Regular Article

Diabetes in Primary Care: Prospective Associations between Depression, Nonadherence and Glycemic Control

Jörg Dirmaier[a]   Birgit Watzke[a]   Uwe Koch[a]   Holger Schulz[a]   Hendrik Lehnert[b, d]
Lars Pieper[c]   Hans-Ulrich Wittchen[c]

[a]Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg,
[b]First Department of Medicine, University of Lübeck, Lübeck, and [c]Institute of Clinical Psychology and Psychotherapy, Center of Clinical Epidemiology and Longitudinal Studies (CELOS), Technische Universität Dresden, Dresden, Germany; [d]Warwick Medical School, University Hospital of Coventry, Coventry, UK

Abstract
Background: Findings are inconsistent regarding the degree to which depression may exert a negative impact on glycemic control in patients with type 2 diabetes. We therefore aimed to examine the longitudinal relationship between depression, behavioral factors, and glycemic control. ***Methods:*** In a prospective component of a nationally representative sample, 866 patients with type 2 diabetes aged ≥18 years completed a standardized assessment including a laboratory screening, questionnaires, and diagnostic measures. Subsequent to baseline (t_0), patients were tracked over a period of 12 months (t_1). Depression was assessed according to DSM-IV and ICD-10 criteria. Glycemic control was determined by levels of glycosylated hemoglobin (HbA_{1c}); a level of ≥7% was judged as unsatisfactory. Regression analyses were performed to analyze the prospective relationship between depression, medication adherence, diabetes-related health behavior, and HbA_{1c}. ***Results:*** Patients with depression at t_0 revealed increased rates of medication non-adherence (adjusted OR: 2.67; CI: 1.38–5.15) at t_1. Depression (adjusted regression coefficient: β = 0.96; p = 0.001) and subthreshold depression (β = 1.01; p < 0.001) at t_0 also predicted increased problems with diabetes-related health behavior at t_1. Adjusted ORs for poor glycemic control (HbA_{1c} ≥7%) at t_1 were also increased for patients with baseline depression (2.01; CI: 1.10–3.69). However, problems with medication adherence as well as problems with diabetes-related health behavior at t_0 did not predict poor glycemic control at t_1. ***Conclusions:*** In a prospective representative study of patients with type 2 diabetes, baseline depression predicted problems with medication adherence, problems with health-related behaviors, and unsatisfactory glycemic control at follow-up.

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Introduction

There is a two- to three-fold risk of depression in patients with type 2 diabetes, suggesting that depression is strongly related to this disease [1]. Comorbid depression in diabetes was thereby found to be associated with in-

Dr. Jörg Dirmaier
Department of Medical Psychology, Medical Center Hamburg-Eppendorf
Martinistrasse 52, Building S 35
DE–20246 Hamburg (Germany)
Tel. +49 40 42803 9137, Fax +49 40 42803 4940, E-Mail dirmaier@uke.uni-hamburg.de

creased instances and severities of medical complications [2], poorer overall health status [3], more absences from work [4], higher health care costs [5], and increased mortality [6], as opposed to diabetes without depression.

Recent research suggests a bidirectional association between diabetes and depression [7]. However, the biological and behavioral mechanisms of this association remain unclear [8]. In addition to the direct negative physiological effects on glucose metabolism (activation of the neuroendocrine and inflammatory responses [9]) and behavioral risk factors such as obesity-promoting health behaviors (e.g. physical inactivity, hypercaloric diets), depression produces an especially poor adherence to a variety of self-care responsibilities (e.g. medications or modification of health behaviors), which is considered to be related to the state of glycemic control [10].

High glycosylated hemoglobin (HbA_{1c}) is an index of long-term glycemic control and an independent predictor of diabetes. High levels of HbA_{1c} are associated with an increased risk of medical complications, mortality, and poor quality of life in patients with type 2 diabetes [11]. However, previous results regarding the association of depression and HbA_{1c} in patients with type 2 diabetes are inconsistent [12–14], which is surprising in light of the strong association between depression and diabetes. Moreover, in the field of primary care, these studies have been cross-sectional.

Given these inconsistent results and the lack of prospective examinations of the effect of depression on HbA_{1c} and relevant behavioral mechanisms (adherence to medications and health behaviors) linking these associations, we used a nationally representative sample of primary care patients with type 2 diabetes to investigate: (1) the effects of depression on adherence to medical recommendations (concerning medication and health behavior), and (2) the effects of depression and adherence to medical recommendations (concerning medication and health behavior) on HbA_{1c} in primary care patients with type 2 diabetes over a 12-month follow-up period.

Patients and Methods

Sample
Analyses were based on the DETECT (Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment) study, which is a cross-sectional clinical-epidemiological study with a prospective-longitudinal component in primary care in Germany. Data collection was performed between September 2003 and December 2004. A complete description of the study methodology and sampling has been published elsewhere [15].

In brief, the DETECT study used a random subsample of 7,519 patients of the core survey, which consisted of 55,518 unselected consecutive patients (aged ≥18 years) attending 3,188 primary care settings at baseline (t_0). It utilized a standardized assessment, including questionnaires for patients and physicians, and an extensive laboratory screening program with follow-up (t_1) after 12 months. At t_1, data from 6,627 (93.1%) patients were collected, including 866 patients attending 466 different primary care settings who had been diagnosed with type 2 diabetes and had a valid score for depression.

In the later analyses, the data were weighted to adjust for the regional distribution of general practitioners and internists to obtain a representative sample of German primary care patients. The study sample of doctors can therefore be regarded as nationally representative in terms of regional distribution, age, years of experience, specialty orientation, and patient load per day [15]. The longitudinally investigated cohort was additionally adjusted to the morbidity status, age, and gender distribution of the main study. Moreover, there were no noteworthy differences in the characteristics of those patients analyzed only at baseline and the subsample followed up for 1 year [15]. The 866 patients for whom a valid score for depression was available did not differ from the 917 patients diagnosed with type 2 diabetes with regard to sociodemographic or clinical variables. Therefore, the patient sample can also be regarded as representative of primary care settings in Germany [15].

The study was approved by the local ethics committee of the Technical University Dresden (AZ: EK149092003; 16.09.2003).

Assessment of Depression
The Depression Screening Questionnaire (DSQ) developed by Wittchen and Perkonigg [16] is a well-established and frequently used instrument in large-scale studies in primary care [17]. This self-report measure consists of 10 items with a 3-point scale with 0 (never) through 1 (on some days) to 2 (on the majority of days) referring to the preceding 2 weeks. The diagnosis of depression can be made according to the ICD-10 criteria: at least 3 questions must be answered with 'on the majority of days' and the total score must be >7. The DSQ has a high internal consistency (Cronbach's α = 0.83 [18]), and the 1-week test-retest reliability found a κ value of 0.82 [16]. The validity of the diagnosis of major depression is very high compared to the Composite International Diagnostic Interview [19]: κ = 0.89 for DSM-IV and κ = 0.84 for ICD-10 [16]. In order to account for recent findings showing that subthreshold levels of depression also have a negative impact on health outcomes in patients with type 2 diabetes [20], the calculated total scores were grouped into 3 categories: 0–4 points indicated no depression, 5–7 points indicated subthreshold depression, and >7 points indicated depression. The cut-off of ≤4 points was chosen for patients whose depressive symptomatology is not sufficient for the subthreshold category, taking into account 4 'somatic' items that diabetic patients might experience due to resulting physical limitations (psychomotor retardation, sleep disturbance, loss of sexual desire, loss of appetite or weight loss).

Assessment of Adherence
Medication nonadherence was assessed by responses to the question 'How often did you have problems taking your medications as prescribed by the physician?' based on a 4-level response scale (almost never/rarely/often/always) during the last 4 weeks.

Due to skewed data, the values were split into 2 categories: 'nearly never' versus 'rarely/often/always'. Nonadherence with health behavior during the preceding 4 weeks was assessed by 5 items covering the frequency of problems with diet (2 items: healthy diet plans, weight control/reduction), stopping smoking, alcohol consumption, and adequate physical activity, with 4 response possibilities (never/rarely/often/almost daily). The values were added to a total score. Both assessments (adherence to medication/health behaviors) have high face validity as they directly capture observable behavior patterns.

Assessment of Diabetes and HbA_{1c}

Type 2 diabetes was assumed when the diagnosis was rated as 'definite' (vs. 'suspected' or 'no') in the questionnaire answered by the physicians. HbA_{1c} values were used as an indicator of glycemic control. The general goal in the treatment of diabetes is a HbA_{1c} of <7% [21]. Therefore, HbA_{1c} values were classified as ≥7% (unsatisfactory glycemic control) and as <7% (good glycemic control).

Statistical Analysis

χ^2 or t tests were used to test for differences between type 2 diabetes patients with various levels of depression.

Logistic regression was used to analyze the effects of depression on problems with medication adherence and glycemic control. Linear regression models were employed to investigate the influence of depression on problems with health behavior. The odds ratios (ORs) and the regression coefficients (β) were calculated with 95% CI. All models were adjusted for gender, age, marital and employment status, education, physical activity, BMI, smoking, drinking, duration of diabetes, and type of diabetes treatment.

Adjustments were also made to account for the stratified sampling design and the resulting possibility of clustered observations: patients may be clustered in primary care units so that correlations within these units can be assumed. Therefore, we calculated CIs for all regression analyses applying the Huber-White sandwich method [22].

Power calculations (χ^2 test of trend in proportions based on the logistic model) revealed that given a sample size of 866 (α = 0.05, two-sided), an OR of 2 for poor glycemic control is detectable with a power of 91%. For all analyses, the level of significance was set at p < 0.05. We employed the statistical package STATA 9.1.

Results

For the prospective cohort study, the sociodemographic, behavioral, and clinical characteristics of the type 2 diabetes patients with no depression, subthreshold depression, or depression are compared in table 1. A total of 179 patients (20.7%) had subthreshold depression, and 102 (11.7%) of the 866 patients suffered from depression. Compared to patients with no depression, patients with depression as well as patients with subthreshold depression were more frequently women with fewer weekly physical activities. Furthermore, patients with depres-

sion were younger, more likely to be smokers, less likely to drink alcohol, and were more often treated with insulin compared to patients with no depression. Patients with depression were also younger and more likely to be smokers than patients with subthreshold depression.

Association of Depression, Medication Adherence, and Health Behavior at Baseline

At baseline, when adjusting for the covariates listed in table 1, patients with depression exhibited a higher risk (OR = 4.45; CI: 2.52–7.84; p < 0.001) of problems with medication adherence. Unfavorable health behavior was associated with subthreshold depression (β = 0.68; CI: 0.29–1.08) and depression (β = 1.47; CI: 0.96–1.98; R^2 = 0.41) at baseline. Having subthreshold depression was not associated with glycemic control at baseline. However, among those who had depression, the odds of problems with glycemic control at baseline were elevated (OR = 1.71; CI: 1.01–2.90; p < 0.05). There were no associations between glycemic control and having problems with medication adherence or health behavior.

Prediction of Glycemic Control, Medication Adherence, and Health Behavior

The prospective association between depression (t_0) and medication adherence and health behavior at follow-up (t_1) is shown in table 2. Having subthreshold depression (t_0) is not associated with medication adherence problems at t_1. However, among those who had depression, the odds of problems with medication adherence (adjusted for all covariates listed in table 1) are elevated at t_1 (OR = 2.67; CI: 1.38–5.15; p = 0.003). Table 2 also shows the crude and adjusted standardized regression coefficients for the association of depression (t_0) and problems with health behavior (t_1). In the adjusted model, having more problems with health behavior is associated with harboring subthreshold depression (β = 1.01; CI: 0.62–1.40) and depression (β = 0.96; CI: 0.40–1.52; R^2 = 0.30) at baseline.

The association between depression (t_0) and HbA_{1c} at t_1 is also shown in table 2. Having subthreshold depression (t_0) is not associated with glycemic control at t_1. However, among those who were classified as depressed, the adjusted odds of problems with glycemic control are elevated at t_1 (OR = 2.01; CI: 1.10–3.69; p = 0.023). These analyses were also run separately for the association of medication adherence and health behavior (t_0) on glycemic control at t_1. After adjusting for the covariates, there are no significant associations between problems with medication adherence and health behavior (t_0) and prob-

Table 1. Sociodemographic and clinical baseline characteristics of primary care patients by severity of depression (n = 866)

Variables	No depression (n = 585)	Subthreshold depression (n = 179)	Depression (n = 102)
Female gender	266 (45.5)	100 (55.6)[a]	57 (55.9)[a]
Age, years	66.8 ± 9.7	66.8 ± 10.0	63.5 ± 11.9 [b, d]
Years of education	9.2 ± 1.9	9.2 ± 1.7	9.2 ± 1.8
Marital status			
Single	24 (4.2)	10 (5.7)	6 (5.9)
Married	400 (69.6)	110 (62.5)	67 (66.3)
Divorced/widowed	151 (26.3)	56 (31.8)	28 (27.7)
Retired/unemployed/housewife	480 (82.9)	161 (90.4)[a]	90 (89.1) [c, d]
Smoking			
Nonsmoker	463 (87.4)	147 (89.1)	78 (83.0)
Smoker	67 (12.6)	18 (10.9)	16 (17.0) [c]
Amount of drinking			
Less than 2 times a month	267 (48.5)	94 (54.7)	68 (68.7)
Less than 2 times a week	111 (20.1)	37 (21.5)	14 (14.1)
3 or more times a week	137 (31.4)	41 (23.8)	17 (17.2)
BMI	29.4 ± 4.7	30.1 ± 5.1	30.5 ± 5.8
Weekly physical activities <2 h	161 (30.1)	75 (46.3)[c]	41 (47.7)[c]
Duration of diabetes, years	7.6 ± 6.7	8.6 ± 7.7	8.4 ± 7.4 [a]
Diabetes treatment			
None or diet	169 (28.9)	46 (25.6)	29 (28.7)
Oral hypoglycemic	352 (60.2)	104 (57.8)	51 (50.5)
Insulin or insulin + oral hypoglycemic	64 (10.9)	30 (16.7)	21 (20.8)

Data are presented as means ± SD or number of patients with percentages in parentheses.
[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ vs. no depression, [d] $p < 0.01$ vs. subthreshold depression.

Table 2. OR for problems with medication adherence and glycemic control, and standardized regression coefficients (β) for problems with health behavior

	Problems with medication adherence (t_1)				Problems with health behavior (t_1)				Problems with glycemic control[1] (t_1)			
	OR crude	p	OR adjusted[2]	p	β crude	p	β adjusted[2]	p	OR crude	p	OR adjusted[2]	p
No depression (t_0)	ref.		ref.		ref.		ref.		ref.		ref.	
Subthreshold depression (t_0)	1.4 (1.0–2.2)	0.14	1.2 (0.7–2.1)	0.43	1.1 (0.7–1.6)	<0.001	1.0 (0.6–1.4)	<0.001	0.9 (0.6–1.3)	0.65	0.7 (0.4–1.1)	0.17
Depression (t_0)	2.9 (1.7–4.8)	<0.001	2.7 (1.4–5.1)	0.003	1.3 (0.7–1.9)	<0.001	1.0 (0.4–1.5)	0.001	2.1 (1.4–3.2)	<0.001	2.0 (1.1–3.7)	0.02
Problems with medication adherence (t_0)									1.4 (1.0–2.1)	0.07	1.3 (0.9–2.0)	0.21
Problems with health behavior (t_0)									1.0 (1.0–1.1)	0.18	1.0 (0.9–1.1)	0.84

95% CI are given in parentheses.
[1] $HbA_{1c} \geq 7\%$. [2] Adjusted for gender, age, marital and employment status, education, physical activity, BMI, smoking, drinking, duration of diabetes, and type of diabetes treatment.

lems with glycemic control at t_1. The association of medication adherence and health behavior (t_0) on glycemic control at t_1 was additionally tested for the subsample of insulin-treated diabetics. Again, there are no significant associations between problems with medication adherence (OR: 1.31; CI: 0.86–1.98; p = 0.210) and health behavior (OR: 0.99; CI: 0.91–1.08; p = 0.844) at t_0 and problems with glycemic control at t_1.

Discussion

As depressive symptoms occur frequently in patients with type 2 diabetes, it is important to understand how depression affects the treatment of diabetes. Therefore, we analyzed a large sample to assess prospective associations between depression, adherence, and glycemic control in patients with type 2 diabetes.

This study showed that depression, but not subthreshold depression, is prospectively associated with higher HbA_{1c} levels over a 12-month follow-up. To our knowledge, this is the first study using a nationally representative cohort of adults in primary health care systems that showed a prospective relationship between depression and glycemic control.

It is still uncertain from current research whether co-existing depression affects glycemic control. Our study found that for patients with type 2 diabetes and co-existing depression at baseline, the odds of $HbA_{1c} \geq 7\%$ versus $HbA_{1c} < 7\%$ at follow-up were doubled, even when various other factors were controlled. This study thus confirmed existing findings from studies using cross-sectional designs indicating that depression is related to glycemic control [23]. In accordance with prior research [24], there was no prospective relationship between subthreshold depression and both medication adherence and HbA_{1c} levels. As shown by Fisher et al. [25], subthreshold or non-clinical levels of depression are more strongly correlated with sources of distress resulting from diabetes specifically, such as diabetes-related health care and economic, social, and family difficulties [25], than with clinical depression. This could be a possible reason for the lack of associations between subthreshold depression and HbA_{1c} levels.

Depression at baseline predicts more problems with medication adherence and health behavior at follow-up among patients with type 2 diabetes. According to Cramer [26], medication adherence is defined as 'the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen', whereas medication persistence is defined as 'the duration of time from initiation to discontinuation of therapy'. Our findings regarding adherence to medication and health behavior are consistent with previous cross-sectional research [23, 27]. Additionally, earlier research has shown that even subclinical levels of depression are associated with nonadherence [10], although again only cross-sectionally. Our study thus confirms these findings through a prospective study design, which indicates that even low levels of depressive symptomatology represent a major prognostic risk factor for poor medication adherence and poor health behavior.

Adherence to self-care behavior – like medication intake, dietary guidelines, or exercise – is crucial in the treatment of diabetes and appears to be an important contributor to glycemic control [27]. Inconsistent with these findings, adherence to medication and health behavior at baseline did not predict problems with glycemic control (HbA_{1c} level $\geq 7\%$). This may be a function of different or imprecise methodology for measuring adherence (e.g. single-item measurement of medication adherence), differences in the complexity of self-care regiments, different study designs, and social desirability or recall biases. In addition, our data show that there are low baseline values for medication adherence as well as health behavior, which might result from sample-specific characteristics such as older age and long duration and treatment of diabetes. Being treated for diabetes for several years might have improved medication adherence, and, with older age, the subjective standard for health behavior might decrease. Thus, the variable probably did not provide enough variance in its distribution. It is also possible that adherence and health behavior improved over the course of the year, e.g. due to interventions of the responsible physician. Furthermore, previous research has shown that the strongest associations between adherence and glycemic control exist in insulin-treated diabetic patients [28], and focusing on this subsample may have revealed a stronger relationship. Testing this hypothesis did not show any significant results, however, probably because the proportion of subjects with insulin treatment was comparatively low [23] in our patients.

Several limitations relevant to interpreting the findings have to be mentioned. One limitation was the use of self-report data on medication adherence and health behavior, because of a resulting tendency to overestimate adherence due to recall biases and social desirability. However, a meta-analysis comparing self-report measures with more objective methods such as electronic monitoring showed that self-report measurements have

sufficient validity and reliability [29]. In addition, electronic monitoring is associated with high costs and therefore not appropriate in large-scale studies. Second, measuring medication adherence with a single item represents another limitation of the study. Yet there are some indications that single-item measurement has sufficient predictive value and concordance with scales including multiple items to measure adherence [30]. Third, we did not have any measurements for diabetes-specific self-care, such as self-monitoring of blood glucose, foot care or dietary habits. This was due to the study design, in which data for several chronic diseases were collected, which prevented the use of diabetes-specific instruments. Moreover, there was no data on the course or treatment of depression during the 12-month follow-up period. However, depression has been shown to be persistent in nearly three quarters of diabetic adults at 6-month follow-up [31], which is consistent with our data where depression was persistent over the 12-month follow-up period in half of the patients. Because depression among primary care patients with diabetes is predominantly unrecognized and untreated, the findings probably would be similar even when treatment was accounted for. During a 12-month period, less than half of the patients with depression were recognized, less than half of them received antidepressant descriptions, and only about 7% received adequate psychotherapeutic treatment [32]. By comparison, in our sample merely one third of the depressed patients were recognized as depressed by their physicians, and therefore the rate of depression-related treatment is presumed to be correspondingly low. Measuring depression with the DSQ may have resulted in an overestimation of depressive symptoms because diabetes and other medical comorbidities in primary care frequently involve somatic symptoms that were probably attributed to depression. However, the 11.8% rate of major depression found in this sample is even lower than the overall prevalence of depression in patients with diabetes of 17.6% found in a prior meta-analysis [1]. Nevertheless, cross-validation in diabetic patients with a well-validated screening instrument for depression for the use in primary care settings may additionally be required.

This study has several major strengths. First, the studied sample constituted a large nationally representative cohort of adults in primary health care. Therefore, the generalizability of the results to countries providing similar health care services is very high. Second, its prospective study design enables causal inferences regarding HbA_{1c} levels and depression. Third, the study combined multiple data perspectives resulting in a broad framework; self-reports, data collected from the physician, and the availability of laboratory data HbA_{1c} provided a large number of diabetes-related variables.

In conclusion, the results of this study of adults with type 2 diabetes show that there is a significant prospective relationship between depression and glycemic control, indexed by HbA_{1c}, and that even subthreshold depression is associated to problems with adherence to treatment recommendations over a 12-month follow-up. These data clearly emphasize the importance of depression in the treatment of adults with type 2 diabetes.

Appendix: DETECT Members

Principal investigator: Prof. Dr. H.-U. Wittchen. *Staff members:* Dipl. Psych. L. Pieper, Dipl. Math. J. Klotsche, Dipl. Psych. T. Eichler, Dipl. Psych. Dr. H. Glaesmer, E. Katze, Dipl. Psych. A. Bayer, Dipl. Psych. A. Neumann. *Steering board:* Prof. Dr. H. Lehnert (Lübeck, Coventry), Prof. Dr. G.K. Stalla (München), Prof. Dr. M.A. Zeiher (Frankfurt) Prof. Dr. M. Wehling (Mannheim). *Advisory board:* Prof. Dr. W. März (Graz/Heidelberg), Prof. Dr. S. Silber (München), Prof. Dr. U. Koch (Hamburg), PD Dr. D. Pittrow (München/Dresden).

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