REVIEW ARTICLE

Depression in diabetes mellitus: a comprehensive review

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Abstract

Although the prevalence of a mental disorder, in general, in patients with diabetes mellitus is regarded to be comparable to the general population, an increased prevalence of depressive disorders, often comorbid with anxiety, has been reported in patients with diabetes mellitus.

The co-occurrence of depression in diabetes is attributed to a variety of factors, including the psychological and psychosocial impact of the disease, a potential common genetic susceptibility and common pathophysiological abnormalities involving neuroimmunological and neuroendocrinical pathways, as well as microvascular brain lesions due to diabetes mellitus. However, issues concerning pathogenesis and causality of this high co-occurrence are not fully determined yet. Still, the presence of depression in patients with diabetes mellitus is of vast importance, as it is usually associated with poor disease control, adverse health outcomes and quality of life impairment.

This article aims to provide a comprehensive review of epidemiological findings, clinical considerations and management strategies concerning depression in patients with diabetes mellitus. Hippokratia 2012; 16 (3): 205-214

Keywords: Diabetes mellitus; depression; epidemiology; glycemic control; complications; mortality; quality of life; treatment

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Mental disorders, in general, in patients with diabetes mellitus (DM)

Patients with DM seem not to be at higher risk for a mental disorder in general compared to non-diabetic individuals.

In a cross-sectional population-based study by Kruse et al[1] among 141 patients with DM, identified out of a community sample of 4169 individuals, the prevalence of any mental disorder - assessed with the Composite International Diagnostic Interview (CIDI) - was comparable between the patients with DM and the non-diabetic individuals [26.6% vs 26.0%; Odds Ratio(OR)=1.11; Confidence Interval (CI):0.73-1.69]. Notably, after adjusting for age, sex, socioeconomic and family status, no significant difference between the two groups was found, concerning affective, somatoform, substance abuse/dependence disorders; only anxiety disorders were found to be significantly more prevalent in the diabetic group (OR=2.05; CI:1.22-3.43).

Das-Munshi et al[2] in another cross-sectional population-based study of 249 patients with diabetes, identified out of a sample of 8580 individuals, reported that the prevalence of any mental disorder - assessed with the Clinical Interview Schedule-Revised (CIS-R) - was 21.6% in the diabetic group vs 16.3% in the non-diabetic group. The crude (unadjusted) odds ratio was non-significant (OR=1.4; CI:1.0-2.0), whereas after adjusting for age, sex and socioeconomical status it became significant (OR=1.5;1.1-2.2; $p<0.05$). Finally, after adjusting further for impairment in everyday functioning and medical comorbidity, the odds ratio was attenuated again in non-significant levels (OR=1.3; CI:0.9-1.9). The same pattern also apllied to mixed anxiety and depression, whereas the odds ratio concerning depressive, anxiety, comorbid anxiety depressive disorders was not statistically significant throughout all the models applied, adjusting for the confounders mentioned.

Depression

Prevalence and relative risk

The prevalence of major depression in patients with DM is mostly estimated around 12% (ranging from 8-18%), while milder types of depression or elevated depressive symptoms, in general, are reported to be present in 15-35%. (Table I) [1-22].

Compared to non-diabetic controls, patients with DM are reported to be about 1.4-3 times as likely to suffer from comorbid depression[9,10,17], although there have also been some studies - including the two forementioned[1,2]– that failed to find any significicant difference in the prevalence of depression (or affective disorders, in general) between diabetic and non-diabetic individuals. Of note, findings of Pouwer et al[3] suggest that the presence of medical comorbidity might be a significant factor contributing to the increased prevalence of depression in DM, since depression rates in patients with DM but no other comorbidity

Table 1: Prevalences, odds ratios and risks concerning comorbid depression in diabetes.

Single studies (Cross-sectional design, point prevalences)

Reference	DM type	Sample	Depression assessment & definition	Major Depression (MD)	Minor Depression (mD) / Dysthymia
Kruse et al, 2003[1]	Both	141 diabetics vs 4028 non-diabetic	1. CIDS 2. CIDI	10.2% vs 6.2% (refers to the prevalence of an affective disorder in general, including bipolar disorder)	
Pouwer et al, 2003[3]	T2DM	a. 52 T2DM without comorbidity b. 162 T2DM with comorbidity c. 1184 healthy controls	CESD≥16	overall T2DM (a+b) vs c :9.3% vs 8.9%** 7.8% vs 8.9%, OR=0.94 (0.3-2.7) DM without comorbidity vs control: 7.8% vs 8.9%, OR=0.94 (0.3-2.7) DM with comorbidity vs control: 19.8% vs 8.9% OR=2.0 (1.1-3.5)	
Egede et al, 2003[4]	Both	1810 diabetics	CIDI-SF	9.7%	-
Katon et al, 2004[5]	T2DM	4193 T2DM	PHQ-9*	12.0%	8.5%
Engum et al, 2005[6]	T1DM & T2DM	a. 223 T1DM, b. 958 T2DM, c. 59329 non-diabetic	HADS≥8	T1DM vs controls: 15.2% vs 10.7% ;p<0.05 T2DM vs controls: 19.0% vs 10.7%;p<0.001	
Lawrence et al, 2006[7]	Both	2266T1DM, 371 T2DM, 35 unspecified type children & adolescents (10-21yrs)	Major depression: CESD≥24 Minor depression: CESD:16-23	8.6%	14%
Li et al, 2006[8]	Both	18814 diabetics	PHQ-8*	7.5% (unadjusted) - 8.3% (age-adjusted)	7.9% (unadjusted) - 8.3% (age-adjusted)
Das-Munshi et al, 2007[9]	Both	249 diabetics vs 8331 non-diabetic	CIS-R	14.7% vs 11.4%	
Lin et al, 2008[9]	Both	multiethinic study (WHO)	CIDI (Major Depression or Dysthymia)	OR=1.4 (1.2-1.6)	OR=1.3 (1.0-1.7) (NS)
Fischer et al, 2008[1-]	T2DM	506 T2DM vs National Comorbidity Study-Revised (NCS-R) sample	CIDI (Major Depression or Dysthymia) CESD≥16	10.7% vs 6.7% 22.6%	1.6% vs 1.5%
Katon et al, 2008[11]	Both	10704 diabetics (beneficiaries)	ICD-9 registry codes	11.5%	-
Egede et al, 2009[12]	Both	16754 diabetics	Major depression:: PHQ-8 score≥10 Minor depression: PHQ-8 score: 5-9	14.7%	19.8%
Pouwer et al, 2010[13]	T1DM & T2DM	random sample of 772 out of 2055 diabetics	CIDI (MD or Dysthymia) CESD≥16	Overall: 9% ** T1DM: 7.8% ; T2DM: 9.8% Overall: 32.9% ** T1DM: 29.9% ; T2DM: 36.3%	Overall: 2.3% ** T1DM:1.4% ; T2DM: 2.9%
Dirmaier et al, 2010[14]	T2DM	866 T2DM	Depression: DSQ score>7 Subthreshold Depression: DSQ score:5-7	11,8%	20,7%
Trento et al, 2011[15]	T2DM	459 T2DM 232 Non-insulin treated (NIT) & 227 Insulin-treated (IT)	Zung Self-Rating Depression Scale	Overall: 14.1% Non-insulin treated: 14.7%; Insulin-treated:13.7%	

Systematic reviews and meta-analyses

Reference	DM type	Sample	Major Depression (MD)	Minor Depression (mD) / Dysthymia
Gavard et al, 1993[16]	Both	18 studies (7 controlled)	14.6%	26%
Anderson et al, 2001[17]	T1DM & T2DM	42 studies (20 controlled)	11.4% Elevated depressive symptoms: 31% controlled studies: 20,5% vs 11.4% ; OR=2.0 uncontrolled studies: 29.7% T1DM: OR=2.9 (1.6-5.5), T2DM: OR=2.9 (2.3-3.7) Overall: OR =2.0 (1.8-2.2) independent of sex, DM type, sample source, depression assessment method	
Grey et al, 2002[18]	T1DM		20% vs 7% (children: OR=2.0 & adolescents:OR=3.0)	
Barnard et al, 2006[19]	T1DM	4 controlled & 10 uncontrolled studies	12% vs 3.2% (controlled studies) 13.4% (uncontrolled sudies)	
Ali et al, 2006[20]	T2DM	10 controlled studies	17.6% vs 9.8% OR=1.6 (1.2-2)	
Mezuk et al, 2008[21]	T2DM	7 prospective studies	RR=1.15 (1.02-1.30)	
Nouwen et al, 2010[22]	T2DM	11 prospective studies	RR=1.24 (1.09-1.40)	

CIDS:Composite International Diagnostic Screener, CIDI: Composite International Diagnostic Interview, CIS-R:Clinical Interview Schedule-Revised, ICD:International Classification of Diseases

CESD: Center for Epidemiological Studies - Depression, PHQ: Patient Health Questionnaire, HADS:Hospital Anxiety and Depression Scale, DSQ: Depression Screening Questionnaire

NS: Non-significant

* Major Depression: PHQ-9 or PHQ-8 symptoms≥5 with at least 1 core symptom (depressed mood or anhedonia) for ≥7 days in the past 2 weeks

* Minor Depression: PHQ-9 or PHQ-8 symptoms:2-4 with at least 1 core symtom (depressed mood or anhedonia) for ≥7 days in the past 2 weeks

** as calculated by the authors of this article

were found to be comparable to healthy controls. However, these results need to be replicated in larger control studies, since the subgroup of patients with DM but no other comorbidity was relatively small in comparison to the other two groups of the study.

Concerning causality, the association between diabetes and depression seems to be bidirectional, though the direction depression being a risk factor for the development of DM seems to be stronger. The relative risk for developing T2DM in depressed patients (Depression→Diabetes) is reported as high as 1.6[21]. Conversely, concerning the relative risk for developing depression in patients with DM (Diabetes→Depression), two recent meta-analyses of prospective studies have yielded a relative risk around 1.2[21,22].

Estimates of depression prevalence vary widely,

mainly depending upon depression assessment tools (standardized interviews vs self-report questionnaires), depression classification (discriminating major from minor depression or referring to elevated depressive symptoms - indicative of depression - in general, using specific cut-off values in self-report questionnaires), study designs (controlled vs uncontrolled), sample sizes and diabetes type. As for assessment method bias, in particular, depression is found at a rate of about 2-3 times higher when specific cut-offs in self-report questionnaires are applied compared to major depression being assessed with standardized interviews[10,17].

Depressive symptoms seem to be slightly more prevalent in T2DM compared to T1DM (Table 1), though this difference is not regarded to be statistically significant[17]. Further studies, comparing the prevalence of depression in samples including patients with diabetes of either type, also adjusting for potential confounders, such as age, diabetes duration, treatment regimen, glycemic control, diabetic complications and medical comorbidity are needed.

The clinical course of depression in diabetes

Depression in diabetes is persistent and/or recurrent. In longitudinal and follow-up studies the rates of depression persistance or recurrence have been reported to range widely, between 11.6% and 92%, depending on sample sizes, depression diagnosis criteria and depression classification (major depression or elevated depressive symptoms).

Lustman et al[23] followed-up 25 patients who had previously participated in a 8-week depression treatment clinical trial with nortriptyline vs placebo. Persistence or recurrence of depression - assessed with the Diagnostic Interview Schedule (DIS) - was identified in 23 patients (92%), with an average of 4.8 depressive episodes over the 5-year follow-up period. Even after successful initial treatment of depression, recurrence was extremely common (80% of the patients) and rather rapid (58.3% of the patients were relapsed within the first year). However, the percentages reported in that study should be interpreted with caution due to small sample size.

Peyrot[24] conducted a follow-up study among 245 patients with DM, who were assesed three times (baseline, after 1-week psychoeducational intervention, and at 6 months). Elevated depressive symptoms [defined as a Center for Epidemiological Studies Depression (CESD) scale score ≥16] were found in 93 patients (38%) at baseline. A percentage of 34.4% of the initially depressed patients remained depressed at all three time points. Predictors of being persistently depressed were lack of high school education, presence of more than 2 complications and treatment other than insulin.

A randomized controlled trial (RCT) in 164 diabetic patients assigned to collaborative care intervention against 165 diabetic patients assigned to usual care, by Katon et al[25], revealed that depressive symptoms - assessed with Hopkins Symptoms Checklist 90 (SCL-90) - persisted (persistance was defined as <50% decrease in SCL-90 score) in 59.9% of the intervention group compared to 68.3% of the usual care group at the 12-month folow-up.

Fischer et al[10] conducted a longitudinal study among 508 patients with type 2 diabetes assessed three times over 18 months (baseline, 9 months and 18months). Major depression - assessed with CIDI - was present in 14.9% of the patients at baseline and in 19.8% at any point during the study. Diagnosis of major depression persisted at all three assessment points in 11.6% of the patients diagnosed with major depression at baseline. Elevated depressive symptoms - defined as CESD scale score≥16 - were present in 15.5% of the patients at baseline and in 34.4% at any point during the study. Elevated depressive symptoms persisted at all three assessment points in 58.1% of the patients with elevated depressive symptoms at baseline. These findings suggest that persistence of depression over time mainly refers to elevated depressive symptoms rather than major depression itself. Of note, younger age and higher comorbidity were independently associated with persistence of major depression over time, whereas younger age, female gender, lower education, higher comorbidity and higher HBA1c values were independently associated with persistence of elevated depressive symptoms.

Katon et al[26], in a prospective study among among 2759 diabetic patients who were followed-up for 5 years, found that 83% of the patients with major depression – defined as reporting ≥5 symptoms in Patient Health Questionnaire-9 (PHQ-9), including at least one core sympom of depression, such as depressed mood or anedonia - at follow-up had also been depressed at baseline, while 42.4% of them had also a positive history of depression - based on previous ICD-9 registry codes - within a period of 18 months prior to the study.

In conclusion, depression is highly persistant and/or recurrent in DM, even after successful initial treatment. Therefore, patients with a history of a depressive episode ever before should be considered at high risk for relapse, especially under the influence of health-related or psychosocial stressors.

Risk factors for the development of depression in patients with diabetes.

Risk factors associated with the presence of depression in patients with diabetes include female sex, younger age, not having a spouse, poor social support, lower education, low socioeconomic status, poor glycemic control, presence of diabetic complications, presence of medical comorbidity, physical impairment and previous history of depression[4-6,26,27].

Pouwer et al[3], in a controlled community-based study among 216 patients with T2DM, identified from a sample of 3107 individuals (age range 55-85), evaluated the association of various factors with depression - assessed both with CIDI and CESD scale - , using a 4-layer stepwise linear regression procedure, with demographics (model1;

R^2=9.0%), clinical characteristics [eye difficulties, cardiovascular disease (CVD), other chronic medical diseases] and medical comorbidity (model2; R^2change=2.0%), functional limitations (model3; R^2change=3.8%), social support and perceived mastery over the disease (model4; R^2change=8.6%) entered successively into the analysis. In the final model (R^2=23.4%), they identified the following risk factors being independently associated with depression: functional limitations (beta=0.18, p=0.034), instrumental social support (beta=-0.26, p=0.017) and mastery (beta=-0.26, p=0.001). The female sex appeared significantly associated with depression only in the 1st model. An association between depression and being unmarried emerged as significant in the 2nd and 3rd model but ended up as marginally non-significant (p=0.057) again in the final model. Of note, clinical characteristics were not significantly associated with depression in any of the stepwise regression models.

Egede et al[12], in a large-scale cross-sectional study among 16754 patients with DM, examined the differences among the 3 groups in which they divided the sample by depression severity status, according to PHQ-8 questionnaire scores (0-4: no depression, 5-9:minor depression, ≥10: major depression). They identified significant differences among the three groups concerning race (four race groups), sex (females), age (four classes), education (four classes), income (four classes), marital status (married), employment status (employed), insurance (insured), while no significant differences were found concerning health provider and diabetes education. The chi-square analysis performed cannot fully determine the differences found across the subgroups of the variables with more than two classes.

In the prospective study mentioned above by Katon et al[26], the following risk factors for major depression were identified: previous history of depression (OR=1.68 CI:1.15-2.45), significant depressive symptoms at baseline (OR=7.70; CI:4.63-12.81 for PHQ-9 score >5, and OR= 2.24; CI:1.30-3.88 for PHQ-9 score >10), elevated diabetes-related symptoms at baseline (OR=1.13; CI:1.05-1.22) and cardiovascular procedures during the study (OR=1.92; CI:1.10-3.3).

As indicated above, the presence of a history of depression is a significant factor that should be adjusted for, when evaluating risk factors associated with the development of depression in DM.

Another factor that has not been sufficiently taken into account is the use of medication with a potential depressiogenic effect, such as certain antihypertensive agents for instance, that are often prescribed in patients with DM and comorbid hypertension.

The impact of depression in diabetes

The presence of depression in DM has been associated with significant negative impact in self-care, glycemic control, health outcomes and quality of life.

Self-care

According to a meta-analysis of 43 studies by Gonzalez et al[28], depression was significantly negatively associated with adherence to DM treatment regimen, regarding almost all self-care aspects evaluated [diet, medication, exercise, self-monitoring of blood glucose (SMBG), medical appointments attendance and composite self-care measures] except for diabetic foot care. Nevertheless, the latter behavior was assessed only in two studies. The overall effect size was moderate (r=0.21 CI:0.17-0.25) and it was significantly higher in studies evaluating self-care as a continuous rather than a categorical variable. The effect sizes for a certain self-care behavior were as follows: medical appointments keeping: 0.31 (CI:0.29-0.34), composite measures of self-care: 0.29 (CI:0.23-0.34), diet: 0.18 (CI:0.13-0.22), medication: 0.14 (CI:0.09-0.20), exercise: 0.14 (CI:0.10-0.17), SMBG: 0.10 (CI:0.04-0.16), foot care: 0.07 (CI:-0.08-0.21). The researchers also reported that the type of diabetes did not seem to significantly affect the association between depression and non-adherence and that studies among children or adolescents with diabetes reported larger effects than studies among adults.

It is worth mentioning the results of two prospective studies; Gonzalez et al[29] followed-up 128 patients with DM for 9 months. They concluded that, after adjusting for baseline self-care – assessed with Diabetes Self-Care Activities (SDSCA) questionnaire -, patients with higher depressive symptoms – assessed with Harvard Department of Psychiatry/National Depression Screening Day Scale (HANDS) - showed lower adherence to general diet recommendations (beta=-0.17, p=0.007) and specific dietary behaviors such as fruits and vegetables consumption (beta=-0.18, p=0.004) and spacing of carbohydrates (beta=-0.23, p=0.001), less exercise and poorer foot care at follow-up. Concerning SMBG, baseline HANDS score predicted lower SMBG in the initial model, but this association remained no longer significant after adjusting for baseline SMBG. As for medication adherence, each one-point increase in baseline HANDS was associated with a 1.08-fold increase in the odds for non-adherence (OR=1.08, CI:1.01-1.16). Furthermore, increases in HANDS scores over time also predicted poorer adherence concerning diet in general (beta=-0.21, p=0.001), spacing carbohydrates (beta=-0.16, p=0.017) high-fat foods consumption (beta=0.15, p=0.036) and exercise (beta=-0.14, p=0.036).

Katon et al[30] in a prospective study among 4117 patients with diabetes, found that major depression - defined as reporting ≥5 symptoms in PHQ-9 questionnaire, including at least 1 core symptom of depression, such as depressed mood or anedonia - was associated with an increased likelihood of poor adherence to medication concerning control of DM (OR=1.98; CI:1.31-29.8; p<0.001), hypertension (OR=2.06; CI:1.47-2.88; p<0.001) and Low-Density Lipoproteins (LDL (OR=2.43; CI:1.19-4.97; p<0.01).

Glycemic control

Depression has generally been regarded to be associated with poor glycemic control in both types of diabetes, with a small to moderate effect size though, as reported in the only meta-analysis performed so far (Lustman et al)[31] and several other studies, either cross-sectional or longitudinal. However, findings are not consistent across literature, since a significant amount of studies argue against such an association, particularly concerning type 2 diabetes.

The subject will be further presented focusing on each type of DM.

Type 1 Diabetes Mellitus

A significant association between HBA1c and depressive symptoms has been reported in several cross-sectional studies[32,33,34,13]. There are also some studies reporting that depressive symptoms prospectively predicted HBA1c[35,36]. Finally, fewer cross-sectional studies either found a significant correlation in univariate but not multivariate analysis[37] or found no significant association at all[38].

Type 2 Diabetes Mellitus:

Some studies revealed a significantly higher mean HBA1c in the group of depressed vs non-depressed patients in a predominantly T2DM sample[30] and a sample of T2DM[39] patients or that depressive symptoms severity was independently associated with HBA1c, in a predominantly T2DM sample[40]. There are also some prospective studies reporting that mean HBA1c difference over time was higher in depressed patients[41] or that baseline clinical - but not subclinical - depression predicted poor glycemic control (defined as HBA1c≥7,0%) at follow-up independent of baseline HBA1c[14].

On the contrary, several cross-sectional studies either have not found any association[13,33,38,42,43] or found an association only in univariate but not multivariate analysis[44]. In addition, there are also some prospective studies where the association found cross-sectionally failed to be replicated longitudinaly[44] or the association of baseline depression and HBA1c at follow-up remained no longer significant after controlling for baseline HBA1c or diabetes clinical characteristics[45,46].

Conclusively, the association between depression and glycemic control reported in previous research seems less doubtful in the case of T1DM compared to T2DM, where the findings have been contradictory, since a significant part of the literature argues against such an association.

Inconsistencies in research findings on this specific subject could be attributed to various methodological issues. First of all, assessment and classification of depressive symptoms through self-report questionnaires might have lead to overestimation of what is considered as depression thus obscuring its relationship with glycemic control. Another important issue, stressed recently, is that a significant part of what has been previously conceptualized as 'depression', might well reflect general emotional distress, or diabetes-related distress, rather than clinical depression, especially when self-report questionnaires are applied for depression assessment. Diabetes-related distress and depression though overlapping represent different constructs, with probably different impact on glycemic control and responsiveness to different treatment strategies[47,48]. Treating depression either as a continuous variable (scores in depression self-report questionnaires) or a categorical one (based either on standardized interviews' categorical diagnosis, or on established cut-offs in self-report questionnaires) could be another issue. Apart from depression, treating HBA1c also as a categorical variable might as well account for inconsistencies, since the cut-off value applied in order to discriminate between poor and good glycemic control varies across studies. Finally, antidepressant medication represents a factor of great significance that should be taken into account when evaluating the effects of depression on glycemic control, on the grounds that antidepressants have been associated with an increased risk for developing diabetes and a negative impact on glycemic control - depending on the type of the antidepressant, the dosage and the duration of the treatment[49] - not necessarily through weight gain. Moreover, antidepressant effects on glycemic control have also been reported to depend upon the type of antidepressant, as will be discussed below. Thus, in order to investigate the association between depression and glycemic control, antidepressant medication is a factor that should be controlled for.

Regarding the investigation of the mechanisms implicated in the association between depression and glycemic control, adherence to self-care is regarded as a potential mediator[34,50], though it cannot fully account for it. The latter implicates that depression might also have a direct negative effect on glycemic control, probably via psychoneuroimmunological and psychoneuroendocrinological pathways.

Diabetes-related symptoms

Diabetes-related symptoms are often amplified and more frequently reported in patients with comorbid depression. Ciechanowski et al[33] found that depression - assessed with SCL-90R - as well as higher levels of diabetic complications were independently associated with the amount of diabetes-related symptoms reported (in Self-Completion Patient Outcome instrument) for both T1DM and T2DM.

Ludman et al[51] in a study among 4168 patients with DM, found that the amount of diabetes symptoms reported - assessed with Self-Completion Patient Outcome instrument - was significantly higher (mean=4.40) in patients with major depression - defined as reporting ≥5 symptoms in PHQ-9 scale, including at least one core symptom of depression, such as depressed mood or anedonia - compared to patients without depression (mean=2.46; $p<0.001$).

McKellar et al[50], in a study among 307 patients with T2DM followed-up over 1 year, found that baseline de-

pressive symptoms - assessed with CESD and the Mental Health Subscale of Mental Outcome Studies 36-short form (MOS-36-SF) - predicted the diabetes-related symptoms (categorized as hyperglycemic, hypoglycemic and microvascular) change over the follow-up period. However, when self-care adherence was entered in the structural equation model applied, the relationship between depressive and diabetes-related symptoms remained no longer significant, indicating that the negative impact of depressive symptoms on diabetes-related symptoms is indirect, probably mediated by the negative impact of depression on diabetes self-care.

Diabetic complications

A significant association between depression and diabetic complications has been identified. According to a meta-analysis by De Groot et al[52], the effect sizes for each complication were as follows: 0.17 for retinopathy, 0.20 for macrovascular complications, 0.25 for nephropathy, 0.28 for neuropathy and 0.32 for sexual dysfunction. The overall effect size was small to moderate (r=0.25), comparable between the two types of diabetes.

The majority of studies on the association between depression and diabetic complications have been cross-sectional, thus making causality difficult to infer. However, prospective studies have shown that depression is associated with a higher and more rapid incidence of diabetic complications (Table 2)[40,53-57]. The association between depression and diabetic complications seems to be bidirectional, since depression might result - probably with poor glycemic control as a mediator - in advanced course of complications on one hand, while, on the other hand, complications might also have a negative impact on patients' physical and mental health and quality of life, thus fostering the development of depression.

Cognitive impairment

People with diabetes have been reported to be at 60% greater risk of developing dementia (OR=1.6; CI:1.4-1.8) according to a systematic review of prospective studies by Cukierman et al (2005)[58].

Studies evaluating the impact of depression on cognitive impairment in patients with DM have produced mixed results.

Bruce et al[59] assessed the longitudinal predictors of dementia in a study among 302 patients with DM. Dementia at follow-up was not significantly associated neither with depression at follow-up (cross-sectionally) nor with depression at baseline (longitudinally).

Katon et al[60], in a prospective cohort study of 3837 primary care patients with DM, evaluated the impact of depression on the risk for developing dementia over a 5-year follow-up period. They found a significantly increased incidence rate of dementia (21.5 per 1000 person-years) in patients with DM and major depression at baseline compared with patients with DM but no depression at baseline (incidence rate of 11.8 per 1000 person-years). Thus, comorbid major depression in DM was pro-

Table 2: Depression and diabetic complications risk.

Studies' results:

Complication		History of depression	Major Depression	Minor Depression	Minimal Depression	other predictors in multivariate analysis	Reference
In general	amount of complications		beta=0.20;p<0.05			Treatment intensity (beta=0.38);p<0.05 Self-care behaviors (beta=-0.23;p<0,05 F(9,99)=5,05;p<0,01;R=0,589;R^2=0,34 adj R^2=0,27	Wagner et al, 2009[40]
Microvascular	retinopathy		OR=2.44 (1.01-5.88;p=0.049)			HBA1c [OR=1.29 (1.18-1.41)]	
	proliferative retinopathy		OR=3.19 (1.30-7.87)			HBA1c [OR=1.40 (1.23-1.58)] Diabetes duration [OR=1.12 (1.06-1.19)] Hypertension [OR=5.89 (2.52-13.74)]	Roy et al, 2007[53]
	in general	HR=2.64 (1.73-4.04)	HR=2.43 (1.90-3.14)		HR=3.56 (1.21-2.00)		Black et al, 2003[54]
	in general		HR=1.36 (1.05-1.76)	Non-Significant			Lin et al, 2010[55]
	peripheral vascular disease		Non-Significant	-			Clouse et al, 2003[56]
	amputations (in general)		HR=1.12 (1.02-1.22)				
	amputations (lower)		Non-Significant				Williams et al, 2011[57]
	amputations (higher)		HR=1.33 (1.15-1.55)				
Macrovascular	CVD / Stroke	HR=11.32 (8.76-15.43)	HR=8.63 (5.40-13.79)		HR=2.40 (1.71-3.36)		Black et al, 2003[54]
	CVD / Stroke		HR=1.25 (1.0-1.54)	Non-Significant			Lin et al, 2010[55]
	CVD		HRage-adj=5.2 (1.4-8.9)	-		age [HR=1.11 (1.03-1.20)]	Clouse et al, 2003[56]
	Cerebrovascular		Non-Significant	-			

Studies' design and methodology

Depression assessment	Study type	Sample	Covariates adjusted for	Reference
CESD score	Cross-Sectional	15 T1DM & 108 T2DM	age, sex, diabetes type, BMI, socioeconomic status, primary care provider	Wagner et al, 2009[40]
No depression: CESD=0 Minimal (CESD=1-15) Minor/Major (CESD≥16) CIDI for Depression history	Prospective (7 yrs)	651 T2DM among 2830 individuals	sex, age, education, marrital status	Black et al, 2003[54]
BDI>14 at both baseline & 6-year f-up	Longitudinal (6yrs)	483 T1DM	age, sex marital status, education, socioeconomic status, smoking, diabetes duration, renal disease, hypertension	Roy et al, 2007[53]
DSM-III DIS	Prospective (10 yrs)	76 female diabetics	diabetes duration, BMI , HBa1c , Hypertension , Hypelipidemia , smoking	Clouse et al, 2003[56]
ICD-9	Retrospective cohort (4.1 yrs)	531973 diabetics	demographics, health-care utilization, insulin use, medical comorbidity, mental health conditions, cardiovascular risk factors, microvascular complications, macrovascular complications, foot-specific complications	Williams et al, 2011[57]
Minor Depression: PHQ-9 symptoms:2-4* Major Depression: PHQ-9 symptoms≥5*	Longitudinal cohort (5 yrs)	4623 T2DM	any prior micro- or macro-vascular event, age, sex ,race, education, marital status, diabetes duration, treatment, comorbidity (RxRisk), hypertension, BMI smoking, physical activity HBA1c	Lin et al, 2010[55]

*including ≥1 DSM-IV core depression symptom (depressed mood or anedonia) for ≥7 days in the past 2 weeks

CVD: Cardiovascular disease

spectively associated with an almost 3-fold higher risk of dementia (HR=2.69; CI:1.77-4.07).

Quality of life (QoL)

QoL has been recognized as a domain of major importance in patients with chronic diseases, including DM. Apart from the significance it entails in its own right, it is also regarded as a major outcome that should be taken into account when evaluating the goals and effectiveness of any therapeutic plan concerning DM management, since QoL has been also associated with several adverse health outcomes and increased mortality.

Depression has been associated with a significant impairment in QoL in patients with DM. However, since the majority of the studies conducted have been cross-sectional, no safe conclusion concerning causality can be easily drawn. Still, the relationship seems to be bi-directional.

Schram et al[61] conducted a systematic literature review including 20 studies (18 cross-sectional and 2 longitudinal). They concluded that QoL (both physical and mental) was significantly impaired in diabetic patients with comorbid depression, demonstrating a mild to moderate impairment of QoL in studies that used generic or domain-specific QoL questionnaires and a moderate to severe impairment of QoL in studies that used disease-specific questionnaires. Despite the fact that potential confounders such as demographics or disease- and comorbidity-related factors were assessed in only half of the studies, controlling for confounders did not significantly affect the association between depression and QoL impairment.

Ali et al[62] conducted a systematic literature review as well, including 14 cross-sectional studies, and concluded that depression had a significant negative impact on QoL of patients with DM, even in studies controlling for potential confounders such as diabetes duration, diabetic complications or medical comorbidity. This negative association was independent of the type of measures of QoL applied (generic or disease-specific). Notably, despite the negative association of depression with overall QoL, depression was not consistently associated with every specific domain of QoL across the studies reviewed.

Mortality

Comorbid depression in patients with DM establishes a potentially life-threatening combination[63]. Prospective studies have shown that depression is associated – besides the increased risk for diabetic complications – with increased risk for cardiovascular disease (CVD) and all-cause mortality, even after controlling for potential mediators, such as health-related behaviors. Concerning mortality risk, a 2-3fold higher risk has mainly been reported, with hazard ratios ranging from 1.36 to 4.94 (Table 3)[11,54,64-68].

Treatment of depression in diabetes

Depression in diabetes is still underdiagnosed and undertreated, despite its high prevalence and its association with adverse health outcomes and QoL impairment.

Concerning the interventions strategies for treating depression in patients with DM, they fall into three broad catecories: diabetes self-management education, psychotherapy and pharmacotherapy. These strategies are, of course, not mutually exclusive.

Van der Feltz-Cornellis et al[70] conducted a meta-analysis of 14 RCTs (6 out of 7 studies of pharmacotherapy, 5 studies of psychotherapy, 3 studies of psychotherapy combined with a diabetes self-management intervention and 3 studies of collaborative care intervention) evaluating the efficacy of interventions applied for the treatment of depression in DM. A moderate (-0.512) overall effect size was identified. It was large (-0.581) for psychotherapeutic interventions combined with educational interventions concerning diabetes self-care and moderate (-0.467) for pharmacological interventions. Collaborative care, with the option of initiating with pharmacotherapy or psychotherapy, yielded a small to moderate effect size (-0.292). With regard to glycemic control, the psychotherapeutic interventions often accompanied by self-care educational interventions yielded a moderate to large effect size. On the contrary, pharmacotherapy, except for sertraline (other pharmacological agents evaluated in RCTs included in this meta-analysis were nortriptyline, fluoxetine and paroxetine) and collaborative care had no significant influence upon glycemic control. Van der Feltz-Cornelis et al concluded that psychotherapy combined with self-care educational interventions emerges as the first-line treatment for depression in DM, based on its large effect size on both depression and glycemic control.

Summarizing in redard with antidepressant pharmacotherapy in DM: it is effective for treating depressive symptoms, but its effect on glycemic control might depend on the type of antidepressant. However, the small number of double-blind randomized-controlled clinical trials as well as the small sample sizes and short duration of the trials performed so far, does not allow definite conclusions to be drawn. Another methodolical issue possibly interfering with the inability to provide a significant association between depression and glycemic control might lie into the levels of glycemic control within the studies' samples. Larger sample studies with larger variance of glycemic control allowing to investigate the effect of antidepressant treatment among subgroups of patients with poor, moderate or good glycemic control are needed.

Conclusion

Depression is a matter of great concern in patients with DM. It is not only highly prevalent, but also highly persistent and recurrent leading to a significant negative impact on both clinical outcomes and QoL. Besides, impaired QoL further deteriorates clinical outcomes and has been prospectively associated with increased mortality in DM[71]. Nevertheless, depression stills remain rather underdiagnosed and undertreated. Katon et al[72], in a retrospective population-based study among 4385 patients with DM, identified an inadequate rate of correct depres-

Table 3: Depression and mortality risk.

Risk factor	*Depression assessment*	Mortality: All-cause	Mortality: Cardiovascular disease (CVD) -related	Mortality: Cancer-related	Mortality: neither CVD nor cancer-related	Sample	Study type	Covariates adjusted for	Reference
Depression Only Diabetes only Diabetes & Depression	CESD≥16	HR=2.02 (1.50-2.73) HR=1.91 (1.19-3.06) HR=4.94 (3.30-7.38)	- - -	-	-	651 T2DM among 2830 individuals	Population-based 7-year f-up	demographics, health behaviours, aspirin use and medical comorbidity at baseline	Black et al, 2003[54]
Depression Only Diabetes only Diabetes & Depression	CESD≥16	HR=1.20 (1.03-1.40) HR=1.88 (1.55-2.27) HR=2.5 (2.04-3.08)	[NS] HR=1.29 (0.96-1.74) HR=2.26 (1.60-3.21) HR=2.43 (1.66-3.56)	-	-	715 diabetics among 10025 individuals	Population-based 8-year f-up	demographics, health behaviours, aspirin use and medical comorbidity at baseline	Egede et al, 2005[64]
Diabetes & Depression	General Health Status (GHS) questionnaire	A: HR=1.38 (1.10-1.73) B: NS	A: HR=1.56 (1.11-2.18) B: NS	-	-	1273 T2DM	Community-based 7,8±2,4 -year f-up	A: demographics, diabetes-specific & cardiovascular risk factors B: diabetic complications added	Bruce et al, 2005[65]
Diabetes & Minor Depression Diabetes & Major Depression	Schedules for Clinical Assessment in Neuropsychiatry (SCAN) 2.1	HR=3.23 (1.39-7.51) HR=2.73 (1.38-5.40)	- -	- -	- -	253 diabetics with 1st foot ulcer	Prospective cohort 18-month	age, sex, smoking, marital status, socioeconomic status, mean HBA1c, ulcer severity no change after addition of presence of macrovascular complications or diabetes type in the model	Ismail et al, 2007[66]
Diabetes & Minor Depression Diabetes & Major Depression	PHQ-9 symptoms:2-4* PHQ-9 symptoms≥5*	NS HR=2.26 (1.79-2.85)	NS NS	NS NS	NS HR=1.48 (1.14-1.93)	4184 T2DM	Prospective cohort 5-years	demographics, baseline clinical characteristics (diabetes duration, treatment intensity) and health-related behaviours	Lin et al, 2009[67]
Diabetes & Depression	ICD-9 registry codes, PHQ-2 score≥3, antidepressant medication	HR=1.36 (1.16-1.59)	NS [CVD and Cerebrovascular accident (CVA) combined]	-	-	10704 diabetics (beneficiaries)	Prospective 2-year	age, sex, race/ethnicity, Charlson comorbidity index prior CVA, CVD or CVD procedure, amputation	Katon et al, 2008[11]
Diabetes & Depression	PHQ-9 symptoms≥5*	HR=2.95 (1.23-7.02)	-	-	-	110 diabetics with stage 5 chronic kidney disease	Prospective 5-year	Age, sex, marital status, education, race, baseline CVD, stroke, peripheral vascular disease, retinopathy, neuropathy, smoking, Hba1c, BMI, years on dialysis, sedentary lifestyle.	Young et al, 2010[68]
Diabetes & Depression	Self-reported depression diagnosis, antidepressant medication, Mental Health Index score≤52	HR=2.07 (1.79-2.40)	HR=2.72 (3.09-3.54)	-	-	78282 women aged 54-79	Population-based 6-year f-up	demographics, health-related behaviours and medical comorbidity.	Pan et al, 2011[69]

*including ≥1 depression core symptom (depressed mood or anedonia) for ≥7 days in the past 2 weeks
NS:Non-significant

sion recognition (51%) over a 12-month period prior to the study. Furthermore, only 31% of the patients correctly diagnosed with depression received adequate dosage of antidepressants, while only 6.7% of them received an adequate amount (defined as ≥ 4) of psychotherapy sessions over the 12-month period. Frequency of primary care visits (≥7), alongside with female gender, poor self-rated physical health, panic attacks and dystymia were factors independently associated with increased likelihood for correct depression recognition. A further sensitization of health care professionals, especially in primary care, is imperative, in order to enhance timely detection and treatment of depression in DM. American Diabetes Association recommends that patients with DM, particularly those with poor disease control, should be screened for psychosocial and psychological disturbances or disorders, such as depression[73]. Concerning the management of depression in DM, psychotherapy combined with psychoeducational interventions or collaborative care (psychotherapy or pharmacological treatment combined with psychoeducation and psychosocial interventions) seem to be cost-effective[74] and yield beneficial results, both on mental health outcomes as well as diabetes management and glycemic control[70]. Pharmacotherapy alone is a significant therapeutic option, particularly in contexts where more integrated strategies are not easily applicable, though its effectiveness in treating depression alongside with improving glycemic control seems not to be equivalent. Furthermore, given the disparities among different antidepressants concerning both their effect on glycemic control and their potential side-effects, further research with longer and larger clinical trials and with larger variance of glycemic control among the samples is needed, in order to provide sufficient data on the optimal antidepressant treatment in patients with DM. Still, even in contexts were a highly organized collaborative care can not be applied, the enhancement of patient-doctor relationship providing the patient with the opportunity to verbalize concerns and emotions related to living with diabetes, could be therapeutic.

Conflict of Interest

None.

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