDI at the end of the trial. We used paired t-test to compare the mean FBS and HbA1c before and after the treatment. A *p*-value less than 0.05 was considered the statistically significant level.

Results. The average of patient age was 48.3±8.6, the duration of diabetes was 7.43±5.45 in the Fluoxetine group, and 8.11±5.28 in the Citalopram group. All 40 patients completed the treatment, and no one was documented to be a drug defaulter. Of 40 patients, 11 (27.5%) were treated with insulin. Others received either Metformin or Glibenclamide, or a combination of both based on their diabetic status. The baseline characteristics of patients in both groups were comparable (**Table 1**). In addition, the 2 groups were comparable in terms of mean serum level of lipids, FBS, and HbA1c. Twelve weeks after starting the treatment, there were significant improvements in both depression and the diabetic status of patients (**Table 2**), and there was no statistical difference between the 2 groups in terms of improvement in depression and the diabetic status of patients (**Table 2**). The improvements in HbA1c and BDI in both groups were not associated with age, BMI, hypertriglyceridemia, or hypercholesterolemia.

Discussion. We found that both Fluoxetine and Citalopram were effective in the improvement of depression symptoms in patients with type 2 diabetes. There were no adverse effects, and both drugs were tolerated well. Similar to other reports on the efficacy of Fluoxetine,[2] we found that Citalopram may be equally

Table 1 - Characteristics of diabetic patients with depression.

Characteristics*	Fluoxetine (n=20)	Citalopram (n=20)	*P*-value
Age	51.57±8.38	47.7±8.63	0.18
Gender (female %)	35	45	0.518
Body mass index	28.78±3.73	30.64±5.85	0.30
Duration of diabetes	7.43±5.45	8.11±5.28	0.72
Triglyceride	178.86±46.91	169.11±38.86	0.52
Cholesterol	201.64±30.11	190.26±26.01	0.25
Glycosylated hemoglobin†	7.68±1.69	8.25±1.34	0.29
Fasting blood sugar†	159.21±39.66	163.37±49.24	0.80
Beck depression inventory†	26.29±3.50	25.26±3.51	0.41

*Values shown as mean ± standard deviation. †Values show blood levels of glycosylated hemoglobin, fasting blood sugar, and Beck depression inventory before starting the antidepressants

Table 2 - Mean absolute improvement in depression and diabetic status in the 2 groups.

Characteristics	Fluoxetine				Citalopram				*P*-value between the 2 groups†
	Before treatment	After treatment	Improvement mean±SD	*P*-value	Before treatment	After treatment	Improvement mean±SD	*P*-value	
Glycosylated hemoglobin	7.68±1.69	5.74±1.06	1.94±1.19	$p<0.001$	7.68±1.69	6.65±1.6	1.59±1.03	$p<0.001$	0.38
Fasting blood sugar	159.21±39.66	110.29±23.66	48.93±28.21	$p<0.001$	159.21±39.66	123.42±46.19	39.95±25.66	$p<0.001$	0.35
Beck depression inventory	26.29±3.50	12.21±2.08	14.07±4.03	$p<0.001$	26.29±3.50	11.84±3.56	13.42±5.42	$p<0.001$	0.71

All values show the mean ± standard deviation difference between the measurement before and after antidepressant treatment.
†The values show *p*-value of differences between the mean of absolute differences between the 2 groups

effective in diabetic patients with major depression. Amsterdam et al[7] found a significant reduction in depressive symptoms and a modest, non-significant reductions in fasting glucose, Fructosamine, and HbA1c levels during SSRI therapy for patients with depression and diabetes. They proposed that one common benefit of treating depression in diabetics would be the ability of the patients to be more motivated to take care of their diabetes. However, age might have a confounding effect; with less improvement in depression in older patients.[8] In our study, such an effect was not statistically significant.

In obese patients, Citalopram is thought to be superior to Fluoxetine in reducing blood sugar. This may be due to the effect of Fluoxetine on peripheral and hepatic insulin action, which is not dependent on weight.[10] Further studies are needed to clearly show whether Citalopram has a similar and stronger effect. In patients taking insulin or Metformin and those who were new cases of depression, Fluoxetine was associated with better FBS control and Citalopram influenced the BDI scores to improve. In patients on Glibenclamide, Fluoxetine was associated with better FBS control and improvement in BDI scores in comparison with the Citalopram group. Although these differences were not statistically significant, our small sample size and short duration of trial (12 weeks), might have affected the significance. Therefore, the results of future studies with a larger sample size, and longer duration should be reexamined. It seems that SSRIs including Fluoxetine and Citalopram in diabetic patients with concurrent depression lead to good control of diabetes and considerable improvement in depression, but such effects might be confounded with factors such as obesity, hyperlipidemia, hypercholesterolemia, and older age. Therefore, the drug of choice might be different from one patient to another.

This study had some limitations, and we had limited power for some analyses. It is suggested that future investigations need to be carried out with a larger sample size. It would also have been more reliable if we had a placebo group, however, prescribing no treatment (placebo) in depressed patients was not ethically acceptable. Also, we did not test postprandial sugar, and checking FBS without checking postprandial sugar is not enough to monitor daily blood sugar. Another limitation was the assay of only type II diabetes patients, in future studies, both types of diabetes should be included.

In conclusion, Fluoxetine and Citalopram can effectively reduce the severity of depression in diabetic patients without an adverse effect on glycemic control.

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