ORIGINAL ARTICLE

Anxiety disorders are associated with quality of life impairment in patients with insulin-dependent type 2 diabetes: a case-control study

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Objective: To assess the presence of anxiety disorders and quality of life in patients with insulin-dependent type 2 diabetes.

Methods: Case-control study of 996 patients with type 2 diabetes and 2,145 individuals without diabetes. The sole inclusion criterion for the case group was insulin-dependent type 2 diabetes. We compared the case and control groups for sociodemographic variables, laboratory and clinical data, and presence of anxiety disorders. Quality of life was evaluated using the WHOQOL-BREF instrument, and the prevalence of anxiety disorder was evaluated by the Mini International Neuropsychiatric Interview (MINI).

Results: Patients with diabetes had a higher prevalence of generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder. The presence of these disorders in combination with type 2 diabetes was associated with worse quality of life in the physical, social, psychological, and environmental domains.

Conclusions: This study demonstrates the importance of diagnosing and treating anxiety disorders in patients with diabetes, so as to prevent more serious complications associated with these comorbidities.

Keywords: Anxiety disorders; quality of life; diabetes; comorbidities

Introduction

Diabetes is a chronic disease that affects about 346 million people around the world,[1] with an additional 7 million people developing diabetes each year. On the basis of this data, the International Diabetes Federation estimates that, by 2030, about 552 million individuals will be affected with the disease.[2] Diabetes mellitus is characterized by progressive destruction of pancreatic beta cells via cytokine-induced apoptosis.[3] The specificity of each type of diabetes is the etiologic mechanism and speed of this apoptosis. In type 2 diabetes mellitus (T2DM), apoptosis is progressive and driven mainly by glucotoxicity and lipotoxicity, whereas in type 1 diabetes mellitus (T1DM), apoptosis is rapid and induced by an irreversible autoimmune process.[3]

Comorbidities are often associated with diabetes, which further increases the cost of this disease to the healthcare sector and, consequently, has an impact on social security costs through lost productivity.[4] These comorbidities include cardiovascular diseases,[5] nephropathy, hypertension, ocular complications, and psychiatric disorders, such as depression and anxiety. It has been found that patients with chronic disease are twice as likely to develop anxiety disorders and depression than the general population.[6] Recent studies have shown that elevated glucose levels can contribute to the development of anxiety and depression.[7] These disorders may also lead to a worsening in the course of diabetes, with complications such as weight gain, increased mortality, and functional disability.[8,9]

The prevalence of diabetes associated with anxiety can reach up to 40%.[10] Anxiety disorders comprise several conditions, such as obsessive-compulsive disorder (OCD), generalized anxiety disorder, panic disorder, social phobia, agoraphobia, specific phobia disorder, and posttraumatic stress disorder.[11] The subtype most commonly found in comorbidity with diabetes is generalized anxiety disorder, which can affect up to 14% of

patients with diabetes.[10] Anxiety disorders correlate directly with poor adherence to treatment, inadequate glycemic control, and increased adrenergic activity.[12,13]

Studies show that patients with diabetes who live in developing countries have a higher prevalence of psychiatric disorders. Potential explanations include a higher level of gender inequality, social insecurity, lower levels of education, a greater level of poverty, financial difficulties, and other forms of economic stressors.[14,15] The combination of diabetes with psychiatric disorders, mainly depression, anxiety, and substance abuse, is associated with a decline in quality of life, as these patients have greater difficulty in regulating their blood glucose levels. This, in turn, increases the risk of complications. Studies have shown that, in these cases, the use of medications combined with physical activity is indicated to increase the effectiveness of treatment, because this combination leads to the release of β-endorphins and cerebral neurotransmitters during exercise. This then causes a reduction in anxiety levels, which should improve quality of life.[15]

As the number of people affected by diabetes increases, it has become ever more important to understand which other factors are related to this disease, particularly psychiatric disorders, that may cause even more impairment of quality of life, thus compounding the health-related and social complications of diabetes as the disease progresses. Within this context, the objective of this study was to evaluate the prevalence of anxiety disorders and the quality of life of patients with insulin-dependent T2DM as compared with non-diabetic community controls. We also address the possible associations of anxiety, quality of life, and adherence to treatment with plasma glucose and glycosylated hemoglobin (HbA1c) levels in diabetic patients.

Methods

Study design

This is a case-control study. Cases (patients) were composed of a sample of individuals with T2DM recruited from outpatient facilities within the public health system of a municipality in the state of Santa Catarina, Brazil. The control group was composed of people from the community who did not have diabetes.

Setting

The municipality in which the study was conducted has a population of 192,308, according to the latest Brazilian Institute of Geography and Statistics (IBGE) census. The study was carried out between March and November 2010.

Participants and study size

At the time of the study, 1,032 patients with T2DM were registered in the Municipal Health Fund of Criciúma, state of Santa Catarina, Brazil. The sole criterion for inclusion in the present study was insulin-dependent T2DM. The

exclusion criteria were: less than 5 years since diagnosis of T2DM, less than 1 year of insulin treatment, illiteracy, and age <18 years. Of the registered patients, 16 has less than 5 years since diagnosis, nine had been on insulin therapy for less than 1 year, three were illiterate, four did not have ability to complete the study questionnaires, and eight refused to participate in the study. Therefore, the total number of patients remaining for the study sample was 996. The control group comprised neighbors of the selected patients who were actively recruited by the investigators. Initially, controls were identified by the case (diabetic patient) and the patient's address. Armed with this information, we set out to identify the neighbors of these patients, choosing first the neighbor to the right of the patient's home and then the neighbor to the left of the first neighbor. To be considered for the non-diabetic control group, the subjects were required to have two fasting glucose levels below 126 mg/dL measured 6 months before the survey, no medical history (current or past) of diabetes, and/or no classic symptoms of hyperglycemia (polyuria, polyphagia, polydipsia, and weight loss). Initially, the control group consisted of 2,262 subjects, of whom 117 were excluded due to glucose levels above the normal reference range (and referred to the relevant health services). Thus, the final sample comprised 996 cases and 2,145 controls.

This study was planned in accordance with Brazilian National Health Council Resolution 196/96 and was approved by the Research Ethics Committee of Universidade do Extremo Sul Catarinense (UNESC), Santa Catarina, Brazil, under protocol number 310/2009. After the introduction and identification of the investigator, each volunteer received information about the procedures that would be undertaken, as well as the purposes of the study, their freedom to accept or to decline participation in the study, and assurances relating to their anonymity. Thus, all participants who enrolled in the study were fully informed and did so of their own free will.

Data measurement

Data collection was performed by a trained interviewer, on a one-to-one basis, at the subjects' own homes. The survey covered information on sociodemographic parameters (age, gender, marital status, and education); history of high blood pressure (hypertension), acute myocardial infarction (AMI), and stroke (CVA); and the laboratory parameters fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and total and low-density lipoprotein (LDL) cholesterol. The cutoff points adopted for these parameters were: 110 mg/dL for blood glucose, 200 mg/dL for total cholesterol, 100 mg/dL for LDL cholesterol, and 7% for HbA1c. The time elapsed between psychiatric evaluation and laboratory testing was 1 week. To screen for anxiety disorders, the Portuguese version of the Mini International Neuropsychiatric Interview (MINI) was used.[16] This instrument is a standardized interview compatible with DSM-IV (APA) and ICD-10 (WHO), which has the convenience of being brief (15 to 30 minutes when

administered by a trained professional) and can be used in clinical and research settings after a short training period (1 to 3 hours).[16] The interview investigated the presence or absence of symptoms that would classify the individuals interviewed as having anxiety disorders. During analysis of interview data, only current symptoms of general anxiety disorders, panic disorders, agoraphobia, social phobia, and OCD were studied (to avoid memory bias). The instrument used to assess quality of life was the WHOQOL-BREF questionnaire, in its validated Portuguese version.[17] This questionnaire, developed by the World Health Organization (WHO), consists of 26 questions (two general and 24 other) addressing four domains (physical, psychological, social relationships, and environment). General items and domains are scored from 0 to 100. The higher the score, the better the quality of life index.

Statistical methods

After collection, data were tabulated and analyzed in the SPSS version 16.0. First, the Pearson chi-square test was used to compare the two groups (patients and controls) in terms of sociodemographic, laboratory, and clinical data. Then, the two groups were compared for anxiety disorders using binary logistic regression, controlling for the following variables: total cholesterol, LDL cholesterol, hypertension, AMI, and CVA. For WHOQOL scores, the factors group (patient or control) and anxiety disorder (present or absent) were assessed by analysis of covariance (ANCOVA). P-values < 0.005 were considered statistically significant.

Results

A general profile of the patient (n=996) and control (n=2,145) groups is provided in Table 1. There were no statistically significant between-group differences in the distribution of sex, marital status, and education. Moreover, there was no any relationship between laboratory data and clinical comorbidities of interest. Patients with T2DM had a higher prevalence of high total and LDL cholesterol, as well as of AMI, hypertension, and CVA.

The MINI assessment revealed higher rates of anxiety in the patient group. As shown in Table 2, we found an association between T2DM and presence of generalized anxiety disorder (GAD) ($OR_{adj} = 1.77$; $p < 0.001$), panic disorder or agoraphobia ($OR_{adj} = 2.31$; $p < 0.001$), and OCD ($OR_{adj} = 2.47$; $p < 0.001$), with the presence of social phobia being statistically similar between the two groups ($p = 0.273$).

Figure 1 shows a comparison of scores on the four domains of the WHOQOL-BREF questionnaire between patients and controls in the presence or absence of GAD. Patients with diabetes had worse quality of life scores in the following domains: physical ($F_{group} = 2149.4$; $p < 0.001$), psychological ($F_{group} = 293.9$; $p < 0.001$), and environment ($F_{group} = 870.3$; $p < 0.001$); however, patients with diabetes exhibited better quality of life

scores for the social domain than did controls ($F_{group} = 29.5$; $p < 0.001$). The presence of GAD was also associated with worse quality of life scores in the physical ($F_{GAD} = 285.6$; $p < 0.001$), psychological ($F_{GAD} = 559.6$; $p < 0.001$), social ($F_{GAD} = 180.7$; $p < 0.001$), and environment domains ($F_{GAD} = 542.1$; $p < 0.001$). Finally, we observed an interaction between diabetes and GAD. In patients with both conditions, there was a greater decline of quality of life scores in the physical ($F_{interaction} = 342.4$; $p < 0.001$), psychological ($F_{interaction} = 127.0$; $p < 0.001$), social ($F_{interaction} = 239.1$; $p < 0.001$), and environment domains ($F_{interaction} = 210.0$; $p < 0.001$), with quality of life scores being similar in controls (both with and without GAD) and lower in patients with diabetes who have GAD.

Figure 2 shows a similar comparison for panic disorder. Patients with diabetes had lower quality of life scores in the physical ($F_{group} = 2085.6$; $p < 0.001$), psychological ($F_{group} = 339.4$; $p < 0.001$), social ($F_{group} = 15.2$; $p = 0.001$), and environment domains ($F_{group} = 1059.9$; $p < 0.001$). The presence of panic disorder alone was associated with a worse quality of life score in the physical ($F_{PD} = 86.5$; $p < 0.001$), psychological ($F_{PD} = 126.5$; $p < 0.001$), and environment ($F_{PD} = 95.0$; $p < 0.001$) domains, but not with impairment in the social domain ($F_{PD} = 1.3$; $p = 0.252$).

Table 1 Distribution of sociodemographic and clinical variables in the patient and control groups

	Patients (%) (n=996)	Controls (%) (n=2,145)	p-value
Sex			
Male	43.4	40.8	0.18
Female	56.6	59.2	
Marital status			
Partner	56.7	55.4	0.45
No partner	43.3	44.6	
Educational attainment			
< 8 years	55.1	55.3	0.89
⩾ 9 years	44.9	44.7	
Cholesterol, total			
< 200 mg/dL	35.3	47.4	0.001*
⩾ 200 mg/dL	64.7	52.6	
Cholesterol, LDL			
< 100 mg/dL	25.7	64.2	0.001*
⩾ 100 mg/dL	74.3	35.8	
Hypertension			
Present	63.4	35.8	0.001*
Absent	36.6	64.2	
AMI			
Present	9.8	6.7	0.002*
Absent	90.2	93.3	
CVA			
Present	10.4	1.1	0.001*
Absent	89.6	98.9	

AMI = acute myocardial infarction; CVA = cerebrovascular accident; LDL = low-density lipoprotein.
* $p < 0.005$ for comparison between patients and controls, chi-square test.

Table 2 Distribution of anxiety disorders in the patient and control groups, adjusted by multivariate logit regression

	Patients (%) (n=996)	Controls (%) (n=2,145)	OR_{adj}	p-value
Generalized anxiety disorder	34.1	21.8	1.77	0.001*
Panic disorder	25.7	12.3	2.31	0.001*
Social phobia	18.8	15.4	1.13	0.273
Obsessive-compulsive disorder	3.2	6.9	2.47	0.001*

OR_{adj} = odds ratio adjusted for total cholesterol, LDL cholesterol, hypertension, myocardial infarction, and stroke.
* $p < 0.005$ for comparison between patients and controls.

There was also an interaction between diabetes and panic disorder, resulting in poorer quality of life in the physical ($F_{interaction}$ = 372.2; $p < 0.001$), psychological ($F_{interaction}$ = 148.2; $p < 0.001$), social ($F_{interaction}$ = 514.0; $p < 0.001$), and environment domains ($F_{interaction}$ = 374.1; $p < 0.001$).

Figure 3 shows the results of a similar analysis for social phobia. Patients with diabetes had lower scores in all four quality of life domains (physical [F_{group} = 1706.1; $p < 0.001$], psychological [F_{group} = 245.9; $p < 0.001$], social [F_{group} = 10.2; $p < 0.001$], and environment [F_{group} = 660.1; $p < 0.001$]). The isolated presence of social phobia was also associated with a worse quality of life score in the physical (F_{SF} = 126.1; $p < 0.001$), psychological (F_{SF} = 232.0; $p < 0.001$), and environment (F_{SF} = 244,2; $p < 0,001$) domains, but with a better score in the social domain (F_{SF} = 101.8; $p < 0.001$) There was an interaction in the four domains when observing quality of life in the physical ($F_{interaction}$ = 167.4; $p < 0.001$), psychological ($F_{interaction}$ = 40.0; $p < 0.001$), social ($F_{interaction}$ = 84.1; $p < 0.001$), and environment domains ($F_{interaction}$ = 59.2; $p < 0.001$). While quality of life was similar in controls with and without the disorder, it was higher in patients with diabetes but without social phobia.

Finally, in the results relating to OCD (Figure 4), patients with diabetes also had the lowest scores within the physical (F_{group} = 392.5; $p < 0.001$), psychological (F_{group} = 85.0; $p < 0.001$), and environment (F_{group} = 184.2; $p < 0.001$) domains; however, scores within the social domain were once again better (F_{group} = 6.6; $p < 0.01$). The presence of this disorder also resulted in lower quality of life scores (physical [F_{OCD} = 18.5; $p < 0.001$], psychological [F_{OCD} = 54.9; $p < 0.001$], social [F_{OCD} = 50.6; $p < 0.001$], and environment [F_{OCD} = 71.0; $p < 0.001$]). There were interactions in the physical ($F_{interaction}$ = 6.3; $p < 0.05$), psychological ($F_{interaction}$ = 8.1; $p < 0.05$), social ($F_{interaction}$ = 4.0; $p < 0.05$), and environment domains ($F_{interaction}$ = 5.8; $p < 0.05$).

Discussion

The present study demonstrated that there is a higher prevalence of hypertension, high total and LDL cholesterol, AMI, and CVA in patients with T2DM. These results corroborate the existing literature, which shows that each 1% increase in the HbA1c level increases the odds of developing diabetes and cardiovascular disease by 18% and the odds of CVA by 17%.[18] Other studies found that more than one-third of patients admitted with CVA are hyperglycemic.[19] There was also a significant presence of hypertension in patients with T2DM. The association of these two comorbidities has a serious negative impact on the patient, as they are responsible for retinopathy, other eye diseases, cardiovascular disability, and an increase in the odds of death.[20-22]

In analyzing the data concerning anxiety disorders, we observed a higher prevalence of anxiety among patients with diabetes than among controls. A study conducted in
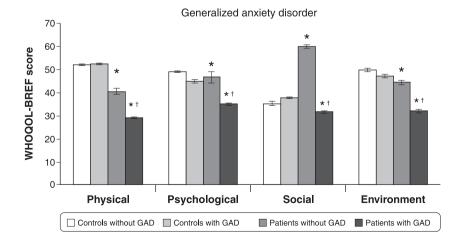

Figure 1 Relationship between generalized anxiety disorder (GAD) and quality of life scores in patients with insulin-dependent type 2 diabetes. * $p < 0.005$ vs. controls without generalized anxiety disorder; † $p < 0.005$ vs. patients without generalized anxiety disorder.
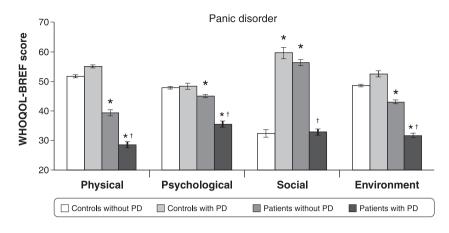
Figure 2 Relationship between panic disorder (PD) and quality of life scores in patients with insulin-dependent type 2 diabetes. * p < 0.005 vs. controls without panic disorder; [†] p < 0.005 vs. patients without panic disorder.

2010 demonstrated a higher probability of patients with diabetes developing depression and anxiety disorders,[6] since the prevalence of anxiety symptoms may reach 40% in patients with diabetes. Among the four anxiety disorders studied in our sample, GAD had the highest prevalence, affecting 34.1% of the patients surveyed. In their systematic review of the literature, which included 2,584 patients with diabetes, Grigsby et al. (2002) also found higher rates (14%) of generalized anxiety than other anxiety disorders.[11] There was a lower rate of comorbid generalized anxiety and diabetes than in the present study, but this discrepancy can be explained by the fact that the review analyzed all recognized anxiety disorders, while the present study examined only four types of anxiety disorders.

The four types of anxiety disorder we investigated were associated with worsening in WHOQOL-BREF scores across all domains (physical, psychological, environmental, and social) in patients with diabetes. There is evidence to suggest that depression is associated with a decrease in some self-care behaviors.[23,24] Alternatively, symptoms of anxiety and depression adversely affect the degree of acceptance of illness and significantly lower the quality of life of those with

diabetes.[25] There is accumulating evidence to suggest that diabetes, depression, and quality of life are closely interrelated, and that diabetes is causally related to depression and vice versa.[26] Whether depression and anxiety should be considered complications of diabetes rather than comorbidities is of interest. In either case, it is clear that additional attention must be paid to diabetic patients with mental health issues such as anxiety and depression, to ensure that they enjoy a quality of life comparable to that of individuals without these mental health problems. Improvements in both quality of life and disease management could be achieved by improving the identification and management of mental health problems among people with diabetes.[27] Still, anxiety disorders are directly related to poor glycemic control, poor adherence to treatment, and increased adrenergic activity.[28] Poor glycemic control, in turn, is directly linked to the comorbidities of diabetes, such as hypertension, coronary heart disease, and high cholesterol.[5] In the present study, we found that poorer quality of life due to the presence of an anxiety disorder directly influenced an increase in these comorbidities. Besides affecting quality of life and disease management, anxiety activates the hypothalamic-pituitary-adrenal axis, stimulating the sympathetic
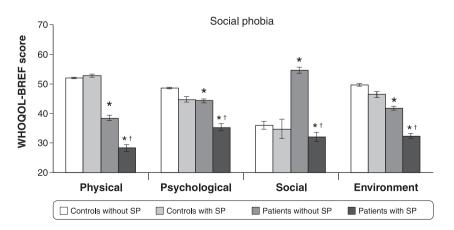

Figure 3 Relationship between social phobia (SP) and quality of life scores in patients with insulin-dependent type 2 diabetes. * p < 0.005 vs. controls without social phobia; [†] p < 0.005 vs. patients without social phobia.
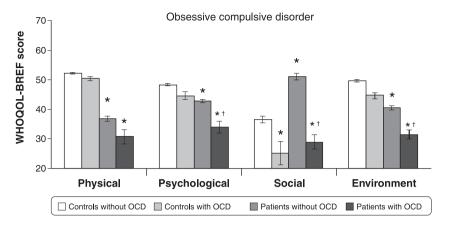
Figure 4 Relationship between obsessive-compulsive disorder (OCD) and quality of life scores in patients with insulin-dependent type 2 diabetes. * $p < 0.005$ vs. controls without obsessive-compulsive disorder; † $p < 0.005$ vs. patients without obsessive-compulsive disorder.

nervous system-adrenal responses, increasing platelet aggregation and inflammation, decreasing insulin sensitivity, worsening glycemic control, and increasing the risk of complications.[29] Maintaining good glycemic control is the focus of all therapies for diabetes – thus the importance of psychological controls in helping diabetic patients control their disease. In addition, anxiety disorders can originate, at least in part, from other mood disorders, such as depression. This was recently reported in another study by our group,[30] which showed an increased prevalence of mood disorders and suicidal ideation in patients with T2DM.

In conclusion, the findings of this study demonstrated a high prevalence of anxiety disorders and impairments in quality of life among patients with T2DM who were receiving treatment with insulin. A positive aspect of this study was the sample size in both the patient and control groups. This was the first study employing a large sample of patients to demonstrate an association between comorbid anxiety disorders/insulin-dependent T2DM and a significant worsening in quality of life.

Some limitations of this study must be mentioned. The MINI was not used for clinical diagnosis, but instead as a rapid screening tool in our interviews. There was no stratification of patients with controlled and uncontrolled diabetes, and our sample was mixed, including patients recruited from clinical settings and community-dwelling controls. Although we controlled for clinical variables (total and LDL cholesterol, hypertension, AMI, and CVA), care should be taken in extrapolating data, because psychiatric comorbidities were excluded, and the presence of mood disorders could be a confounding factor. However, this study demonstrated the importance of diagnosing and treating anxiety disorders in patients with diabetes, thus helping to avoid more serious complications associated with its comorbidities.

Disclosure

The authors report no conflicts of interest.

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Corrigendum

On behalf of Maria Augusta B. dos Santos, Luciane B. Ceretta, Gislaine Z. Réus, Helena M. Abelaira, Luciano K. Jornada,1 Mágada T. Schwalm, Morgana V. Neotti, Cristiane D. Tomazzi, Karina G. Gulbis, Renan A. Ceretta, and João Quevedo, authors of the paper entitled "Anxiety disorders are associated with quality of life impairment in patients with insulin-dependent type 2 diabetes: a case-control study," published in this journal in 2014, volume 36, issue 4, pages 298-304, we hereby inform that the figures originally published in ahead of print mode were wrong. Below please find new versions for the four figures included in the manuscript.
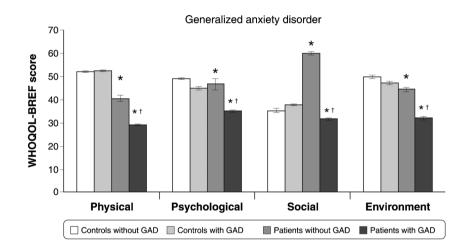

Figure 1 Relationship between generalized anxiety disorder (GAD) and quality of life scores in patients with insulin-dependent type 2 diabetes. * $p < 0.005$ vs. controls without generalized anxiety disorder; † $p < 0.005$ vs. patients without generalized anxiety disorder.
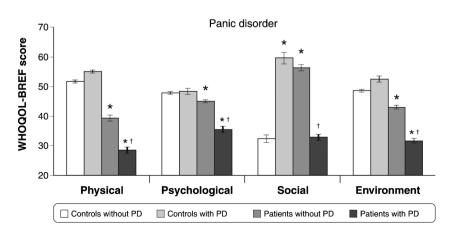

Figure 2 Relationship between panic disorder (PD) and quality of life scores in patients with insulin-dependent type 2 diabetes. * $p < 0.005$ vs. controls without panic disorder; † $p < 0.005$ vs. patients without panic disorder.
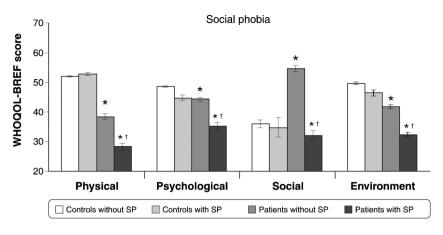
Figure 3 Relationship between social phobia (SP) and quality of life scores in patients with insulin-dependent type 2 diabetes. * p < 0.005 vs. controls without social phobia; † p < 0.005 vs. patients without social phobia.
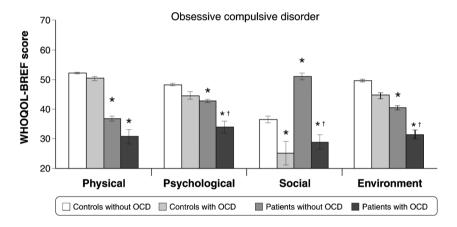

Figure 4 Relationship between obsessive-compulsive disorder (OCD) and quality of life scores in patients with insulin-dependent type 2 diabetes. * p < 0.005 vs. controls without obsessive-compulsive disorder; † p < 0.005 vs. patients without obsessive-compulsive disorder.