Depression, anxiety, cognitive impairment and their association with clinical and demographic variables in people with type 2 diabetes: a 4-year prospective study

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Depression, anxiety, cognitive impairment and their association with clinical and demographic variables in people with type 2 diabetes: a 4-year prospective study

M. Trento · M. Trevisan · M. Raballo ·
P. Passera · L. Charrier · F. Cavallo ·
M. Porta

Abstract

Objective To investigate depression, anxiety and cognitive impairment and their associations with clinical and socio-demographic variables in type 2 diabetes.

Methods The Zung Self-Rating Depression–Anxiety Scale and Mini-Mental State Examination (MMSE) were administered at baseline and after 4 years to 498 consecutive patients, 249 non-insulin treated (NIT) and 249 insulin treated (IT), aged 40–80 years.

Results At baseline, IT patients were older, had longer disease duration, higher HbA1c and did more glucose monitoring ($p < 0.001$, all) but their depression scores were lower than among NIT ($p = 0.006$), with no differences for anxiety or MMSE. After 4 years, 72 patients were lost to the follow-up, of whom 18 had died. 41 NIT had switched to insulin and increased BMI ($p = 0.004$), blood pressure ($p < 0.001$), retinopathy severity ($p = 0.03$) and microalbuminuria ($p = 0.0045$), but did not change their scores for depression, anxiety or MMSE. The remaining 171 NIT improved fasting glucose ($p = 0.006$), total cholesterol ($p < 0.0001$), triglyceride ($p = 0.0026$) and HbA1c ($p = 0.0006$). Despite increased prevalence of microalbuminuria and retinopathy ($p < 0.0001$, both), depression ($p = 0.04$) and MMSE ($p = 0.0007$) improved. Foot ulcers ($p = 0.03$), retinopathy ($p < 0001$), microalbuminuria ($p = 0.0047$) and hypertension ($p < 0.0001$) increased in the remaining 214 IT patients, in whom depression ($p = 0.0005$) and anxiety ($p < 0.0001$) worsened while MMSE improved slightly ($p = 0.0002$). On multivariate analysis, depression was associated with being a woman and anxiety with diabetes duration and lower schooling, which also affected MMSE scores.

Conclusions Depression was associated with female gender and worsening complications but not modified by diabetes duration or switching to insulin therapy. Diabetes duration and lower schooling may affect anxiety and cognitive impairment.

Keywords Depression · Anxiety · Cognitive function · Type 2 diabetes · Metabolic control

Introduction

Diabetes represents a serious challenge for health authorities and society because of its chronic complications, increasing costs and impaired quality of life. Its worldwide prevalence is projected to rise from 2.8 % in 2000 to 4.4 % in 2030 and the total number of patients to increase from 171 to 366 million [1]. Diabetes is associated with increased risk of physical [2, 3] and psychological [4] complications, both of which impact on mortality [5].

Chronic diseases, including diabetes, cause deep psychological suffering [6]. Diabetes is chronic and disabling, transforms the lives of patients and requires continuous commitment to self-care and management. Hence, both biologic and behavioral factors play a role in the interplay between depression and type 2 diabetes, which appears to be bidirectional. Depression may impair glycemic control through negative effects on self-care behaviors [7], poor

M. Trento (✉) · M. Trevisan · M. Raballo · P. Passera · M. Porta
Laboratory of Clinical Pedagogy, Department of Medical Sciences, University of Turin, Corso AM Dogliotti 14, 10126 Turin, Italy
e-mail: marina.trento@unito.it

L. Charrier · F. Cavallo
Department of Public Health and Pediatrics, University of Turin, Turin, Italy

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adherence to medication and diet regimens, reduced quality of life and increased health-care costs [8]. On the other hand, individuals with depression are at higher risk of developing type 2 diabetes [7]. Anxiety disorders may also be an important co-morbidity of diabetes. They are associated with complications [9], high blood glucose levels [10], reduced quality of life [11] and increased body mass index [12]. Finally, a number of studies report accelerated cognitive decline, independent of common cardiovascular risk factors, in association with poor metabolic control in patients with type 2 diabetes [13].

In a recent review, the authors reported that depression is not only highly prevalent but also highly persistent and recurrent in diabetes, leading to a significant negative impact on both clinical outcomes and quality of life [14].

We reported previously on a cross-sectional study of depression, anxiety and cognitive function in 498 patients with type 2 diabetes (T2D), half of whom were insulin treatment (IT) and half non insulin treatment (NIT), confirming increased prevalence of depression in a population of patients with type 2 diabetes who did not show impaired cognitive function. The lack of correlation with disease duration, metabolic control and complications suggested that depression may not appear/worsen with diabetes or its complications but rather supported suggestions that it might predate both [15].

This study reports on a 4-year follow-up of the same cohort, aimed at investigating the possible correlations between evolving clinical conditions, socio-demographic determinants and levels of depression, anxiety and cognitive impairment.

Research, design and methods

Subject selection

In total, 498 consecutive outpatients with type 2 diabetes, aged 40–80, routinely followed in our diabetes clinic gave their informed consent to participate in the study, which conformed with the Declaration of Helsinki principles. The diabetes clinic is located in a city of about one million inhabitants and collects mostly Caucasian residents from areas that can be reached easily by public transport, suggesting that the sample was representative of the local diabetic population.

Of the patients, 249 were treated by lifestyle intervention alone or with oral agents but non insulin treatment (NIT), whereas 249 insulin-treated (IT) individuals received insulin as part of their glucose-lowering treatment. Exclusion criteria were history of psychiatric illnesses in the patients or their families, presence of cancer, renal replacement therapy or other severe chronic conditions.

After 4 years, in 2010–2011, on the occasion of routine visits, the patients were invited to participate in the follow-up, and were consecutively enrolled as they attended the clinic. When no visits were programmed, the patients were specifically contacted by telephone.

The following variables were collected at baseline and after 4 years: age, sex, schooling, occupation, family status, smoking status, self-monitoring of blood glucose, family history and duration of diabetes. Body weight, glycated hemoglobin (measured by HPLC), fasting blood sugar (glucose oxidase), blood pressure, serum creatinine, total and HDL cholesterol, triglyceride, microalbuminuria/creatininuria ratio were measured and foot and fundus examinations (2-field, 45° digital color photography) were performed in all patients at baseline and after 4 years.

Assessment: questionnaires

Three questionnaires were administered at baseline and after 4 years to evaluate depression, anxiety and cognitive performance. Depression and anxiety were assessed by the relevant Zung self-rating scales [16] and cognitive status by the Mini-Mental State Examination (MMSE) [17]. The Zung scales were translated into Italian and revalidated [18].

The Zung Self-Rating Depression Scale includes 20 items on a scale that rates four common characteristics of depression: the pervasive effect, the physiological equivalents, other disturbances, and psychomotor activities. There are 10 positively worded and 10 negatively worded questions, each scored on a scale of 1–4, and total scores range from 20 to 80. The four possible outcomes are: 20–49 normal range, 50–59 mildly depressed, 60–69 moderately depressed, 70 and above severely depressed.

The Zung Self-Rating Anxiety Scale is also a self-administered 20-item test, each scored on a scale of 1–4. 15 questions are worded toward increasing and 5 toward decreasing anxiety levels. Total scores range from 20 to 80: 20–44 normal range, 45–59 mild to moderate anxiety, 60–74 marked to severe anxiety, 75–80 extreme anxiety.

The MMSE is administered as a semi-structured interview and includes 30 items assessing orientation, attention, immediate and short-term recall, language and the ability to follow simple verbal and written commands. Cognitive performance varies by age and educational level, with an inverse relationship between MMSE scores and age, ranging from a median of 29 for individuals 18–24 years of age, to 25 for those 80 years of age and older. The median MMSE score is 29 for individuals with at least 9 years of schooling, 26 for those with 5–8 years of schooling, and 22 for those with 0–4 years of schooling. If the patients had literacy problems, the questionnaires were completed with the help of a health operator.

Statistical methods

Descriptive data are shown as absolute and/or relative frequencies of the different modalities for categorical data and as mean ± standard deviation (SD) for continuous variables. Chi-square test for categorical variables and t test for independent data for continuous variables were carried out to assess whether significant differences could be demonstrated between IT and NIT groups at baseline.

After 4 years, an analysis of variance (ANOVA) for continuous variables, with Bonferroni correction, and Chi-square test for categorical variables were carried out in order to evaluate differences among NIT and IT groups, and the 41 patients having started insulin therapy during the follow-up.

Differences between values at baseline and after 4 years were tested in these 3 groups by means of t test for dependent data and McNemar test, for continuous and categorical variables, respectively.

The difference between scores for depression, anxiety and MMSE at baseline and after 4 years was assessed by fitting different types of multivariate linear regression models, in order to adjust for the independent effect of clinical and behavioral variables. Finally, we took into account 3 models where, for each variable—depression, anxiety and MMSE—the difference between baseline and final scores represented the dependent variable and clinical or behavioral variables with statistically significant effects were taken as independent variables.

Patients previously treated with antidepressants were excluded from all analyses.

A p value < 0.05 was taken as significant. All analyses were performed with Stata 12.

Results

At baseline, patients on insulin were older (68.96 ± 7.14 vs. 66.20 ± 8.05 years, $p < 0.001$), had longer duration of disease (20.27 ± 8.03 vs. 13.77 ± 7.11 years, $p < 0.001$), greater prevalence of hypertension (86.3 vs. 79.1 %, $p < 0.05$) and practiced more frequent blood glucose self-monitoring (98.8 vs. 77.5 %, $p < 0.001$). They also had lower total cholesterol (179.67 ± 36.03 vs. 193.65 ± 36.2 mg/dl), higher fasting plasma glucose (173.64 ± 67.40 vs. 150.97 ± 39.26 mg/dl), glycated hemoglobin (8.46 ± 1.48 vs. 7.85 ± 1.23), and prevalence of ulcers, retinopathy and microalbuminuria ($p < 0.001$, all). With regard to the questionnaires, IT patients had lower scores for depression than the NIT (37.46 ± 9.32 vs. 39.69 ± 8.33, $p < 0.01$) but were not significantly different for anxiety (36.16 ± 8.30 vs. 35.92 ± 8.72) or MMSE (24.56 ± 3.22 vs. 25.10 ± 3.45). The full results were reported previously [14].

Of the initial 249 NIT patients, 171 were still not on insulin after 4 years. Another 41 had started insulin therapy, 31 were transferred to other clinics and 6 had died. Of the initial 249 IT patients, 214 were still available for the study, 23 were transferred to other clinics and 12 had died. In total, 72 patients were lost to the follow-up, of whom 18 had died.

Table 1 shows that, among the 171 patients who remained non-insulin treated, fasting blood glucose ($p = 0.006$), total cholesterol ($p < 0.0001$), triglyceride ($p = 0.0026$) and HbA1c ($p = 0.0006$) had decreased from baseline. Home monitoring ($p < 0.0001$) and HDL cholesterol increased ($p = 0.0012$) but also did hypertension ($p < 0.0001$), foot ulcers ($p = 0.04$), retinopathy ($p < 0.0001$) and microalbuminuria ($p < 0.0001$), with one incident case of legal blindness and one amputation. However, the mean scores for depression decreased among these patients ($p = 0.0395$) and MMSE improved ($p = 0.0007$), whereas anxiety did not change.

The prevalence of hypertension increased ($p < 0.0001$), together with BMI ($p = 0.004$), retinopathy ($p = 0.03$) and microalbuminuria ($p = 0.0045$), among the 41 patients who had started insulin therapy, but there were no differences in the scores for depression, anxiety and cognitive impairment (Table 1).

Among the 214 IT patients studied 4 years later, the prevalence of hypertension ($p < 0.0001$), ulcers ($p = 0.03$), retinopathy ($p < 0.001$) and microalbuminuria ($p = 0.0047$) had increased, although total cholesterol ($p = 0.024$) and triglyceride ($p = 0.001$) had decreased. Anxiety and depression scores had worsened ($p < 0.0001$ and $p = 0.0005$, respectively) while MMSE improved ($p = 0.0002$).

The 72 patients who dropped out of the study differed from the remaining 426 for lower ownership (82 vs. 92 %, $p = 0.004$) and less use of glucometers (21 % did not practice self-monitoring vs. 10 % of the remainder $p = 0.011$). These 72 patients had greater prevalence of active ulcers (4.2 vs. 0.24 %, $p = 0.002$) and microalbuminuria (43 vs. 21.2 %, $p < 0.001$) but there were no differences with the remaining 426 patients in the scores for depression, anxiety and MMSE. The 18 patients who died were older (74 ± 5.97 vs. 67.3 ± 7.69, $p = 0.0003$), practiced more frequent daily blood glucose monitoring ($p = 0.02$), smoked more (33.3 vs. 10.6 %, $p = 0.02$) and had more microalbuminuria (50 vs. 23 %, $p = 0.03$) than the survivors.

Multivariate analysis (Table 2) showed that women had higher levels of depression ($p < 0.001$) than men with no significant differences for anxiety and cognitive function. People with higher schooling had lower levels of anxiety ($p < 0.03$) and higher scores for cognitive function ($p = 0.046$). The scores for anxiety increased with diabetes duration ($p = 0.011$).

Table 1 Comparisons between t0 and t4

	Insulin treated at baseline (t0) (n = 249)	Insulin treated after 4 years (t4) (n = 214)	Difference t0 vs. t1	Non-insulin treated at baseline (t0) (n = 249)	Non-insulin treated after 4 years (t4) (n = 171)	Difference t0 vs. t4	Non-insulin treated at baseline but insulin treated after 4 years (t0) (n = 41)	Non-insulin treated at baseline but insulin treated after 4 years (t4) (n = 41)	Difference t0 vs. t4
Smoking status (no/yes/former)	124/24/101	104/17/92	NS	139/33/77	87/24/60	NS	23/5/13	22/4/15	NS
Hypertension (yes/no)	215/34	187/22	$p < 0.0001$	197/52	154/15	$p < 0.0001$	12/29	39/2	$p < 0.0001$
Menopause (no/current/over)	0/8/113	0/1/113	$p = 0.0082$	6/7/101	3/4/146	NS	1/2/16	0/2/36	NS
Owning glucose meter (no/yes)	2/247	0/214	NS	43/206	9/159	$p < 0.0001$	2/39	1/40	NS
Self-monitoring blood glucose (no/yes)	3/246	0/214	NS	56/193	11/157	$p < 0.0001$	5/36	2/39	NS
Self-monitoring >1/day (no/yes)	92/157	86/128	NS	231/18	156/12	NS	36/5	30/11	NS
BMI	28.18 ± 4.80	28.91 ± 8.74	NS	28.65 ± 5.42	27.88 ± 4.62	NS	30.89 ± 6.38	31.89 ± 7.38	$p = 0.004$
Total cholesterol (mean ± SD, mg/dl)	179.67 ± 36.03	173.59 ± 39.41	$p = 0.024$	193.65 ± 36.20	176.30 ± 35.69	$p < 0.0001$	191.5 ± 36.78	177.39 ± 35.74	$p = 0.037$
HDL cholesterol (mean ± SD, mg/dl)	49.49 ± 15.82	50.16 ± 18.86	NS	48.14 ± 13.17	50.36 ± 13.98	$p = 0.0012$	45.41 ± 10.97	47.17 ± 10.81	NS
Triglyceride (mean ± SD, mg/dl)	150.40 ± 93.81	133.94 ± 67.76	$p = 0.001$	148.90 ± 91.58	129.73 ± 70.33	$p = 0.0026$	165.46 ± 127.63	160.61 ± 140.69	NS
Fasting blood glucose (mean ± SD, mg/dl)	173.64 ± 67.40	166.43 ± 64.96	NS	150.97 ± 39.26	136.88 ± 32.24	$p = 0.006$	160.51 ± 48.38	161.02 ± 56.60	NS
HbA1c (% of total Hb)	8.46 ± 1.48	8.35 ± 1.39	NS	7.85 ± 1.23	7.31 ± 0.98	$p = 0.0006$	8.62 ± 1.18	8.73 ± 1.32	NS
Foot ulcers (never/previous/active/amputation after 4 years)	221/23/4	181/26/6/0	$p = 0.0313$	246/3/0	153/10/2/1	$p = 0.0396$	41/0/0	37/2/1/0	NS
Retinopathy (no/mild/moderate-severe/blindness after 4 years)	80/62/103	29/70/113/0	$p < 0.0001$	160/48/24	85/56/24/1	$p < 0.0001$	22/9/6	17/10/14/0	$p = 0.0341$
Microalbuminuria (no/yes/dialysis after 4 years)	160/87	97/76/4	$p = 0.0047$	207/28	102/43/1	$p < 0.0001$	33/7	18/18/0	$p = 0.0045$

	Insulin treated at baseline (t0) (n = 227)	Insulin treated after 4 years (t4) (n = 186)	Difference t0 vs. t4	Non-insulin treated at baseline (t0) (n = 232)	Non-insulin treated after 4 years (t4) (n = 156)	Difference t0 vs. t4	Non-insulin treated at baseline but insulin treated after 4 years (t0) (n = 38)	Non-insulin treated at baseline but insulin treated after 4 years (t4) (n = 37)	Difference t0 vs. t4
Depression (mean ± SD)	37.46 ± 9.32	38.48 ± 9.15	$p = 0.0005$	39.69 ± 8.33	37.11 ± 8.10	$p = 0.0395$	40.95 ± 8.95	40.28 ± 9.50	NS
Anxiety (mean ± SD)	36.16 ± 8.30	38.50 ± 9.97	$p < 0.0001$	35.92 ± 8.72	35.22 ± 9.23	NS	37.32 ± 10.71	39.73 ± 10.91	NS
MMSE (mean ± SD)	24.56 ± 3.22	25.35 ± 2.79	$p = 0.0002$	25.10 ± 3.45	26.47 ± 2.08	$p = 0.0007$	24.45 ± 2.91	25.14 ± 2.58	NS

Table 2 Results from multivariate analyses

Depression	t0 (n = 429)	p value t0	Δ (t0–t4) (n = 313)	p value Δ (t0–t4)	Effect[b] on Δ depression (SE) (n = 312)	p value Δ (t0–t4) adjusted
Female[a]	41.79 ± 8.24	<0.001	−0.74 ± 5.55	0.51	–	0.001
Male	35.16 ± 7.75		−0.34 ± 5.18		2.59 (0.75)	
Never smokers[a]	39.38 ± 8.25	0.006	−0.55 ± 5.43	0.14	–	
Former smokers	36.68 ± 9.0		−0.93 ± 5.05		−1.40 (0.73)	0.055
Smokers	36.96 ± 8.36		1.11 ± 5.67		0.88 (0.99)	0.377
Known diabetes duration					−0.058 (0.04)	0.101
Anxiety	**t0 (n = 434)**	**p value**	**Δ (t0–t4) (n = 320)**	**p value Δ (t0–t4)**	**Effect[c] on Δ anxiety (SE) (n = 318)**	**p value Δ (t0–t4) adjusted**
Female[a]	39.55 ± 8.76	<0.001	−1.74 ± 6.77	0.697	–	0.061
Male	32.78 ± 6.67		−1.48 ± 5.14		1.38 (0.73)	
Schooling 0[a]	37.67 ± 9.24	<0.001	−1.84 ± 6.41	0.039	–	
Schooling 1	35.45 ± 7.61		−2.43 ± 5.78		−0.75 (0.81)	0.355
Schooling 2	32.54 ± 6.25		−0.19 ± 4.54		1.79 (0.84)	0.033
Known diabetes duration					−0.102 (0.04)	0.011
MMSE	**t0 (n = 443)**	**p value**	**Δ (t0–t4) (n = 326)**	**p value Δ (t0–t4)**	**Effect[d] on Δ MMSE (SE) (n = 324)**	**p value Δ (t0–t4) adjusted**
Female[a]	24.73 ± 3.17	0.318	−0.90 ± 2.45	0.997	–	0.496
Male	25.01 ± 2.73		−0.90 ± 2.45		0.17 (0.25)	
Schooling 0[a]	24.69 ± 3.11	0.295	−0.59 ± 2.58	0.035	–	
Schooling 1	24.88 ± 3.13		−1.44 ± 2.57		−0.74 (0.29)	0.010
Schooling 2	25.24 ± 2.29		−0.96 ± 1.97		−0.59 (0.29)	0.046
Known diabetes duration					0.024 (0.01)	0.097

[a] Reference category

[b] Model with Δ (t0–t4) for Zung depression score as dependent variable and Zung depression score at baseline, gender, smoking status and known diabetes duration as independent variables

[c] Model with Δ (t0–t4) for Zung anxiety score as dependent variable and Zung anxiety score at baseline, gender, schooling (0 = no formal schooling/primary education; 1 = middle school; 2 = high school/university education) and known diabetes duration as independent variables

[d] Model with Δ (t0–t4) for MMSE score as dependent variable and MMSE score at baseline, gender, schooling (0 = no formal schooling/primary education; 1 = middle school; 2 = high school/university education) and known diabetes duration as independent variables

Discussion

This study confirms that type 2 diabetes is a chronic, progressively disabling condition [19], with microvascular complications either appearing or worsening over the 4 years of follow-up. Increasing blood pressure was associated with diabetic retinopathy, as highlighted in other studies [20], and nearly half the patients developed microalbuminuria. In particular, people who dropped out of the study had higher prevalence of active ulcers and microalbuminuria and those who died, though performing more frequent self-monitoring, had established cardiovascular risk factors as they were older, smoked more, and had more microalbuminuria.

In a previous cross-sectional study of these 498 patients [15], we could confirm more prevalent depression and anxiety, though not in association with longer duration of

diabetes and/or insulin treatment, suggesting that these psychopathological dimensions may not worsen with the natural history of diabetes but rather be independent personality traits. Indeed, as suggested by Lustman [21] depression might be a risk factor for diabetes, rather than the opposite. In addition, despite the numbers investigated, we could not detect differences in cognitive function in relation to duration of diabetes, type of glucose-lowering treatment or the presence of complications. A limit for drawing firm conclusions from those data, however, derived from the cross-sectional nature of the survey. Consequently, a 4-year follow-up was conducted on the initial cohort to verify if any changes would occur with time, progression of disease and onset of complications. The results of this second observation suggest that, despite clinical worsening of type 2 diabetes with progression of complications and the necessity to start insulin therapy in part of the patients, only

anxiety increased with diabetes duration, while depression and anxiety worsened only in those already on insulin who developed more severe complications. We could not confirm worsening in cognitive function in any of the subgroups studied and found that the only determinant affecting MMSE scores was lower schooling.

Other studies reported worsening of depression and cognitive function with duration of diabetes and appearance of complications. Differences in sample size and methods used to assess these psychopathological dimensions may account for the discrepancies with our findings. Though not the largest in terms of population or length of follow-up, this is the only study in which depression, anxiety and cognitive function are assessed together in the same patients.

This 4-year observation also supports the results of our multivariate analysis at baseline, showing higher depression among women and worse scores for anxiety and cognitive function among individuals with lower schooling, indicating that being a woman with lower levels of education may be a stronger determinant of depression and anxiety than having type 2 diabetes. During the MMSE interviews the patients described their efforts to manage their disease. Women in particular had many concerns related to diabetes management in everyday life and their existential fragility emerged strongly. Marmot et al. [22] showed recently that special attention should be devoted in the European region to older women who, due to a longer and different life course, develop more health problems and are at greater risk of poverty. Chronic rather than acute morbidity is the most consistent explanatory factor for health and disability differences between men and women [22].

While our data do not support an association between depression, anxiety, cognitive impairment and hyperglycemia in diabetes, intervention studies are required to determine if their successful treatment improves glycaemic control. The finding that male gender and higher education correlate with significantly lower levels of anxiety supports the necessity to help women overcome the obstacles of social disadvantage and illiteracy, which can turn into psychological problems [23]. We suggest that, while men might benefit from knowledge-based diabetes management giving them more informational and instrumental support, female patients could benefit from individualized diabetes care offering social support.

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