ORIGINAL ARTICLE

Glycemic control improvement through treatment of depression using antidepressant drugs in patients with diabetes mellitus type 1

Jana Komorousová [1], Jiří Beran [1], Zdeněk Rušavý [2], Zdeněk Jankovec [2]

1 Department of Psychiatry, University Hospital Pilsen, Czech Republic
2 Department of Internal Medicine I., University Hospital Pilsen, Czech Republic

Correspondence to: Jana Komorousová, MD.
Department of Psychiatry, University Hospital Pilsen
Na Celchu 15, 32600, Plzeň, Czech Republic.
tel: +420 777 32 64 31; e-mail: komorousovaj@fnplzen.cz

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Abstract

OBJECTIVE: Depression is a common disorder among diabetic patients and affects negatively the treatment of their basic disease. The aim of the study was to assess, whether antidepressant medication could positively influence glycemic control of diabetes type 1 in depressive or anxious patients.

METHODS: A six-month, double-blinded, randomized, placebo-controlled study was performed to investigate the reaction of type 1diabetic patients (n=21) to treatment of depression and anxiety symptoms using antidepressant drug sertraline. The patients were given sertraline (100 mg/day) or placebo. The evolution of mental change was assessed using Zung Self-Rating Depression Scale (SDS), Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD) along with development of somatic parameters commonly assessed in diabetic patients, especially glycosylated hemoglobin, insulin dose and body weight. The level of active substance in serum of the patients was also measured.

RESULTS: Mental state improved at the level of statistical significance of $p<0.001$ in both patients using antidepressant and placebo. From somatic parameters, body weight and systolic blood pressure increased statistically significantly also in both groups of patients.

CONCLUSIONS: The mental state of most patients who successfully completed the study improved regardless of the fact if they were using antidepressant or placebo. No statistically significant connections between the mental and somatic changes were found. This finding points out to the placebo effect of the medication, to the importance of a contact with patients, but also to the need to concentrate on their mental state.

Abbreviations:

SDS	- Zung Self-Rating Depression Scale	HbA1c	- Glycosylated hemoglobin
HAMA	- Hamilton Anxiety Rating Scale	FN	- University Hospital
HAMD	- Hamilton Depression Rating Scale	LF UK	- Faculty of Medicine, Charles University
SSRI	- Selective serotonin reuptake inhibitors	IK	- Department of Internal Medicine
CBT	- Cognitive behavioral therapy		

INTRODUCTION

Diabetes mellitus type 1 is a serious chronic life-long disease. It brings numerous significant changes and restrictions to life of a patient. The disease is omnipresent, it is necessary to think about it constantly, even if it does not remind itself at the moment, e.g. through pain. The sufferer should assume a regular life rhythm, accept numerous diet restrictions, regularly exercise, regularly measure blood glucose and administer insulin, and monitor body weight gain and other parameters such as blood pressure and level of cholesterol. The patients live in fear of complications, and even threat to life. Onset of complications brings along other restrictions and necessary measures. A disease with no hope of cure triggers short-term natural psychological defense reactions, such as anger, sadness, denial, but also mental problems and disorders such as depression and anxiety.

People with diabetes are proven to have higher incidence of psychiatric disorders (Medved *et al.* 2009). Prevalence of depression is higher in type 1 diabetic patients (Gendelman *et al.* 2009). According to one study, prevalence of depression among patients with diabetes may be up to 30% (Suwalska *et al.* 2004).

Comorbid depression leads to a decrease in metabolic control. It results in reduction of treatment response, as well as noncompliance with diet restrictions in type 1 diabetic patients. Furthermore, it deteriorates the quality of life and increases health care costs (Lustman & Clouse 2005). Adult diabetics with depression exhibit decreased self-care behavior and have lower quality of life (Egede *et al.* 2009). The mortality risk of patients with depression suffering from diabetes compared to non-diabetic population is significantly elevated (Zhang *et al.* 2005).

In treatment of diabetic patients it is decisive, whether they fully become aware of their disease and decide to focus on it. Therefore, attitude of a man to the disease plays the main role here – the disease can be best influenced by the one, who controls it. A significant association between depression and "treatment nonadherence" was found in diabetic patients (Gonzales *et al.* 2008).

A trend towards expanding complex treatment of diabetes by mental health care has been appearing in recent years. Studies examining the influence of mental problems and their treatment on glycemic control are under way. The results differ. According to a study from Georgiades *et al.* (2007), the changes in depressive symptoms are not associated with changes in glycosylated hemoglobin (Georgiades *et al.* 2007). Nevertheless, in a study with sertraline it was proven that a specific minor low-income population showed a significant decrease in glycosylated hemoglobin levels and systolic blood pressure after pharmacologic treatment of depression compared to placebo (Echeverry *et al.* 2009). It is generally acknowledged that increased mental health care of diabetic patients produces alleviation from mental problems, however, it does not significantly influence glycemic control (Wayne *et al.* 2005). According to a study by Lustman *et al.* (2006), glycosylated hemoglobin levels decrease during the open treatment phase and remain significantly lower than baseline during the depression-free maintenance, independently of the fact, whether the patients are treated by antidepressant (sertraline in this case) or placebo (Lustman *et al.* 2006). No single treatment that would lead to better medical outcomes in patients suffering from both diabetes and depression has been clearly indentified to date (Petrak & Herpertz 2009).

Results of existing research done in the field are inconsistent, however, they advocate the unquestionable suitability of psychological or psychiatric help employment in treatment of diabetic patients. The authors are concerned with the pharmacologic treatment of depressive symptoms especially with the regard of the influence of antidepressants on individual symptoms that may be affected by the treatment (depression, body weight, blood glucose, and diabetic neuropathy) as well as interactions with other medicaments, which are commonly used in diabetic patients. Drugs of choice are antidepressants from the SSRI group – selective serotonin reuptake inhibitors.

Other psychiatric treatment modalities, such as psychoeducation and CBT have been scrutinized in recent research. According to a study performed in Zagreb, psychoeducational treatment seems to be beneficial in diabetics with depression, however, its effects are comparable with a non-specific support given to patients in control group (Pibernik-Okanovic *et al.* 2009). Motivational enhancement therapy conducted by nurses and cognitive behavioral therapy are suitable for patients with poor glycemic control. Combined therapy leads to a decrease in glycosylated hemoglobin levels compared with usual care, but motivational enhancement therapy alone does not (Ismall *et al.* 2007). The abovementioned conclusions imply the need for further research in the field.

The aim of our research was to improve glycemic control through amelioration of mental state and to determine, whether the change in mental state of diabetes mellitus type 1 patients with depression or anxiety using antidepressant drugs would affect glycemic control. We focused on patients with diabetes type 1 since most studies regarding mental state do not study individual types of diabetes separately or are concerned predominantly with type 2 diabetic patients. Concurrently, it is obvious that mental problems, their treatment, and response to them rather differ in individual types.

In contrast to already published research, our study further focused on determining, whether patients actually took the recommended medication.

METHODS

A double-blinded, randomized, placebo controlled study was performed between 2004 and 2008 in Diabetes Center, Department of Internal Medicine I., University Hospital in Pilsen. 33 patients were enrolled after the study had been approved by ethical committee of FN and LFUK in Pilsen. All patients signed an informed consent. 21 patients successfully completed the trial; 10 used active substance sertraline at a dose of 100 mg per day with gradual titration of the dose (50 mg a day for the first week), and 11 were given placebo. The entry characteristics of the group are summarized in Table 1.

Sealed-envelope randomization was performed. The patients were given medication for the time period until their next check-up according to their identification number. Neither patient, nor doctor thus knew whether the patient was using antidepressant or placebo. Upon study termination the doctor acquired the information and communicated it to the patient. Further potential cooperation was settled accordingly.

The patients were recruited based on the results of depression and anxiety symptom scales – the completion of questionnaires was done by the patients with a help of an educated dietitian while waiting for their diabetic examination – and based on subsequent clinical psychiatric interview. A patient was enrolled in the study if desired score was reached at least in one of three scales used. They were Zung Self-Rating Depression Scale (SDS) – enrolled from score 51 points, Hamilton Anxiety Rating Scale (HAMA) – enrolled from score 18 points, and Hamilton Depression Rating Scale (HAMD) – enrolled from score 8 points (Filip *et al.* 1997) Patients were informed in advance that the interview was a psychiatric intervention. The purpose of the interview was to ascertain, whether the client had any mental problems.

Patients with mild to moderate depression or anxiety, who signed an informed consent, were enrolled in the study. Patients with severe depression or suicidal tendencies were not enrolled for the risk of possible placebo use during the study. Patients with contraindications for sertraline (severe hepatic or renal affection, epilepsy, in women pregnancy) or suffering from other psychiatric disorder (active addiction to psychoactive drugs, schizophrenia, schizoaffective disorder, mania) were not included either. Patients not tolerating the dose given or uncooperative patients were excluded in course of the trial.

Following enrollment in the study the patients were invited after one, three and six months for reiteration of rating of their depression and anxiety symptoms, evaluation of actual mental state using a psychiatric clinical examination and assessment of laboratory parameters of glycemic control – glycosylated hemoglobin (HbA1c), standard deviation of glycemia values in glucometer of the patient, actual glycemia and other metabolic parameters (daily insulin dose, body weight, blood pressure, level of triglycerides and cholesterol). Glycosylated hemoglobin is assessed by hemolysis in the laboratory of the FN, level of cholesterol and triglycerides using photometry. All somatic parameters were additionally measured another three months after study termination, as they change with time delay.

Compliance was also monitored – every subject of the trial was taken serum for sertraline level analysis after three months of drug use. The samples of patients, who were supposed to take the active substance, were sent for analysis after study termination. This way the patients who were really using the medication were differentiated. Patients with non-measureable sertraline levels were excluded from the final evaluation of the study results. Other parameters of patient compliance, such as adherence to appointment keeping, a number of hypoglycemia episodes, diabetic ketoacidosis, amount of blood glucose test strips used, and the number of diabetes visits in course of the study duration were also evaluated.

Other factors that could additionally affect mental state of a patient (diabetes duration, age at onset of diabetes, social history and occupation, presence of diabetes complications, etc.) were also taken in consideration.

The psychiatric interviews did not have a character of a systematic psychotherapy, the aim was not to look for causes of mental problems or elaborate cognitive behavioral plans etc. In spite of this, the sessions had some psychotherapeutic potential.

Non-parametric rank tests, such as Wilcoxon test both paired and unpaired, rank correlation coefficients and Friedman test were used for statistical evaluation in view of the fact that values mostly did not have a normal distribution (tested according to skewness and kurtosis). The results are presented as median and interquartile range for nonparametric distribution of the data.

RESULTS

33 patients with diabetes mellitus from Diabetes Center, department of Internal Medicine I., University Hospital in Pilsen were enrolled in the study. 24 patients thereof completed the study, 9 patients quitted prematurely – two for subjectively experienced adverse effects of the medication (one of them used placebo), two for inadequate improvement or deterioration of mental problems during the study (one of them used sertraline), one for unrelated oncological disease deterioration. In 4 patients the study was terminated prematurely for noncompliance. 13 patients used the active substance sertraline, measurable level of sertraline in blood serum was found only in 10 patients thereof. These were considered as actually taking the medication. 11 patients used placebo.

The entry characteristics of the patients are summarized in Table 1. Out of 21 evaluated patients, 15 were women and 6 men at the age from 20 to 63 years at the

Tab. 1. Entry criteria of the study group – values presented as median and interquartile range.

Characteristic	placebo (n=11)		sertraline (n=10)		*p*-value
Age (years)	25	(19–30)	24.5	(21–33)	NS
Diabetes duration (years)	23	(10–31)	20	(9–25)	NS
SDS (points)	34	(24–38)	30	(25–35)	NS
HAMA (points)	18	(12–21)	17	(10–25)	NS
HAMD (points)	8	(7–9)	10.5	(9–13)	0.01
Insulin dose (IU/day)	36	(27–49)	49.5	(28–53)	NS
Body weight (kg)	67	(56–75)	70	(62–83)	NS
SBP (torr)	130	(120–140)	120	(110–130)	NS
DBP (torr)	70	(70–80)	75	(70–80)	NS
SD	4.7	(3.8–5.6)	4.95	(4.2–5.9)	NS
HbA1c (%)	6.9	(6.6–8.7)	6.9	(5.9–7.7)	NS

SDS - Zung Self-Rating Depression Scale, HAMA - Hamilton Anxiety Rating Scale, HAMD - Hamilton Depression Rating Scale, SBP – Systolic blood pressure, DBP – diastolic blood pressure, SD – standard deviation of blood glucose values in glucometer of a patient, HbA1c – glycosylated hemoglobin

Tab. 2. Differences in values regarding mental state and somatic parameters at the beginning and the end of the study – values are presented as median and interquartile range.

Parameter	Sertraline (n=10)		Placebo (n=11)		*p*-value
D SDS	–2.5	(–16 to 5)	–8	(–19 to –4)	NS
D HAMA	–5	(–11 to –3)	–5	(–11 to –4)	NS
D HAMD	–7	(–9 to –6)	–2	(–5 to 1)	0.01
D TG	0.11	(0 to 0.46)	–0.01	(–0.15 to 0.56)	NS
D CHOL	–0.255	(–1.29 to 0.53)	0.27	(–0.11 to 0.97)	NS
D WEIGHT	–0.5	(–3 to 1)	0	(–2 to 4)	NS
D SBP	0	(0 to 20)	10	(0 to 20)	NS
S DBP	0	(–10 to 10)	5	(–10 to 10)	NS
D HbA1c	0.3	(–0.5 to 0.8)	0.2	(0.1 to 0.7)	NS
D SD	–0.05	(–0.4 to 0.3)	0.6	(–0.3 to 2.3)	NS
D INSULIN	0	(–3 to 4)	–1	(–6 to 2)	NS

D SDS, D HAMA, D HAMD – differences in depressive and anxiety scale values at the beginning and in the end of the study, D TG, D CHOL, D WEIGHT, D SBP, D DBP, D HbA1c, D SD – differences in abovementioned laboratory results at the beginning and in the end of the study, D INSULIN – difference in total insulin daily dose at the beginning and in the end of the study.

time of study enrollment. Age at onset of diabetes was from 0 to 50 years. Diabetes duration was from 1 to 48 years. 12 patients used insulin pens for insulin administration, 9 used an insulin pump. At least one complication of diabetes was present in 13 patients at time of enrollment; 2 had retinopathy, 3 had neuropathy, in 2 patients a combination of retinopathy and neuropathy was present, 3 suffered from a combination of retinopathy and nephropathy, and 3 had a combination of all these complications. 8 patients were without complications, 13 patients entered the study with mild anxiety or depressive symptoms, 8 with moderate depression. No enrolled patient suffered from severe depression as this was an exclusion criterion for the risk of possible placebo use. 10 patients used the active substance sertraline and 10 used placebo.

Adverse effects of the medication were observed by 11 patients, 3 thereof were using placebo and 6 were using active substance. They included feelings of fatigue and somnolence, stomachache, pyrosis, sensation of throat constriction, decreased attention, trembling, weight gain, reduction of sexual appetence and increased perspiration.

Changes in mental and physical state of the patients in course of the study are demonstrated in Table 2.

After statistical evaluation of results we found that mental state improved at a level of statistical significance of $p<0.001$ in both, patients using active substance and placebo, and that in SDS, HAMD and HAMA scale. Furthermore, the decrease in HAMD scale values in time was statistically significantly higher in sertraline group compared with placebo.

A statistically significant increase in body weight in time (level of significance $p<0.05$) and elevation of systolic blood pressure (borderline level of significance) was found in both groups of patients, using active substance and placebo. Association between HbA1c level reduction and insulin pump treatment compared with multiple daily injection of insulin using insulin pens was confirmed as a secondary result. No statistically significant changes were found in other somatic parameters.

DISCUSSION

The fact that current and long term mental state of a patient influences his glycemic control is evident already from former observations (Egede *et al.* 2009; Lustman & Clouse 2005). It has been shown that type 1 diabetic patients with mental problems and deteriorated glycemic control benefit the most, apart from diabetes care, from individually set usually combined psychiatric treatment (i.e. pharmacological and psychotherapeutic), since single psychopharmacologic intervention did not bring glycemic control improvement (Petrak & Herpertz 2009). It is important that physicians and other medical staff taking care of patients with diabetes mellitus ask their patients about mental problems. Concealed mental problems may play a considerable role in deterioration of glycemic control of diabetic patients.

In course of our study the mental state improved in most patients, regardless of the fact if they were using active substance or placebo. This fact may have several possible explanations. These include "study effect", "placebo effect" or psychotherapeutic effect. All the factors

undoubtedly affected the results of the study, however, they were not assessed and evaluated separately. Probable consequence of psychotherapeutic potential of a contact of a patient with a psychiatrist is another evidence of the importance of a combined treatment, i.e. pharmacologic and psychotherapeutic. Patients using sertraline improved statistically significantly more in HAMD score compared to placebo, which confirms the fact that sertraline is an effective antidepressant drug in treatment of depressive symptoms.

Due to the fact that it was necessary to set strict inclusion criteria, a small number of patients was included in the study. Therefore, upon statistical analysis, the results were not unequivocal. When testing for connections between mental and physical parameters, it is important to consider that the search for connections may be impeded by an unknown time delay, with which some changes occur. At the same time, in order to perform the study at all, the observations had to be time restricted.

Our study is unique by verification of sertraline level. This way, the number of patients included in the final evaluation of the results of the trial decreased approximately by 14 %, since 3 out of 13 patients, who received the active substance, did not have a measurable level in serum.

Another reason for the small number of patients included in the study is that we examined type 1 diabetic patients. Other studies that pursue similar topic deal with type 2 diabetic patients or do not differentiate between the two types of the disease. This enables them to broaden entry criteria considerably and thus to increase the number of patients enrolled in the study (Georgiades 2007). Nevertheless, we believe that both mental problems and their treatment differ significantly in different types of diabetes. We thus considered appropriate to devote our time to patients with diabetes mellitus type 1, in whom significantly less studies had been performed.

An often discussed topic in diabetic patients is their adherence to the treatment. It concerns mainly the adherence to regime restrictions, but also to appointment keeping. Noncompliance in diabetic patients (and possibly more in those with mental problems) was another reason for the small number of patients, who successfully completed the trial.

CONCLUSIONS

Mental health of majority of the patients included in the study improved statistically significantly in both, patients using the active substance as well as those using placebo. Regarding physical parameter changes, the body weight gain and systolic blood pressure elevation was statistically significant in all patients irrespective of the fact if they were using sertraline or placebo. No statistically significant connections between mental and physical state were found.

Improvement in mental state of patents using antidepressant and placebo demonstrates the efficiency of mental health intervention in diabetic patients. Those who have mental problems improve merely because they feel someone is taking care of them.

Difficulties in interpretation of results predominantly stem from the small number of patients, which was caused by strict inclusion criteria, by exclusion of patients who did not verifiably use the active substance from the final evaluation of results, and last but not least by difficult cooperation with the patients.

The importance to intervene in mental health of diabetic patients with mental problems has already been demonstrated. Although our study did not clearly prove a direct connection between mental health amelioration and glycemic control improvement of diabetic patients, we consider the psychologic and psychiatric intervention in these patients indispensable. A patient, whose mental condition improves, cooperates on the treatment of their basic disease distinctly better, which is essential in diabetes from a long term perspective.

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