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Association between symptoms of depression and glycaemic control may be unstable across gender

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Abstract

Aims Lloyd and colleagues (*Diabetic Med* 2000; **17,** 198–202) have described an association between poor glycaemic control and moderate to severe depression in male but not in female diabetes patients. However, the validity of this study may be limited by its small sample size and the influence of uncontrolled confounders. Therefore, we set out to replicate this study by investigating the associations between depression and glycaemic control in larger samples, while controlling for potential confounders.

Methods Out-patients with diabetes (n = 174) and 1437 patient members of the Dutch Diabetes Association (DDA) completed the Hospital Anxiety and Depression Scale. Demographic and clinical characteristics were obtained using medical records (out-patients) or self-report (DDA).

Results After controlling for number of complications, years of education and body mass index, depression showed significant, low positive correlations with HbA_{1c} in three of the four female samples and in one of the four male samples. Only for out-patients with Type 2 diabetes was the correlation between HbA_{1c} and depression significantly higher for women when compared with men (0.19 vs. 0.04; P = 0.02).

Conclusions The association between depression and HbA_{1c} may be stronger in women with Type 2 diabetes. Oestrogen levels and self-care behaviours may play a mediating role in this association. Further research is required before we can conclude that the association between symptoms of depression and glycaemic control differs across gender.

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Keywords glycaemic control, depression, anxiety, diabetes mellitus

Abbreviations HADS, Hospital Anxiety and Depression Scale; DDA, Dutch Diabetes Association

Introduction

In a fascinating study, Lloyd and colleagues recently described a significant association between depression and poor glycaemic control in men but not in women [1]. To our knowledge this is the first study to show that this association is not stable across gender. If this finding is true, it may have important consequences for clinical practice. Yet, the validity of their finding can be questioned given their small sample size and the fact that confounders such as number of complications, type of diabetes, body mass index (BMI) and years of education [2–4] were not controlled for [1]. We therefore set out to investigate the

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associations between depression and glycaemic control in a larger sample, controlling for potential confounders.

Patients and methods

Our first sample consisted of 174 consecutive diabetes out-patients: 95 subjects were participants in a randomized controlled trial testing the effects of monitoring psychological well-being and treatment satisfaction (response rate 78%). Eighty-nine patients participated in another study (response rate 85%) [5], of which 10 were excluded because they also participated in the randomized controlled trial. The second sample comprised 1472 patient members of the Dutch Diabetes Association (DDA, response rate 49%) who participated in a validation study [6,7]. We used data of 1437 subjects, since sex or type of diabetes were unknown for 35 subjects. The Hospital Anxiety and Depression Scale (HADS) was used to assess depression and anxiety [8]. In the out-patient group, type of diabetes, diabetic complications and glycaemic control were determined from the medical records, and in the DDA group by means of self-report [5–7]. SPSS 9.0 for Windows was used to calculate frequencies; χ^2 tests (for dichotomous variables) and Student's *t*-tests (continuous variables) were used to test the hypothesis that values of men and women did not differ. Partial correlation coefficients were calculated to investigate the linear relationship between HbA_{1c} and depression while controlling for the effects of BMI, years of education and number of complications. An approximate test based on the use of Fishers's Z transformation was utilized to test the hypothesis that the correlations of men and women were similar [9]. Poor glycaemic control was defined as HbA_{1c} > 9.0%, and moderate–high depression or anxiety as a HADS Depression or HADS Anxiety score ≥ 11 [1].

Results

In the out-patient sample, responders did not differ significantly from non-responders regarding HbA_{1c}, sex, age, type of diabetes or history of psychological treatment. In the DDA sample, we had no data about characteristics of non-responders. As can be seen in Table 1, the prevalence of moderate/severe anxiety was approximately twice as high in the out-patient sample when compared with the DDA sample, ranging between 6% (men with Type 1 diabetes, DDA) and 27% (female out-patients with Type 2 diabetes). For depression these percentages ranged between 8% and 13% (out-patients) and between 4% and 10% (DDA), with only minor differences between the female groups of both samples. The DDA sample with Type 2 diabetes appeared to contain lower percentages of men with moderate to high depression scores.

Like Lloyd *et al*. we used χ^2 tests in eight subgroups of men and women with Type 1 or Type 2 diabetes to study associations between the dichotomized variables regarding depression, anxiety and HbA_{1c}. None of the 16 χ^2 tests yielded a significant association. Partial correlations were also calculated, controlling for BMI, years of education and number of complications. These analyses showed that depression and HbA_{1c} were significantly and positively associated in both groups of women with Type 1 diabetes (0.30, 0.11), but not in men with Type 1 diabetes (0.00, 0.05). We also found a significant positive partial correlation of 0.32 for HbA_{1c} and depression in men with Type 2 diabetes in the out-patient sample, but not in the DDA sample (0.04). For women with Type 2 diabetes, the partial correlations were 0.16 (P = 0.20) in the out-patient sample and 0.19 (P = 0.01) in the DDA sample. Two correlations appeared to be significantly higher in women when compared with men: anxiety with HbA_{1c} (–0.12 vs. 0.47, P = 0.003, out-patient sample with Type 1 diabetes) and depression with HbA_{1c} (0.04 vs. 0.19, P = 0.02, DDA sample with Type 2 diabetes). The other correlations were not significantly different between men and women, although the association between depression and HbA_{1c} tended to be stronger for women in the out-patient sample with Type 1 diabetes (0.30 vs. 0.00, P = 0.08).

Discussion

The main aim of the present study was to investigate the association between symptoms of depression and HbA_{1c} across sex and type of diabetes. We found small but consistent positive associations between symptoms of depression and HbA_{1c} in women with diabetes. The positive association between HbA_{1c} and depression was less clear in men with Type 2 diabetes, while partial correlations close to zero were found consistently in men with Type 1 diabetes. However, only in the DDA sample with Type 2 diabetes was the correlation between HbA_{1c} and depression significantly higher for women when compared with men.

Thus, results of our study provide further evidence for the notion that the association between symptoms of depression and HbA_{1c} may differ across gender. Interestingly, while Lloyd *et al*. described a positive association between glycaemic control and depression in men but not in women, we have found the opposite. The findings of Lloyd *et al*. may be biased since they compared the glycaemic control of seven men and two women with moderate/severe depression with that of 58 men and 42 women with mild/no depression, without controlling for confounders such as complications and type of diabetes [1]. Our study also had important limitations: the small size of our out-patient sample, the relatively low response rate in the DDA sample and the fact that clinical characteristics were self-reported (DDA sample). In the present study we did control for BMI, years of education and number of complications, but there are probably other confounding variables that we could not control for. To date, depression has been directly associated with other factors such as physical inactivity, non-compliance with the treatment regimen and changes in food intake; these

Table 1 Demographic/clinical/psychological characteristics, and associations between HbA_{1c} and mood for the group of out-patients and the patient members of the Dutch Diabetes Association (DDA)

	Out-patients with diabetes (n = 174)				Members of the DDA (n = 1437)			
	Type 1 diabetes		Type 2 diabetes		Type 1 diabetes		Type 2 diabetes	
	Men 39	Women 49	Men 45	Women 41	Men 388	Women 349	Men 346	Women 354
Demographic/clinical characteristics								
Mean (SD) age (years)	37 (16)	40 (15)	61 (12)	61 (12)	42 (14)	40 (13)	61 (9)	62 (10)
Mean (SD) HbA_{1c}	8.1 (1.5)	8.0 (1.3)	7.8 (1.1)	7.8 (1.1)	7.7 (1.4)	7.7 (1.5)	7.7 (1.3)	8.0 (1.7)
Mean (SD) duration of diabetes (years)	18 (12)	19 (12)	10 (7)	12 (9)	21 (13)	20 (13)	12 (9)	12 (9)
n (%) retinopathy	14 (37)	15 (33)	13 (30)	11 (27)	100 (26)	95 (27)	78 (23)	88 (25)
n (%) hypertension	10 (27)	5 (11)	25 (57)	28 (70)	48 (12)	40 (12)	95 (28)	127 (36)*
n (%) cardiovascular	2 (5)	5 (11)	16 (36)	13 (32)	23 (6)	20 (6)	55 (16)	50 (14)
n (%) nephropathy	5 (13)	4 (9)	15 (34)	12 (30)	22 (6)	18 (5)	14 (4)	9 (3)
n (%) neuropathy	1 (3)	5 (11)	13 (29)	14 (34)	43 (11)	39 (11)	35 (10)	44 (12)
n (%) with poor glycaemic control†	9 (29)	7 (17)	8 (19)	5 (14)	48 (17)	41 (16)	30 (18)	23 (16)
n (%) using insulin	39 (100)	49 (100)	39 (87)	30 (73)	388 (100)	349 (100)	251 (73)	251 (71)
Psychological characteristics								
n (%) history of treatment by psychologist/psychiatrist	5 (13)	11 (24)	4 (9)	4 (10)	33 (9)	57 (16)***	42 (12)	51 (14)
n (%) moderate/severe anxiety†	6 (15)	9 (18)	5 (11)	11 (27)	22 (6)	31 (9)	24 (5)	46 (13)**
n (%) moderate/severe depression†	5 (13)	4 (8)	4 (9)	5 (12)	11 (3)	15 (6)	19 (4)	36 (10)*
Mean (SD) HADS anxiety	6.7 (3.9)	7.5 (3.5)	6.0 (4.0)	8.0 (4.2)*	4.2 (3.4)	5.3 (3.4)***	4.4 (3.4)	5.8 (3.9)***
Mean (SD) HADS depression	4.5 (4.4)	4.4 (4.0)	3.9 (3.7)	5.3 (4.0)	3.0 (3.1)	3.1 (3.3)	3.8 (3.6)	4.4 (4.1)*
Partial correlations HbA_{1c} with								
HADS anxiety‡	**–0.12**	**0.47*****	0.06	–0.02	0.02	0.07	0.05	0.07
HADS depression‡	0.00	0.30*	0.32*	0.16	0.05	0.11*	**0.04**	**0.19***

†Poor glycaemic control,: HbA_{1c} > 9.0; moderate/severe anxiety or depression, HADS anxiety or HADS depression ⩾ 11.
‡Controlling for BMI, years of education and number of complications.
*$P \leqslant 0.05$; **$P \leqslant 0.01$; and ***$P \leqslant 0.001$.

variables could have indirectly contributed to impaired levels of glycaemic control [10].

Despite these limitations, the results for both samples appeared strikingly similar. Moreover, the strength of the associations we have found between depression and HbA_{1c} are in the same range as those described by others [11,12] for groups consisting of both men and women (0.12 and 0.15, respectively).

In a large sample of patients with Type 2 diabetes we found that the positive association between symptoms of depression and HbA_{1c} was significantly higher in women when compared with men. If it is true that the positive association between depression and HbA_{1c} is different for men and women with Type 2 diabetes, what are the mechanisms which might explain why the relationship is stronger for women than for men? In general, both physiologic and behavioural mechanisms have been hypothesized to underlie the relationship between symptoms of depression and poor glycaemic control in diabetes, that is probably reciprocal. In industrialized countries, major depression occurs twice as frequently in women than in men [13] and seems to be increased at times of changing hormone levels in women [14]. There is now suggestive evidence that oestrogen replacement therapy can alter serotonergic activity and is an appropriate treatment for mild to moderate depression in peri- and post-menopausal women [14,15]. Interestingly, oestrogen replacement therapy in post-menopausal obese women with Type 2 diabetes has been found to be associated with an improvement in glycaemic control [16]. Thus it is reasonable to hypothesize that (changes in) oestrogen levels play a mediating role in the relation between glycaemic control and depression.

From a behavioural perspective, persistent poor glycaemic control may also add to feelings of uncontrollability, a low self-esteem and fatigue. Conversely, since depression often includes symptoms such as pessimism, disturbed memory function, low self-esteem and lack of energy, it is reasonable to assume that adherence to the treatment regimen is adversely affected in diabetes patients with depression [17]. This in turn may well increase levels of HbA_{1c}. Therefore, another possible explanation for a stronger association between HbA_{1c} and depression in female patients with Type 2 diabetes may be for example that symptoms of depression have a more profound negative effect on self-care behaviours in women with

Type 2 diabetes when compared with men with Type 2 diabetes.

Further longitudinal research is needed to clarify the direction of the association between depression and HbA_{1c} in men and women with diabetes, and to test whether our findings regarding the instability of the association across sex can be replicated in other samples.

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