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ARTICLE

Associations between vascular co-morbidities and depression in insulin-naive diabetes patients: the DIAZOB Primary Care Diabetes study

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Abstract
Aims/hypothesis The aim of the study was to determine the prevalence of depression in insulin-naive diabetes patients and to investigate the associations between different forms of vascular co-morbidity and depression.
Methods Cross-sectional data were used from a primary-care sample of 1,269 insulin-naive (i.e. not using insulin therapy) diabetes patients participating in the DIAZOB Primary Care Diabetes study. Demographics, vascular co-morbidities, clinical and lifestyle characteristics, and psychosocial factors were assessed. Depression symptoms were measured with the Edinburgh Depression Scale, with a score >11 defined as depression. The χ^2 and Student's *t* tests were used to compare groups with and without vascular co-morbidities. Rates and odds ratios of depression were calculated for each vascular co-morbidity, with diabetes only as the reference group, correcting for age and sex. Single and multiple logistic regression analyses were performed to test a more comprehensive model regarding the likelihood of depression in diabetes.
Results The prevalence of depression was 11% in the total sample with little difference between the groups with and without any vascular co-morbidity (11.2% vs 10.0%). Single vascular co-morbidities were not associated with increased rates of depression. The final model predicting depression included: having multiple vascular co-morbidities compared with none; having less social support; having experienced a recent stressful life event; female sex; and being a smoker.
Conclusions/interpretation Rates of depression in those with one additional vascular co-morbidity did not differ from patients with diabetes only. Vascular co-morbidities were only associated with higher depression scores in case of multiple co-morbidities.

Keywords Co-morbidity · Depression · Diabetes · Vascular disease

Abbreviations

DIAZOB	Diabetes Care Zuidoost Brabant
EDS	Edinburgh Depression Scale
LADA	Latent autoimmune diabetes in adults
PAD	Peripheral arterial disease

Introduction

Depression is one of the leading contributors to the burden of disease worldwide, and it is an important cause of disability [1]. There is mounting evidence that depression is more common in people with type 2 diabetes [2]. Depression in people with diabetes is associated with a decreased quality of life [3], poor glycaemic control [4], increased healthcare costs [5] adverse health outcomes and a higher mortality risk [6, 7].

The reasons for the increased prevalence of depression in type 2 diabetes are still not fully understood, but the general

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notion is that the burden of having diabetes, and particularly having complications of diabetes, plays an important role in the aetiology of depression in diabetes. For example, a Dutch study showed that the prevalence of depression was particularly high in diabetes patients with co-morbid medical disease(s) (20%), compared with patients with type 2 diabetes only (8%) or no chronic disease at all (9%) [8]. This was confirmed in a meta-analysis in which depression was significantly associated with the presence of several macro- and microvascular diabetes complications [9].

It is important to emphasise that the studies that were included in the meta-analysis of Ali et al. [2], were based on data from relatively small samples of patients with type 2 diabetes. This obviously prevented adequate detection of potential confounding factors in the pooled population. Little research has been performed in patients with type 2 diabetes in which the odds for depression are corrected for potential confounders, particularly those involving the coexistence of vascular diseases [8, 10–15]. The sole large population-based primary-care sample included in the meta-analysis above [2] did provide adjusted and unadjusted rates of depression and corrected for cardiovascular disease, but not for other diabetes related complications [16]. Additionally, Egede et al. (2005) are probably the only authors who identified the contribution of specific chronic conditions to depression [11]. However, the authors did not discriminate between type 1 and type 2 diabetes, nor did they examine the contribution of specific co-morbidities to depression. Finally, none of the previous studies was conducted in insulin-naive (i.e. not using insulin therapy) diabetes patients only. Patients on insulin therapy may have an increased likelihood of depression, as a result of their longer diabetes duration and increased disease severity. Moreover, insulin therapy is generally regarded as more demanding in comparison with oral agents or diet only [17].

Therefore, the main aims of the present study were to determine the prevalence of depression in a large well-defined population of insulin-naive diabetes patients, comparing patients with diabetes only with those with vascular co-morbidity and to determine the associations between different forms of vascular co-morbidity and depression.

Methods

Participants

The data collection for this study was anchored in general practice which is, in the Dutch healthcare system, the main provider of care and the gatekeeper of access to specialist medical care [18]. Accordingly, in the Netherlands 80–85% of diabetes management is sited in general practice, whereas complicated diabetes patients (type 1/type 2) are generally treated in secondary care by an internist [19].

Data were collected between September and December 2005 from a cohort (n=1,770) of patients diagnosed with diabetes in a large ongoing diabetes routine primary-care programme ‘DIAZOB’ (Diabetes Care Zuidoost Brabant) [20]. To assemble this cohort, all patients diagnosed with diabetes registered with 77 general practitioners in the Eindhoven region (n=2,470), the Netherlands, were invited by their diabetes-management-trained nurse practitioner to join this project during their regular diabetes check-up. The intention is to follow this cohort during their lifetime, and to assess biological, demographic, psychosocial, and lifestyle variables periodically at 1 year intervals.

Diabetes was diagnosed and classified according to the WHO guidelines (1999) [21]. These guidelines do not include the measurement of C-peptides or anti-GAD or other antibodies and therefore about 10% of the patients diagnosed with type 2 diabetes may have latent autoimmune diabetes in adults (LADA) [22]. The rates of vascular complications are similar for LADA and type 2 diabetes [23].

For the purpose of this study, only insulin-naive patients were included in the analyses, thereby excluding 117 (7%) patients using insulin. As we were not able to discriminate between type 2 diabetes and LADA we use the term ‘insulin-naive diabetes patients’ instead of ‘insulin-naive type 2 diabetes patients’. After exclusion of responders who gave no informed consent (n=90), and after excluding patients with data missing from their records (n=294), the study sample included 1,269 participants. The study protocol was approved by the ethics committee of the Máxima Medical Centre Veldhoven, the Netherlands, located in the DIAZOB region. All 1,269 participants gave written informed consent.

Assessments Demographic variables (age, sex, marital status and educational level), and lifestyle factors (smoking status and alcohol consumption) were assessed by a nurse-led interview.

Marital status was dichotomised as being single vs being with a partner. Educational level was classified as low education (i.e. primary school, pre-vocational education) vs middle/high education. Smoking status was assessed as current smoker (yes/no) and alcohol consumption was assessed as number of drinks consumed per week.

Vascular co-morbidities Vascular co-morbidities, including coronary heart disease, peripheral arterial disease (PAD), stroke, neuropathic foot, ischaemic foot, retinopathy and nephropathy, were assessed during an interview led by the nurse practitioner, who also checked this information in the medical files of the general practitioner.

Coronary heart disease and stroke were diagnosed in hospital by angiography and ECG, and angiography and

computed tomographic (CT) or magnetic resonance imaging (MRI), respectively.

Peripheral arterial disease, atherosclerosis distal to the aortic bifurcation, was diagnosed by a general practitioner or vascular surgeon using the ankle–arm index. An ankle–arm index of <0.90 indicates peripheral arterial disease, and this can be divided into four stages (1, 2, 2a, 2b, 3 and 4) of increasing severity. Stages 3 and 4 of peripheral arterial disease (systolic ankle pressure <50 mmHg) include ischaemic foot and foot ulcer, which in this study were grouped as 'ischaemic foot' [24]. Ischaemic foot was diagnosed by a podotherapist specialising in diabetes. Neuropathic foot was diagnosed according to the national guideline for the diabetic foot by a specialist podotherapist [25, 26].

Nephropathy was diagnosed according to the national guideline for diabetic nephropathy [27, 28], using the albumin–creatinine ratio and a calculation of the glomerular filtration rate assessed by the Cockcroft–Gault formula [29].

Retinopathy was diagnosed by a specially trained biometrist or an ophthalmologist by means of fundus photography according to the national guideline for diabetic retinopathy [30, 31].

All vascular co-morbidities were recorded using the same definitions by all the healthcare professionals involved.

Finally, the variable 'number of vascular co-morbidities' was obtained by summing the vascular co-morbidities as defined above.

Other clinical characteristics HbA_{1c} and body mass index (kg/m^2) values were collected at the Diagnostic Centre Eindhoven, the Netherlands, a primary-care diagnostic institute responsible for the periodic assessment of biological variables as well as eye and foot examinations in patients with diabetes. HbA_{1c} was measured using the ion-exchange high performance liquid chromatography method.

Both HbA_{1c} and BMI were included in the analyses as continuous variables.

Psychosocial factors Depressive symptoms during the last week were assessed using the Dutch validated version of the Edinburgh Depression Scale (EDS) (Cronbach's alpha 0.84) [32–36], which was originally designed to assess postpartum depression, but which has been validated in other age strata [37–39], and in men [36]. This is a ten-item self-rating scale in which each item is scored on a four-point Likert scale. Total scores range from 0 to 30 points, in which a score higher than 11 points indicates the presence of depression. This cut-off was also used in the present study. In general, up to 50% of participants with scores higher than 11 on the EDS suffer from syndromal major depression [37].

Social support was determined by three items adapted from O'Hara et al. (Cronbach's alpha 0.87), namely: 'There are many people that I can count on', 'There is always someone that I can talk to about my day to day problems', and 'There are plenty of people that I can lean on in case of trouble' [40]. Response categories range from zero to four points, in which a score of zero points indicates 'no social support at all' and a score of four points indicates 'extensive social support'. Social support was measured using the sum of the three items.

Furthermore, respondents were asked if they had experienced a stressful life event (yes/no) in the previous 12 months (e.g. loss of a loved one, a divorce, loss of their job, serious financial problems or physical/mental abuse). The number of stressful life events was summed.

Statistical analyses

Differences in demographic, clinical and lifestyle characteristics between the group with and without co-morbidity were analysed using χ^2 or Fisher's exact test when appropriate for categorical data and the Student's t test for continuous data.

Logistic regression analyses adjusted for sex and age (ORs with 95% confidence intervals) were performed for each vascular co-morbidity separately with depression as the dependent variable. The group with diabetes without vascular co-morbidities was used as a reference group and was compared with the group with a specific vascular co-morbidity (e.g. stroke) with and without co-existing vascular diseases. Finally, to assess the relative importance of potential confounders and risk factors of depression, single and multiple logistic regression (backwards) analyses were performed in the total group by including the following independent variables: age, female sex, being single, low education, quantity of vascular co-morbidities, treatment with oral hypoglycaemic medication, HbA_{1c}, BMI, smoking status, alcohol intake, social support and having experienced a recent stressful life event. In order to deal with possible multiplicity issues, we applied a Bonferroni correction testing at a significance level of α (0.05)/k (number of tests) to lower the chance of a type 1 error.

Prior to these analyses, possible multi-colinearity was examined using the variance inflation factor as a diagnostic factor. However, this was found not to occur. Analyses were conducted using the Statistical Package for the Social Sciences, version 16.

Results

Total sample

The study sample (n=1,269) was predominantly white (98%), with an equal sex distribution. Mean age (±SD) was 66±10 years, and the mean HbA_{1c} level was 6.7%. About

58% had had diabetes for more than 3 years. The prevalence of depression in the total study sample was 11% (men 7%; women 14%; $p<0.001$).

Between-group differences

The characteristics of the study sample are summarised in Table 1. In total, 562 patients (44%) had diabetes without vascular co-morbidity. Of the remaining 707 patients, 431 (61%) had one vascular disease, while 276 (39%) had two or more vascular co-morbidities. The prevalence of macrovascular disease ranged from 7% (stroke) to 22% (PAD and CHD) of the total sample, whereas microvascular disease was diagnosed in 3% (ischaemic foot) to 25% (neuropathic foot) of the total sample. Patients with vascular disease were significantly older, and were more frequently men and single. As can be seen in Table 1, the prevalence of depression did not differ significantly between the group of patients without vascular co-morbidities and those with vascular co-morbidities for the group as a whole (10.0% vs

Table 1 Characteristics of participants without (n=562) and with (n=707) vascular co-morbidity

Characteristic	Diabetes patients	
	Without vascular co-morbidity *n* (%)	With vascular co-morbidity *n* (%)
Demographic features		
White	550 (97.9)	688 (97.3)
Female sex	305 (54.3)	329 (46.5)*
Age (mean, SD)	62.6 (10.1)	68.7 (9.4)[a]
Low education	343 (61.0)	452 (63.9)
Single status	105 (18.7)	186 (26.3)[a]
Clinical characteristics		
Diabetes duration (>3 years)	320 (56.9)	418 (59.1)
Treatment with oral hypoglycaemic medication	444 (79.0)	582 (82.3)
HbA_{1c} (mean, SD)	6.6 (0.8)	6.7 (0.8)
BMI (mean, SD)	29.1 (4.7)	28.8 (4.5)
Psychosocial factors		
Depression score EDS (mean, SD)	5.6 (4.7)	5.8 (4.6)
EDS score >11	56 (10.0)	79 (11.2)
Social support (mean, SD)	7.8 (3.1)	8.1 (2.9)
Recent stressful life event (previous 12 months)	188 (33.5)	243 (34.4)
Lifestyle factors		
Current smoker	93 (16.5)	97 (13.7)*
Alcohol intake (>14 consumptions/week)	40 (7.1)	54 (7.6)
Vascular co-morbidities[b]		
Macrovascular diseases		457 (36.0)
Peripheral arterial disease	–	274 (21.6)
Coronary disease	–	274 (21.6)
Stroke	–	85 (6.7)
Microvascular diseases		422 (33.3)
Neuropathic foot	–	312 (24.6)
Ischaemic foot	–	34 (2.7)
Retinopathy	–	73 (5.8)
Nephropathy	–	48 (3.8)
Number of vascular co-morbidities		
1	–	431 (34.0)
2	–	183 (14.4)
≥3	–	93 (7.3)

[a] Significant after Bonferroni correction ($p<0.0033$) ($\alpha=0.05/15$ tests=0.0033)

[b] Vascular co-morbidities: rates are depicted as proportion of total population (n=1,269)

*$p<0.05$

11.2%, p=0.49), as well as in men (6.2% vs 7.4%, p=0.56) and women (13.1 vs 15.5%, p=0.39) separately (data not shown).

Prevalence of depression per vascular disease

Table 2 shows the rates and the likelihood (adjusted for age and sex) of depression for each vascular disease separately. As 39% of the patients with vascular co-morbidities had multiple vascular co-morbidities, the prevalence and the likelihood of depression are shown for the group with one specific vascular disease only, and the group with this same vascular disease together with one or more co-existing vascular co-morbidities. Except for the group with CHD only (13.3%), and the group with retinopathy only (10.7%), the prevalence of depression tended to be lower in the groups with only one co-existing vascular disease compared with the group having only diabetes. However, apart from the two above-mentioned exceptions, the co-existence of multiple vascular co-morbidities at least doubled the prevalence of depression compared with having only one specific vascular co-morbidity. CHD and neuropathic foot in co-existence with other vascular co-morbidities were significantly associated with depression (p<0.05); however, this significance did not remain after the Bonferroni correction (Table 2).

Multiple logistic regression analyses

The single associations between each independent variable and depression as well as the results of the multiple logistic regression analyses are shown in Table 3. The stepwise backward elimination analyses (OR, 95% confidence interval) show that in the final model (omnibus test of model coefficients: χ^2 107.13, df 14, p<0.001) depression was significantly predicted by having two (OR 2.50) vascular co-morbidities, lower social support (OR 1.29), having experienced a stressful life event in the previous 12 months year (OR 2.24), female sex (OR 2.98), and current smoking (OR 2.31), after Bonferroni correction.

Discussion

In the present study, the prevalence of depression in insulin-naive diabetes patients was 11%, which was lower than the prevalence reported in a previous meta-analysis (17%) and the rates reported in two previous studies in Dutch type 2 diabetes patients [2, 8, 14]. It was even comparable with the prevalence of depression in non-diabetic individuals and type 2 diabetes patients without co-morbidities [2, 8]. Furthermore, results of our study show that the prevalence of depression was not increased in insulin-naive diabetes

Table 2 Rates and odds for participants with a specific vascular disease (with and without co-existing vascular diseases) compared with participants without vascular co-morbidity

	Co-existing vascular diseases	n	Depression (EDS score >11)	
			Prevalence (%)	Adjusted OR (95% CI)[a]
Diabetes only (reference group)	–	562	10.0	1.0
Macrovascular diseases				
Peripheral arterial disease	No	81	6.2	0.61 (0.23–1.57)
	Yes	193	11.9	1.58 (0.90–2.76)
Coronary disease	No	90	13.3	1.72 (0.85–3.52)
	Yes	184	14.7	2.03 (1.18–3.48)[b]
Stroke	No	28	7.1	0.87 (0.20–3.83)
	Yes	57	14.0	2.07 (0.88–4.89)
Microvascular diseases				
Neuropathic foot	No	166	9.6	1.22 (0.65–2.30)
	Yes	146	13.0	1.87 (1.06–3.51)[b]
Ischaemic foot	No	20	5.0	0.70 (0.09–5.47)
	Yes	14	14.3	1.67 (0.35–8.08)
Retinopathy	No	28	10.7	1.02 (0.30–3.53)
	Yes	45	15.6	2.25 (0.90–5.64)
Nephropathy	No	18	5.6	0.58 (0.08–4.57)
	Yes	30	20.0	2.38 (0.89–6.35)

[a] Adjusted for sex and age

[b] Significant odds ratio (p<0.05), but not after Bonferroni correction (p<0.0036) (α=0.05/14 tests=0.0036)

Table 3 Single and multiple logistic regression predicting depression by demographic features, vascular co-morbidity, clinical and lifestyle characteristics, and psychosocial factors in insulin-naive diabetes patients (n=1,269)

Variable	Single logistic regression models (OR, 95% CI)	Multiple logistic regression models (method backwards) (OR, 95% CI)
Demographic features		
Age	0.99 (0.98–1.01)	
Female sex	2.25 (1.54–3.29)[a]	3.29 (2.08–5.18)[a]
Being single	1.48 (0.99–2.20)	
Low education	1.72 (1.13–2.62)*	
Vascular co-morbidities		
0	1.00	1.00
1	0.92 (0.60–1.42)	1.07 (0.64–1.77)
2	1.63 (1.00–2.66)*	2.50 (1.40–4.46)[a]
≥3	1.21 (0.61–2.41)	2.23 (1.01–4.93)*
Clinical and lifestyle factors		
Treatment with oral hypoglycaemic medication	1.11 (0.70–1.76)	
Higher HbA_{1c}	1.03 (0.83–1.28)	
Higher BMI	0.99 (0.95–1.03)	
Current smoker	1.57 (1.00–2.46)*	2.31 (1.37–3.91)[a]
Alcohol intake >14 consumptions/week	0.55 (0.24–1.29)	
Psychosocial factors		
Lower social support	1.26 (1.19–1.35)[a]	1.29 (1.20–1.38)[a]
Recent stressful life event	2.55 (1.78–3.66)[a]	2.24 (1.47–3.40)[a]

[a] Significant odds ratio after Bonferroni correction (p<0.0033; α=0.05/15 tests=0.0033)

*Significant odds ratio (p<0.05)

patients with co-morbidities (even when stratified for sex). Further, more detailed, analyses demonstrated that the presence of multiple vascular co-morbidities approximately doubled the likelihood of depression. However, the association between having three or more comorbidities and depression was not significant after Bonferroni correction (p=0.047), which may due to a lack of statistical power as this group is relatively small.

In line with the findings of previous research [8, 11, 13, 41], the number of vascular co-morbidities was related to higher levels of depression. For example, in one of these studies, the risk of developing depression was increased in patients with three or more vascular co-morbidities [41]. However, in another study, the number of diabetes co-morbidities was associated with major depression in men only, and with minor depression in older patients only [13].

We believe that there are two main explanations for our finding that depression was more common in patients with multiple vascular co-morbidities. First, the burden of having several chronic diseases may have contributed to feelings of depression. Second, there may also be biological mechanisms that have an important role in the pathophysiology of type 2 diabetes and cardiovascular disease, as well as in depression. For example, an ongoing cytokine-induced acute phase response appears to be closely involved in the pathogenesis of type 2 diabetes and associated complications [42]. Considerable evidence has accumulated over the past decade that the atherosclerotic process is regulated by inflammatory mechanisms. Cardiovascular disease is increasingly being viewed as a chronic inflammatory response to injuries of the vascular endothelium [43]. In the field of psychiatry, depressed patients have been found to have higher levels of cytokines, acute phase proteins, chemokines and cellular adhesion molecules [44].

It should be noticed that the current primary care sample consisted of insulin-naive patients with relatively 'uncomplicated' diabetes. As could be expected, the proportion of patients with vascular co-morbidities was still relatively low (56%). In other studies the percentages of patients with co-morbid disease typically ranged from 69% to 75% [8, 11–13].

Except for the number of vascular co-morbidities, no other diabetes-specific factors were associated with depression. This is in contrast with the conclusion of a meta-analysis that elevated HbA_{1c} levels were associated with higher levels of depression [45]. We believe our result may reflect the relatively good glycaemic control in our sample. Similarly, BMI was not associated with depression, which was similar to the result in another study [46] in diabetes patients, but in contrast with the results from two other studies in this patient group [13, 16]. In general, studies of

the relationship between overweight/obesity and depression have shown mixed results. Some have found a positive association, while others have found a negative association between overweight and depression (supporting the 'jolly fat' hypothesis), and some did not find an association at all [47, 48]. In a meta-analysis of this subject, it was therefore concluded that some may suffer psychological distress from being overweight/obese while others may not. More extensive studies are needed to identify factors that protect from or increase vulnerability to psychological distress [47].

Finally, in the current study the low levels of social support and the occurrence of major life events were also strongly associated with depression, which has also been reported in the literature of depression in general.

A major strength of our study is the detailed documentation of the presence specific vascular co-morbidities. Other strengths are the relatively large sample size and the homogeneous character of the sample of insulin-naive diabetes patients.

However, some limitations need to be mentioned. First, the cross-sectional design does not allow for making causal inferences, such as statements on whether co-morbidities preceded depression or vice versa. Second, although the total sample was relatively large, it was difficult to identify the contribution to depression of the individual vascular co-morbidities, as they are often accompanied by other vascular co-morbidities. The lack of significant associations between the individual vascular co-morbidities and depression may therefore be partly explained by the low number of cases with the separate specific vascular co-morbidities within the total sample. Third, depressive symptoms rather than syndromal depression were assessed. For obvious reasons, in large samples, self-rating scales are preferentially used. Fourth, we did not measure anti-GAD antibody, and some of the patients in our sample may have LADA rather than type 2 diabetes. In the UK Prospective Diabetes Study, for example, about 10% of participants with presumed type 2 diabetes had evidence of islet autoimmunity [22]. In the Hoorn study, a large population-based study of diabetes patients aged 50–74 years in Dutch primary care, anti-GAD antibodies were also measured [49]. The patients with known diabetes in the Hoorn study sample are comparable with the participants with diabetes in our DIAZOB study. In the Hoorn study, the prevalence of GAD65-A was 1% in participants with normal glucose tolerance, 2% in those with impaired glucose tolerance, 0% in patients with screen-detected diabetes, and 4% in patients with known diabetes. Moreover, both studies showed that GAD65-A was strongly associated with insulin use in known diabetic individuals [22, 49], with 84–94% of the patients with LADA progressing to insulin therapy within 6 years [22]. Based on these findings we can assume that the proportion of patients with LADA in our study sample of non-insulin-using diabetes patients will be rather low, with about 90–95% of the patients having type 2 diabetes.

Finally, the duration of each vascular co-morbidity was not recorded, which may confound the relationship between the presence of vascular co-morbidities and depressive symptoms.

In conclusion, in the current relatively healthy primary-care sample, rates of depression in insulin-naive diabetes patients with vascular co-morbidities were not higher than in patients without vascular co-morbidities. However, more detailed analyses showed that having multiple vascular co-morbidities, and in particular coronary heart disease or neuropathic foot combined with other vascular diseases, increased the likelihood of depression compared with having diabetes without vascular co-morbidities.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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