Depression Is Associated With Progression of Diabetic Nephropathy in Type 1 Diabetes

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OBJECTIVE

To investigate the relationship between depression and diabetic nephropathy progression in type 1 diabetes.

RESEARCH DESIGN AND METHODS

Data from 3,730 participants without end-stage renal disease (ESRD) at baseline, participating in the Finnish Diabetic Nephropathy Study, were included. Depression was assessed in three ways. Depression diagnoses were obtained from the Finnish Care Register for Health Care. Antidepressant agent purchase data were obtained from the Drug Prescription Register. Symptoms of depression were assessed using the Beck Depression Inventory (BDI). Based on their urinary albumin excretion rate (AER), participants were classified as those with normal AER, microalbuminuria, and macroalbuminuria. Progression from normal AER to microalbuminuria, macroalbuminuria, or ESRD; from microalbuminuria to macroalbuminuria or ESRD; or from macroalbuminuria to ESRD, during the follow-up period, was investigated.

RESULTS

Over a mean follow-up period of 9.6 years, renal status deteriorated in 18.4% of the participants. Diagnosed depression and antidepressant purchases before baseline were associated with 53% and 32% increased risk of diabetic nephropathy progression, respectively. Diagnosed depression assessed during follow-up remained associated with increased risk of disease progression (32%). BDI-derived symptoms of depression showed no association with the progression, but the total number of antidepressant purchases modestly reduced the risk (hazard ratio 0.989 [95% CI 0.982–0.997]), $P = 0.008$). With the sample divided based on median age, the observations followed those seen in the whole group. However, symptoms of depression additionally predicted progression in those age ≤36.5 years.

CONCLUSIONS

Diagnosed depression and antidepressant purchases are associated with the progression of diabetic nephropathy in type 1 diabetes. Whether successful treatment of depression reduces the risk needs to be determined.

Depression is a common comorbidity in people with type 1 diabetes. The prevalence rates of depressive symptomatology vary based on the methods used (1,2). Trief et al. (3) assessed depression in 6,172 adults with type 1 diabetes using the PHQ-8 (Patient Health Questionnaire), scored in three different ways. Depression prevalence was 5% when the PHQ-8 was scored by algorithm, (i.e., closest to a clinical interview) and 10% when it was scored with a basic cutoff. Pouwer et al. (2) investigated a random sample

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of 772 adults with diabetes from three outpatient diabetes clinics. Depressive affect was measured with the World Health Organization-Five Well-Being Index (WHO-5), the Center for Epidemiologic Studies Depression Scale (CES-D), and a diagnostic interview. Approximately 25–30% of the individuals with type 1 diabetes reported depressive affect (WHO-5). Based on the diagnostic interview, 8% of individuals with type 1 diabetes suffered from a depressive disorder. Finally, in the Finnish Diabetic Nephropathy (FinnDiane) Study, 17% of the individuals with type 1 diabetes were identified to have symptoms of depression (4), while in another study, 5 years after the diagnosis of type 1 diabetes, 8% and 10% were diagnosed with moderate and severe depression, respectively (5).

Mostly investigated in samples of individuals with type 2 diabetes, or in mixed populations of individuals with type 1 or 2 diabetes, diabetes complicated by depression has been associated with less optimal diabetes self-care behaviors (6), reduced quality of life (7), higher number of diabetes-related symptoms as assessed by the Whitty nine-item questionnaire (8,9), higher frequency of self-reported disability or unemployment (10), and increased health care resource utilization and costs (11). Importantly, depression in people with diabetes is also related to worse glycemic control (12), higher number of cardiovascular risk factors (13), higher risk of micro- and macrovascular complications (14), and increased risk of premature mortality (15).

Diabetic nephropathy is the leading cause of renal insufficiency (16) and an independent risk factor for the increased risk of premature mortality seen in individuals with type 1 diabetes (17). In a sample of individuals with mostly type 2 diabetes, higher incidence of major depressive symptoms were associated with an 85% increased risk of incident end-stage renal disease (ESRD) over a 10-year follow-up period (18). Moreover, in a large sample of U.S. veterans with diabetes not otherwise specified, Novak et al. (19) reported that baseline depression increased the odds of developing chronic kidney disease by 20%. Again, prospective studies in people with type 1 diabetes are lacking.

The FinnDiane Study is a large nationwide study established to investigate the potential causes of diabetes complications in type 1 diabetes. Within this realm, we sought to investigate whether diagnosed depression, purchases of antidepressant agents, or a higher score on a questionnaire assessing symptoms of depression is associated with the progression of diabetic nephropathy.

RESEARCH DESIGN AND METHODS

The FinnDiane Study was launched in 1997. Participants are recruited to the study on an ongoing basis at their regular diabetes-related visits to their attending physician. To date, 5 university hospitals, 16 central hospitals, the majority of the regional hospitals, and several primary health care centers all around Finland have participated in the recruitment. Since the start of the study, >5,000 individuals with type 1 diabetes have participated in an initial baseline visit. Following the baseline visit, participants are invited for follow-up visits approximately every 5 years. In the current analyses, data were used from all adults (>18 years old) with type 1 diabetes participating in the FinnDiane Study with a functioning kidney at baseline and at least one assessment of renal status over the follow-up period. Type 1 diabetes was defined as onset of diabetes before the age of 40 years and permanent insulin treatment initiated within 1 year of diagnosis and by ensuring insulin deficiency by C-peptide concentration. The study protocol was approved by the Ethics Committee of Helsinki and Uusimaa Hospital District, and the study was performed in accordance with the ethics standards laid down in the Declaration of Helsinki. Written informed consent was obtained prior to participation.

At the FinnDiane Study visits, participants were thoroughly examined, as previously described (4). Among other assessments, height and weight were measured with participants in light clothing. From these measurements, the BMI (weight in kilograms divided by the square of height in meters) was calculated. Seated blood pressure was measured twice; the first measurement was conducted after a minimum of 10 min rest and the second followed with a 2-min interval. Mean of the two measurements was calculated. Prior to the study visit, participants were instructed either to fast or, if required to treat a low blood glucose level, consume a light breakfast. Blood was drawn, and HbA_{1c} was determined locally using standardized assays. Serum lipid and lipoprotein concentrations were measured centrally at the research laboratory of the Helsinki University Hospital. Serum triglyceride concentrations were measured with a Konelab 60i analyzer (Thermo Fisher Scientific, Waltham, MA), and serum HDL cholesterol concentration was measured with an HTS 7000 Plus Bio Assay Reader (PerkinElmer, Waltham, MA).

Renal status at baseline was assessed based on urinary albumin excretion rate (AER) in at least two of three timed 24-h or overnight urine collections. Accordingly, the participants were classified as having normal AER (AER <20 μg/min or <30 mg/24 h), microalbuminuria (AER ≥20 and <200 μg/min or ≥30 and <300 mg/24 h), macroalbuminuria (AER ≥200 μg/min or ≥300 mg/24 h), or ESRD (undergoing dialysis or having had a kidney transplant). Progression of diabetic nephropathy was defined as any adverse change from the baseline classification (i.e., from baseline normal AER to microalbuminuria, macroalbuminuria, or ESRD; from baseline microalbuminuria to either macroalbuminuria or ESRD; or from baseline macroalbuminuria to ESRD) over the follow-up period. Data on progression were obtained both from the FinnDiane Study follow-up visits and from medical records.

Depression was assessed in three ways. First, data on any depression-related hospital visits (henceforth denoted as diagnosed depression) were obtained from the Finnish Care Register for Health Care. In this register, data on all discharges from Finnish hospitals, including specialized outpatient care, and associated diagnoses and treatment codes are collected. Here, the ICD-9 codes 2961 and 2968 and the ICD-10 codes F32, F33, and F34.1 were used for identification of diagnosed depression. Second, data on the purchases of antidepressant agents were obtained from the Drug Prescription Register (DPR) of the Social Insurance Institute of Finland. Since late 1994, all prescriptions in outpatient care are included in the DPR and the register contains complete information of all prescribed, purchased, and reimbursed medications. From the register, we searched for all drugs in the classes N06A and N06CA (The Anatomical Therapeutic Chemical Classification System

with Defined Daily Doses). However, individuals with purchases of antidepressants that, based on the clinical judgement of the physicians in the FinnDiane Study Group, have been commonly used for the treatment of painful neuropathy (Supplementary Tables 1 and 2) were not considered "depressed." We additionally conducted post hoc analyses considering individuals with purchases of antidepressants commonly used for the treatment of painful neuropathy as depressed if purchases of other neuropathic pain medication (N03AF02, N03AX09, N03AB05, N02AX02, N02AA05, N03AF01, N03AX12, N03AF12, N03AB02) were not evident. Data on antidepressant purchases were used as a dichotomous variable, describing whether any antidepressant agents were purchased, and as continuous variable showing the number of antidepressant agent purchases. Both the depression diagnoses and the antidepressant agent purchases were assessed separately for the time periods before (history of) and after (during follow-up) the FinnDiane Study baseline visit. Finally, depression symptom severity was measured using Beck Depression Inventory (BDI) (20). This self-report questionnaire includes 21 symptom-attitude categories with four to six statements of increasing symptom severity in each. Of the statements, participants selected the one that best described their current situation. The BDI score of each participant was calculated, ranging between 0 and 63 (with higher scores indicating higher depression severity). For assessing symptoms of depression, cutoff point of $\geq$16, scored at any FinnDiane Study visit, was used, as it has previously been shown to exhibit adequate predictive value (21). The BDI was not introduced to the FinnDiane Study protocol until August 2004. Since then, the participants were asked to complete the inventory at every FinnDiane Study visit.

Statistical Analyses

Descriptive statistics are reported as percentages for categorical data and medians (interquartile range) for continuous, nonnormally distributed data. The respective between-group comparisons were done using χ^2 test and Mann-Whitney *U* test. Independent associations between depression variables and progression of diabetic nephropathy were studied with Cox regression analysis. All data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM, Armonk, NY). A two-tailed *P* value $<$0.05 was considered statistically significant.

RESULTS

Study Sample

Data from 3,730 participants were available for the analyses (51% men, median age 37 years [range 18–80]). Over the mean ($\pm$ SD) follow-up time of 9.6 $\pm$ 5.4 years (range 0.1–24.1), the renal status deteriorated in 688 (18.4%) participants (Table 1). Relative to the proportion among nonprogressors, the proportion of men was higher among the progressors. The progressors were also older and had longer diabetes duration but lower age at diabetes onset. Moreover, the progressors exhibited an overall worse clinical profile, including higher HbA_{1c}, total cholesterol concentration, triglyceride concentration, and blood pressure.

Diagnosed Depression

In all, 511 (13.7%) individuals had diagnosed depression either before or after the baseline visit (Supplementary Table 3). More frequently those with diagnosed depression were women, had longer diabetes duration, had lower age at diabetes onset, and had worse glycemic control. The frequency of history of (i.e., prior to the baseline visit) diagnosed depression was comparable between the two groups of diabetic nephropathy progression (Table 2). However, during follow-up (i.e., after the baseline visit), a higher proportion of those with deteriorating kidney status had diagnosed depression (19.0% vs. 9.9%, $P < 0.001$). After adjustment for potential confounders (sex, diabetic nephropathy status at baseline, diabetes duration, age at diabetes onset, systolic blood pressure, HbA_{1c}, triglyceride concentration, and HDL cholesterol concentration), history of diagnosed depression, diagnosed depression during follow-up, and any diagnosed depression predicted renal decline (from 32% to 53%) (Table 3).

Antidepressant Agent Purchases

A total of 798 (21.4%) participants had antidepressant agent purchases either before or after the baseline visit (Supplementary Table 4). More frequently those with antidepressant purchases were women, were older, and had longer diabetes duration. Among the progressors, a significantly higher proportion of individuals had history of antidepressant agent purchases (14.8% vs. 11.6%, $P = 0.024$) and antidepressant purchases during follow-up (29.9% vs. 23.7%, $P = 0.001$) (Table 2). In a multivariable model, history of antidepressant agent purchases (by 32%) predicted the progression of diabetic nephropathy (Table 3). Instead, antidepressant purchases during the follow-up were not related to disease progression. The number of antidepressant agent purchases had a modest negative association with the odds of progression (hazard ratio 0.989 [95% CI 0.982–0.997], $P = 0.008$).

Symptoms of Depression

Altogether, 1,489 participants completed the BDI. Of these individuals, 191 (12.8%) had symptoms of depression judged by BDI score $\geq$16 (Supplementary Table 5). Those with symptoms of depression more frequently were women, had longer diabetes duration, had younger age at diabetes onset, and had worse glycemic control. Progressors and nonprogressors were no different in the BDI-derived symptoms of depression (13.3% and 12.7%, respectively, $P = 0.835$) (Table 2). Moreover, the symptoms of depression did not predict the progression of diabetic nephropathy in a multivariable model (Table 3).

Age-Stratified Results

Due to a large age range of the sample, we repeated the analyses dividing participants into two groups based on the median age. In these analyses, progression of kidney disease was observed in 298 (16.0%) participants age $\leq$36.5 years and 390 (20.9%) age $>$36.5 years (Supplementary Table 6). In both age-groups, the progressors had longer diabetes duration, had lower age at diabetes onset, and had worse glycemic control. Similarly, in both groups, the progressors had higher frequency of diagnosed depression (age $\leq$36.5 years, 22.8% vs. 11.4%, respectively, $P < 0.001$, and $>$36.5 years, 18.7% vs. 12.9%, $P = 0.005$) (Supplementary Table 7). Only in the older group, there was a higher frequency of antidepressant purchases among progressors (29.2% vs. 23.5%, $P = 0.025$). In both age-groups, in the multivariable analyses with diagnosed depression and antidepressant agent purchases, the direction of the associations followed those seen in the analyses with samples combined (Supplementary

Table 1—Basic characteristics of the population divided by progression of diabetic nephropathy

	Nonprogressors, n = 3,042 (81.6%)	Progressors, n = 688 (18.4%)	P
Men	49.2	60.3	<0.001
Age, years	35.9 (27.8–46.0)	38.6 (30.9–46.8)	0.001
Diabetes duration, years	19.5 (10.7–29.3)	24.3 (16.0–32.8)	<0.001
Age at diabetes onset, years	14.7 (9.5–23.5)	12.6 (8.3–19.0)	<0.001
Follow-up time, years	9.7 (5.7–14.3)	7.2 (3.6–12.5)	<0.001
HbA_{1c}, mmol/mol	66 (56–75)	76 (65–88)	<0.001
HbA_{1c}, %	8.2 (7.3–9.0)	9.1 (8.1–10.2)	<0.001
Total cholesterol, mmol/L	4.8 (4.2–5.4)	5.2 (4.5–5.9)	<0.001
HDL cholesterol, mmol/L	1.3 (1.1–1.6)	1.2 (1.0–1.5)	<0.001
Triglycerides, mmol/L	1.0 (0.7–1.3)	1.4 (1.0–2.1)	<0.001
SBP, mmHg	130 (120–140)	138 (125–154)	<0.001
DBP, mmHg	79 (72–85)	82 (76–89)	<0.001
BMI, kg/m^2	24.8 (22.8–26.9)	24.9 (22.5–27.7)	0.156

Data are presented as percentages for frequencies or medians (interquartile range) for continuous, nonnormally distributed data. Nonprogressors, participants with no adverse change in the renal classification over the follow-up; progressors, participants with any adverse change in the renal classification over the follow-up period (i.e., change from baseline normal AER to microalbuminuria, macroalbuminuria, or ESRD; from baseline microalbuminuria to either macroalbuminuria or ESRD; or from baseline macroalbuminuria to ESRD). DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 8). Observations were significant for diagnosed depression (≤36.5 years, during follow-up hazard ratio 1.545 [95% CI 1.148–2.078], $P = 0.004$, and any time 1.508 [1.128–2.017], $P = 0.006$; >36.5 years, history of diagnosed depression 1.775 [1.148–2.743], $P = 0.010$) and number of antidepressant purchases (>36.5 years, 0.987 [0.976–0.997], $P = 0.011$). Additionally, in those ≤36.5 years, symptoms of depression were observed to increase the odds of progression by 226%.

CONCLUSIONS

In the current study, independent of traditional risk factors for diabetic nephropathy, including male sex, diabetes duration, blood pressure, glycemic control, and dyslipidemia, diagnosed depression and use of antidepressant medication were observed to increase the risk of progression of diabetic nephropathy. This risk increment was evident both for depression-related hospital visits, independent of the timing of the visit, and for history of antidepressant agent purchases. In addition, a higher number of antidepressant purchases over time had a small but significant negative association with the progression. Instead, in the multivariable analyses, BDI-derived symptoms of depression and antidepressant purchases during the follow-up period were not associated with the risk of disease progression. As the emergence of diabetes complications is strongly related to

Table 2—Depression in the sample divided by progression of diabetic nephropathy

	Nonprogressors, n = 3,042 (81.6%)	Progressors, n = 688 (18.4%)	P
History of diagnosed depression	4.2	5.2	0.257
Diagnosed depression during follow-up	9.9	19.0	<0.001
Any diagnosed depression	12.2	20.5	<0.001
History of antidepressant purchases	11.6	14.8	0.024
Antidepressant purchases during follow-up	23.7	29.9	0.001
Any antidepressant purchase	20.5	25.3	0.006
Number of any antidepressant purchases			0.034
0	79.5	74.7	
1–24	17.0	21.7	
25–49	2.5	2.8	
≥50	1.0	0.9	
BDI score ≥16 (n = 1,489)	12.7	13.3	0.835

Data are presented as percentages. Between-group comparisons were done with χ^2 test. Nonprogressors, participants with no adverse change in the renal classification over the follow-up; progressors, participants with any adverse change in the renal classification over the follow-up period (i.e., change from baseline normal AER to microalbuminuria, macroalbuminuria, or ESRD; from baseline microalbuminuria to either macroalbuminuria or ESRD; or from baseline macroalbuminuria to ESRD); history of diagnosed depression, depression diagnosed prior to baseline; diagnosed depression during follow-up, depression diagnosed after baseline; any diagnosed depression, depression diagnosed before or after baseline; history of antidepressant purchases, antidepressant purchases prior to baseline; antidepressant purchases during follow-up, antidepressant purchases after baseline; any antidepressant purchase, antidepressant purchases before or after baseline; BDI score ≥16, symptoms of depression judged by the BDI scores.

Table 3—Multivariable associations between depression-related variables and progression of diabetic nephropathy in type 1 diabetes

	Hazard ratio (95% CI)	*P*
History of diagnosed depression, yes	1.527 (1.086–2.146)	0.015
Diagnosed depression during follow-up, yes	1.320 (1.081–1.611)	0.006
Any diagnosed depression, yes	1.315 (1.083–1.597)	0.006
History of antidepressant purchases, yes	1.316 (1.061–1.632)	0.013
Antidepressant purchases during follow-up, yes	0.871 (0.735–1.033)	0.112
Any antidepressant purchase, yes	0.862 (0.721–1.030)	0.102
Number of any antidepressant purchases	0.989 (0.982–0.997)	0.008
BDI score ≥16	0.816 (0.562–1.185)	0.285

Cox regression. Models are adjusted for sex, diabetic nephropathy status at baseline, diabetes duration, age at diabetes onset, systolic blood pressure, HbA_{1c}, triglyceride concentration, and HDL cholesterol concentration. History of diagnosed depression, depression diagnosed prior to baseline; diagnosed depression during follow-up, depression diagnosed after baseline; any diagnosed depression, depression diagnosed before or after baseline; history of antidepressant purchases, antidepressant purchases prior to baseline; antidepressant purchases during follow-up, antidepressant purchases after baseline; any antidepressant purchase, antidepressant purchases before or after baseline; BDI score ≥16, symptoms of depression judged by the BDI scores.

age, we repeated the analyses dividing the sample into two based on median age. In these analyses, the direction of the associations followed those observed in the whole sample for diagnosed depression and antidepressant purchases. However, potentially due to issues related to power, not all observations were significant. Of interest, in the younger cohort, the BDI-derived symptoms of depression also predicted the progression of diabetic kidney disease.

The current observations are in line with a number of previous reports that have shown depression to be associated with an increased risk of chronic kidney disease in diabetes (18,19,22). Similarly, in a recent review and meta-analysis of nine studies involving more than one million participants, depression was associated with an increased risk of incident macrovascular (by 38%) and microvascular (by 33%) diseases (14). In The Pathways Study, a prospective observational investigation for studying the associations of depression with diabetes outcomes, at the end of a median of 8.8-year follow-up, major depressive symptoms were associated with an increased risk of incident ESRD in a sample of 3,886 individuals with diabetes (18). Minor depressive symptoms, instead, exhibited no increased risk (18). In a longitudinal cohort of 4,623 primary care participants with type 2 diabetes, major symptoms of depression were associated with a 36% increased risk of adverse microvascular outcomes over a 5-year follow-up period. In that study, however, no distinction between different complication types was made (23). Finally, in a sample of 340,806 U.S. veterans with either type 1 or type 2 diabetes, depression, defined according to the ICD-9-CM codes for depression or by the use the of antidepressant medication at the study inclusion, was associated with a 20% increased risk of incident chronic kidney disease over the median follow-up of 7.3 years (19). To our knowledge, the current study is the first to show the deleterious longitudinal association of depression with the progression of diabetic nephropathy in a sample exclusively comprised of participants with type 1 diabetes.

The mechanisms connecting depression to less favorable outcomes of diabetes are unclear but may be related to biological and behavioral factors (24). Indeed, a meta-analysis of 47 studies showed that depression is associated with less optimal diabetes self-care behaviors (6). Of the individual self-care practices investigated, a negative association was observed between depression and glucose monitoring, attendance at medical appointments, and adherence to exercise, diet, and medication prescriptions (6). Irregularly adhering to the glucose monitoring may impede with reaching the targeted blood glucose ranges and therefore increase the risk of long-term complications. Moreover, some studies have associated prudent diet and exercise with better glycemic control (25,26). Less optimal self-management may also be an indication of an overall reduced attention to one's health or an inability to manage the complexities of the condition and subsequently contribute to the emergence of diabetes complications. Of importance, we also investigated the role of glycemic control in determining the progression of diabetic nephropathy. While in our analyses HbA_{1c} was associated with progression (data not shown), its inclusion into the model did not change the association between depression and disease progression. In other words, HbA_{1c} did not have a mediating role between depressive symptomatology and progression of renal disease. Therefore, it is likely that other mechanisms also exist linking depressive affect to the increased risk of long-term complications. Depression and vascular complications also share a number of biological phenomena such as reduced heart rate variability, endothelial dysfunction, increased inflammation and platelet function, and hyperactivity of the hypothalamic-pituitary-adrenal axis (22), which could link depression with the long-term complications. The precise mechanisms between depression and complications is, however, beyond the scope of the current study. Currently, it is unclear whether recognition and successful treatment of depression contribute to the prevention of diabetic nephropathy. However, as in addition to the prevention of diabetes complications also the maintenance of good quality of life is stressed as an important goal of diabetes management, annual screening for depression in individuals with diabetes is commonly recommended (27). Of note, despite not improving glycemic control, a number of interventions have been successful in alleviating the symptoms of depression in individuals with diabetes (28–30).

It is not known why different estimates of depression resulted in conflicting results in the current analyses. It may be speculated, however, that of the methods used to approximate depression, the register-based hospital visit variable is likely the most reliable. Importantly, it covers not only inpatient hospitalizations but also outpatient visits at all hospitals in Finland. While, being register-based, it does not miss any such cases, it should be noted that depression is frequently

treated also in other units, such as in primary care and in occupational health care, so a number of cases are also missed. Moreover, not all patients seek treatment for their depression. It is likely, however, that hospitals treat the most severe cases, suggesting that major or severe depression would be associated with increased risk, seen in the current study.

Data on antidepressant purchases were also obtained from a register. Using such purchases as a proxy of depression also has its limitations. Again, not all depression is treated with antidepressants. Moreover, besides depression, antidepressants may also be used to treat other conditions, such as anxiety, obsessive-compulsive disorder, sleeping disorders, migraine, eating disorders, enuresis, and neuropathic pain (31). As neuropathic pain is a common complication in type 1 diabetes, we excluded antidepressants commonly used for this condition from the analyses to better ensure that the antidepressants were used specifically to treat depression. We did, however, repeat the analyses considering individuals with any such antidepressants with no evidence of other medication used for neuropathic pain as depressed. The significance of the results did not change (data not shown). Of interest, history of antidepressant purchases but not purchases done over the follow-up period was associated with higher risk of progression. This could be due to the fact that, compared with the follow-up time, the "history of purchases" covers a longer time period and therefore better represents the depressive mood experienced over the lifetime. Importantly, the progression of diabetic nephropathy may take years to develop. Therefore, it is reasonable to assume, should depression be causal of complications, that the prior history of depression was a stronger determinant of the increased risk compared with the concomitant depression. Surprisingly, the total number of antidepressant purchases exhibited a small but significant negative association with the progression of diabetic nephropathy, suggesting that there was a protective effect. The mechanisms behind this association are not known, but it is possible that, should regular antidepressant usage alleviate the symptoms of depression, their use would thereby help affected individuals to better take care of their diabetes. On the other hand, meticulous management of one's depression could simply be a marker of overall conscientiousness, suggesting that diabetes also would be well managed. Finally, it cannot be ruled out that some compound in the antidepressants could also have renoprotective qualities.

We used BDI to estimate elevated symptoms of depression. Here, in the whole sample, the symptoms of depression were not associated with the disease progression. Instead, when investigated separately, depressive symptomatology predicted the progression of kidney disease in the younger group. While the reasons behind this age difference are not known, it may be speculated that the increased depressive symptomatology earlier in life may more strongly impact the self-care behaviors. It could also be that older individuals with a positive BDI screen may constitute a more heterogeneous group with less severe symptoms compared with those with diagnosed depression or those using antidepressant medication (32). Notable in the use of the BDI is that, unlike for the above-discussed register-based data for which missing data were not an issue, data on the symptoms of depression were available only for a subset of participants. Moreover, the BDI is a self-report method and as such has its known limitations, including social desirability and nonresponse bias, which may distort the actual phenomenon. Also, data on BDI-derived symptoms of depression were available only for the follow-up period, and even then the measurements were conducted only a few times per participant.

In addition to the use of register-based data for diagnoses and antidepressant purchases, discussed above, this study also has a number of other important strengths. First, the longitudinal study design enables us to assess the relationship between depression and the progression of diabetic nephropathy while taking into account the traditional risk factors related to the long-term complications. Second, a large sample of well-defined individuals with type 1 diabetes is also an important asset of the study. The FinnDiane Study participants are nationally recruited, and the sample closely follows the distribution of the general Finnish population. Considering that the FinnDiane Study sample represents ~20% of the total number of individuals with type 1 diabetes in Finland, the sample may be considered fairly representative of the country. Despite this, some selection bias may still be evident, as those with more severe psychological issues and those less interested in health-related studies may be underrepresented. Should this be the case, the current observations likely show a somewhat diluted picture of the actual phenomenon. A major strength of this study is that the sample consists solely of adults with type 1 diabetes, unlike most of the previous studies, which have been conducted either in individuals with type 2 diabetes or in samples pooling data from participants with type 1 and type 2 diabetes. While the use of register-based data on purchases of antidepressant agents and symptoms of depression from the self-reported BDI are proxies of depression, they further strengthen the message conveyed from the analyses with the actual diagnoses. A number of limitations are also worth noting. In our analyses, we adjusted the models with a large number of well-known risk factors. Residual confounding due to variables not accounted for cannot, however, be excluded. Also, although the study was longitudinal, causality between depression and progression of diabetic nephropathy cannot be ascertained based on our observations. It is possible that, despite the timely connection between the two phenomena, the disease progression is, rather, explained by some third unidentified variable. While, in the FinnDiane Study, measures to ensure true type 1 diabetes diagnosis in those diagnosed before the age of 40 years have been taken, it may be possible that a number of individuals diagnosed beyond this age point also have type 1 diabetes but have been excluded from the current analyses. Should this have taken place, the number of missed cases would be low. Finally, no data were available on the duration of the antidepressant medication use. Prolonged use of certain antidepressants may be associated with an increase in the risk factors related to renal decline (33). Also, short treatment periods may expose individuals to side effects without the anticipated benefits, or may be indicative of drug-drug interactions, which would cause a person to refrain from continuing the treatment.

In conclusion, depression diagnosis and history of antidepressant agent purchases are associated with progression of

diabetic nephropathy in people with type 1 diabetes. Moreover, in younger adults, depressive symptoms may also be predictive of progression. Whether identifying individuals with depression and targeting effective interventions could prevent deterioration of diabetic nephropathy should be investigated.

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