Diabetes Symptoms and Distress in ACCORD Trial Participants: Relationship to Baseline Clinical Variables

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Type 2 diabetes may lead to a variety of symptoms such as excessive thirst, frequent urination, fatigue, and burning feet. These symptoms diminish quality of life, impair functional status, and contribute to the psychological distress experienced by patients with diabetes.[1–4] However, there is no established metric for the severity of diabetes symptoms and associated distress.

Many diabetes symptoms are linked through established pathophysiological mechanisms to inadequate short- or long-term glucose control or acute hypoglycemia. But studies to date suggest that the relationship between severity of diabetes symptoms and measures of glucose control such as A1C is weak.[5–7]

A better understanding of factors that amplify or dampen diabetes-related symptoms could lead to improved approaches to maximize the quality of life of diabetes patients. The purpose of this study was to describe the relationship of scores on the Diabetes Symptoms Distress Questionnaire to demographic and clinical variables for patients with type 2 diabetes. This included an evaluation of the cross-sectional association of diabetes symptoms and distress with demographic and clinical variables such as A1C, LDL cholesterol, blood pressure, diabetes duration and complications, and depression status. We also examined the association of diabetes symptoms and distress with patients' overall health state as measured by a feeling thermometer. The feeling thermometer allows patients to rate their current overall health between 100 (perfect health) and 0 (death).

Study Methods

Study population

The rationale and design of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and its health-related quality of life substudy have been reported previously.[8,9] Briefly, the ACCORD trial, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was conducted in 77 clinical centers across the United States and Canada.

We recruited participants with type 2 diabetes and an A1C ≥ 7.5% and who either were *1*) between the ages of 40 and 79 years and had cardiovascular disease (CVD) or *2*) between the ages of 55 and 79 years and had anatomical evidence of significant atherosclerosis, albuminuria, left-ventricular hypertrophy, or at least two additional CVD risk factors (dyslipidemia, hypertension, current status as a smoker, or obesity). Key exclusion criteria included frequent or recent serious hypoglycemia events, unwillingness to perform self-monitoring of blood glucose or inject insulin, a BMI > 45 kg/m^2, a serum creatinine level > 1.5 mg/dl, or other serious illness. A total of 10,251 participants were recruited and randomly assigned to either intensive glycemia-lowering with a target A1C < 6.0% or standard glycemia management with a target A1C of 7.0–7.9%.

The study protocol was approved by the institutional review board or ethics committee at each center, as well as by an ethics review panel at the NHLBI. All patients provided written informed consent.

Of the 10,251 patients enrolled in the trial, a randomly selected subsample of 2,053 participants from each of the clinical centers was enrolled in a substudy concerning health-related quality of life (HRQL). The ACCORD HRQL substudy was designed to assess three distinct outcomes: general health, treatment satisfaction, and diabetes-related symptoms. This report focuses on associations between baseline symptoms and symptom distress, a feeling thermometer used to rate patients' general health state, and multiple demographic and clinical variables. It includes all ACCORD study subjects who were enrolled in the

IN BRIEF

Our study demonstrates strong associations of diabetes symptoms and distress with female sex, higher BMI, history of neuropathy, and current depressive symptoms. Many diabetes-specific symptoms may be significantly shaped by factors such as depression and obesity.

ACCORD HRQL substudy and who completed baseline data collection. The ACCORD HRQL methods have been described previously.[10]

Key measures

We used the Diabetes Symptom Distress Questionnaire developed by Anderson and Testa[11] to assess 60 individual symptoms of diabetes and its treatment. This measure has been previously validated against physician report of patient symptoms.[11] It discriminates between patients with diabetes and those with hypertension[12] and distinguishes between patients with type 2 diabetes randomized to glipizide or placebo.[1] With this questionnaire, subjects reported whether they had experienced a given symptom or feeling. If they had experienced it, then they were asked "How distressing was it?" according to this scale: 0 = not at all; 1 = somewhat; 2 = moderately; 3 = very much; and 4 = extremely. For each participant, we calculated the total symptom count and the mean symptom distress (assigning participants not experiencing the symptom a distress score of 0). We also examined the relationship between these and an overall rating of the patient's health state using a feeling thermometer.

Participant age, sex, ethnicity, educational level, social support (living alone vs. living with others), diabetes duration, history of eye disease, history of neuropathy, and medication use were based on self-report. A central laboratory (with National Glycohemoglobin Standardization Program level I certification) analyzed blood for A1C and lipid levels. Total cholesterol, HDL cholesterol, and fasting triglyceride concentrations were measured enzymatically, and LDL cholesterol was calculated using the Friedewald formula.[13] BMI and Michigan Neuropathy Screening Instrument (MNSI) scores were determined by physical exam. Systolic and diastolic blood pressure levels were determined using the average of three readings using an Omron device (Omron Inc., Kyoto, Japan).

Depression was assessed using the nine-item depression measure from the Patient Health Questionnaire (PHQ-9). The PHQ-9 is the self-report version of the Primary Care Evaluation of Mental Disorders questionnaire, a well-validated psychiatric diagnostic interview for use in primary care settings.[14] In this analysis, we used the PHQ-9 mean score and whether the score exceeded the threshold suggesting major depression (a score ≥ 10 on the PHQ-9). We also assessed patients' history of depression and use of antidepressant medications at baseline.

Finally, a feeling thermometer instrument[15] was used to assess each participant's overall health perceptions.[16] This instrument consists of a single-item visual analog scale with which participants are asked to rate their current (today) health state from 0 (worst imaginable) to 100 (best imaginable).

Statistical analysis

We used both simple and multiple linear regression analyses to assess relationships between demographic, diabetes, and depression status and the specified dependent variables. Separate models were fit for each of the four dependent variables. Multiple linear regression models generally took this form: Diabetes symptoms = demographics (step 1) + diabetes duration and A1C and complications (step 2) + depression (step 3) + glucose, blood pressure, and lipid treatments (step 4). Given the large number of tests performed, only those associations significant at the $P < 0.001$ level were considered statistically significant. Pearson and Spearman rank correlations were used to assess associations between the four dependent variables and the feeling thermometer. Results for the two methods were quite similar (all coefficients agreed ± 0.05), and only Pearson correlation coefficients are presented here.

Ethical approval

The University of Washington Institutional Review Board for the Protection of Human Subjects approved this research, as did the Institutional Review Boards of the other ACCORD clinical networks and the clinics where data were collected.

Study Results

Baseline sample characteristics

Table 1 displays the characteristics of the 1,950 study subjects who were included in the ACCORD HRQL substudy and provided complete baseline data. The study sample had a mean age of 62 years and was 60% male; 60% had post-secondary education, 80% lived with other adults, and 66% were Caucasian. The mean duration of diabetes was just over 11 years. The mean baseline A1C was 8.3 ± 1%, with 56% of the sample having an A1C of ≥ 8%.

Patient responses to Diabetes Symptoms Distress Questionnaire

The 10 most commonly endorsed symptoms on the Diabetes Symptoms Distress Questionnaire were: drowsy or sleepy (59%), getting up often at night to urinate (57%), feeling overweight (57%), tired or being weary (57%), being thirsty (50%), numbness of hands or feet (50%), having to urinate frequently (50%), drinking a lot of fluids (50%), general weakness or fatigue (48%), and lethargy or no energy to do things (44%). These were generally also rated as the most distressing symptoms. The most distressing symptom (range 0–4) was feeling overweight (mean

Table 1. Demographic and Clinical Characteristics of Study Subjects (n = 1,950)	
Characteristic	**Percentage or Mean (SD)**
Mean age (years)	62.3 (6.7)
Female (%)	39.8
Having post-secondary education (%)	59.8
Living with other adults (%)	80.0
Caucasian (%)	65.9
Mean duration of diabetes (years)	11.1 (7.9)
Mean baseline A1C (%)	8.3 (1)
Having baseline A1C ≥ 8% (%)	55.6
Reporting history of neuropathy (%)	27.5
Having foot amputation or MNSI score > 2 (%)	43.1
Reporting history of eye disease (%)	29.7
Mean BMI (kg/m^2)	32.4 (5.5)
Mean systolic blood pressure (mmHg)	136.3 (17.1)
Mean diastolic blood pressure (mmHg)	74.4 (10.9)
Mean total cholesterol (mg/dl)	182.8 (41.1)
Mean LDL cholesterol (mg/dl)	104.1 (33.8)
Mean HDL cholesterol (mg/dl)	42.1 (11.6)
Mean triglyceride level (mg/dl)	189.2 (140.2)
Reporting history of depression (%)	24.6
Using antidepressant medications (%)	14.0
Mean PHQ-9 score	5.4 (5.1)
Having PHQ-9 score ≥ 10 (%)	19.6
Using oral hypoglycemic medications only (%)	56.9
Using insulin (%)	35.9
Using thiazides (%)	26.8
Using β-blockers (%)	30.4
Using ACE inhibitors (%)	52.0
Using statins (%)	63.5

distress score of 2.2). Eight symptoms tied for the second most distressing (mean distress score 1.8), including numbness or tingling of hands or feet, having to urinate frequently, lethargy or no energy to do things, foot cramps or foot pain, high blood glucose reaction, pain in legs or calves when walking, gaining weight, and inability to sleep or insomnia.

Figure 1 displays the distribution of symptom counts in the study population. Less than 2% of subjects reported no symptoms, with the vast majority reporting multiple symptoms. The mean symptom count was 17.1. The median number of symptoms was 15.0. Figure 2 displays the distribution of symptom distress in the study population. Symptom distress was generally low, with 73% reporting mean distress between 0 and 1 on the four-point scale. The overall mean for distress was 0.7, and the median distress score was 0.6.

Total symptom count was highly correlated with mean symptom distress (Pearson $r = 0.88$, $P < 0.0001$). Symptom count ($r = -0.35$, $P < 0.0001$) and symptom distress ($r = -0.36$, $P < 0.0001$) were significantly and similarly correlated with the overall health state rating on the feeling thermometer.

Univariate relationships between symptoms, distress, and clinical variables

Table 2 displays the univariate relationships between symptoms, distress, and clinical variables. Total symptom count was significantly and negatively associated with age. It was significantly and positively associated with female sex, history of neuropathy, BMI, serum triglygeride level, history of depression, use of antidepressants, mean PHQ-9 score, having a PHQ-9 score ≥ 10, and use of insulin. Mean symptom distress was significantly and negatively associated with age and use of only oral hypoglycemic medications. Mean symptom distress was significantly and positively associated with female sex, baseline mean A1C, having a baseline A1C ≥ 8%, history of neuropathy, BMI, total cholesterol, triglyceride level, history of depression, use of antidepressants, mean PHQ-9 score, having a PHQ-9 ≥ 10, and use of insulin.

Multivariable models for symptom count, distress, and factors

Multivariable models were derived in a progressive manner, entering demo-

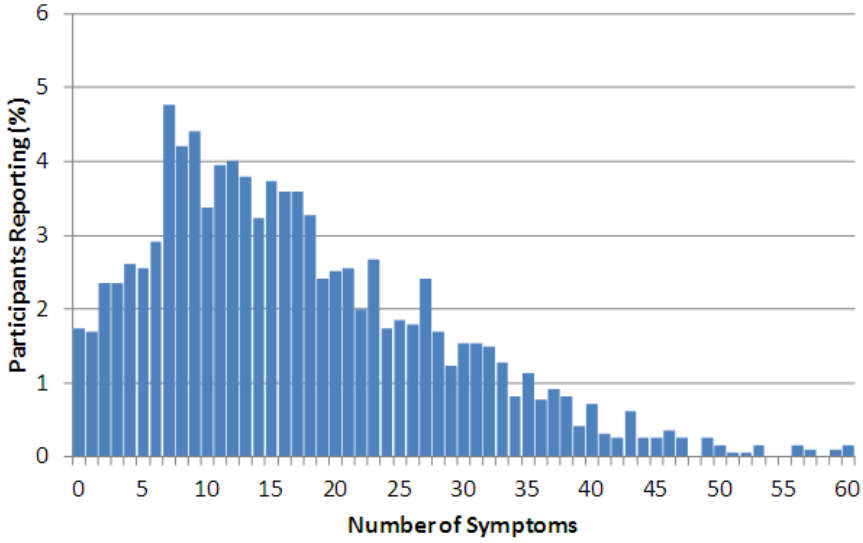

Figure 1. Number of symptoms per participant.

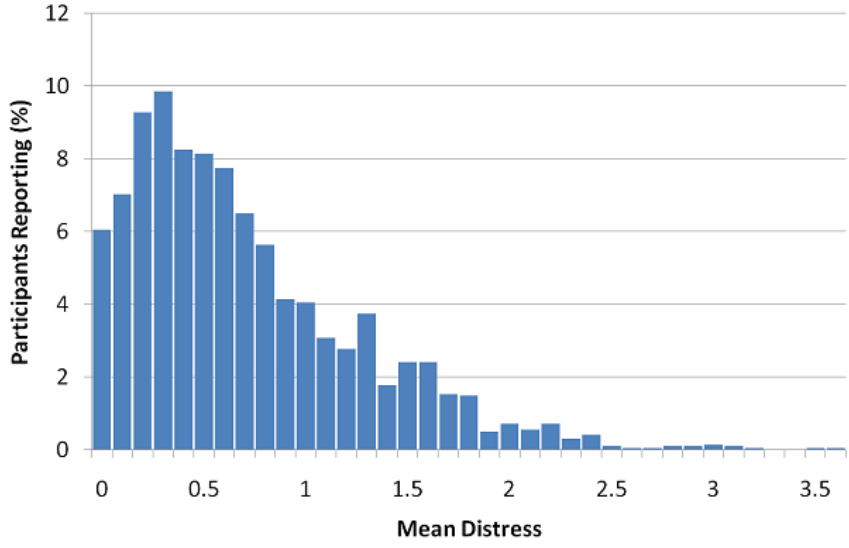

Figure 2. Distribution of mean distress scores.

graphic variables first, then diabetes and cardiovascular risk variables, then depression variables, and then treatments for diabetes, blood pressure, and lipid control. These models are displayed in Table 3.

Most predictor variables that entered the multivariable models were significant at the $P \leq 0.001$ level, and most remained significant in the more complete models. We therefore report only the final models including variables significant at $P < 0.0001$ for each of the two primary outcomes:

- Total symptom count was significantly associated with female sex ($\beta = 2.24$), history of neuropathy ($\beta = 3.71$), and having a PHQ-9 score ≥ 10 ($\beta = 11.13$).
- Symptom distress was significantly associated with history of neuropathy ($\beta = 0.10$), BMI ($\beta = 0.01$), and PHQ-9 score ≥ 10 ($\beta = 0.48$).

Discussion

Diabetes symptom count and symptom-related distress appear to be associated with multiple factors when these are considered individually, including demographic and psychological variables and measures of diabetes control and complications. However, in multivariable models, diabetes symptoms and distress are significantly associated only with sex, BMI, history of neuropathy, and current depressive symptoms (PHQ-9 score ≥ 10). These findings suggest that efforts to reduce diabetes symptoms should focus on strategies to reduce neuropathy and depression. We did not correct for any ongoing depression treatment (medications or psychotherapy) in our analyses.

Previous research on diabetes symptoms has shown a stronger relationship between diabetes symptom severity and the mental component score of the Short Form-36 Health Survey than the physical component score.[2] Other research has suggested an important role for depression in diabetes symptoms. In a primary care sample of 4,168 patients with diabetes, Ludman et al.[6] found that patients with major depression had more diabetes symptoms after adjusting for demographic characteristics, objective measures of diabetes severity, and medical comorbidity. The overall number of diabetes symptoms was related to the number of depressive symptoms, and depression was significantly related to all of the 10 diabetes symptoms assessed. Previously, Ciechanowski et al.[5] reported strong associations between diabetes symptoms and depression in a sample of 273 diabetic patients recruited from a specialty care setting.

Depression in patients with diabetes is likely both a cause and a consequence of diabetes symptoms, complications, and related health behaviors.[17] Diabetes symptoms and complications, smoking, and obesity (BMI) have all been associated with an increased risk of depression in

Table 2. Univariate Relationships With Symptom Outcomes

Characteristic	Total Symptom Count			Mean Distress		
	β	SE	*P*	β	SE	*P*
Age (years)	–0.169	0.038	< 0.0001	–0.007	0.001	< 0.0001
Sex (female vs. male)	3.817	0.512	< 0.0001	0.137	0.018	< 0.0001
Post-secondary education (yes vs. no)	–0.118	0.519	0.821	–0.018	0.018	0.317
Living alone (yes vs. no)	–1.00	0.636	0.114	–0.015	0.022	0.506
Caucasian (yes vs. no)	0.246	0.537	0.646	0.001	0.019	0.962
Duration of diabetes (years)	0.054	0.033	0.098	0.002	0.001	0.150
Baseline A1C (%)	0.557	0.243	0.022	0.037	0.009	< 0.0001
Baseline A1C ≥ 8% (yes vs. no)	1.590	0.511	0.002	0.079	0.018	< 0.0001
History of neuropathy (yes vs. no)	5.827	0.559	< 0.0001	0.195	0.020	< 0.0001
Foot amputation or MNSI score > 2 (yes vs. no)	1.596	0.513	0.002	0.051	0.018	0.005
History of eye disease (yes vs. no)	0.797	0.558	0.154	0.030	0.020	0.125
BMI (kg/m^2)	0.387	0.045	< 0.0001	0.015	0.002	< 0.0001
Systolic blood pressure (mmHg)	0.000	0.015	0.989	0.000	0.001	0.892
Diastolic blood pressure (mmHg)	0.048	0.023	0.040	0.002	0.001	0.012
Total cholesterol (mg/dl)	0.021	0.006	0.001	0.001	0.000	< 0.0001
LDL cholesterol (mg/dl)	0.007	0.008	0.3669	0.000	0.000	0.154
HDL cholesterol (mg/dl)	–0.004	0.022	0.8242	0.000	0.001	0.799
Triglyceride level (mg/dl)	0.008	0.002	< 0.0001	0.000	0.000	< 0.0001
History of depression (yes vs. no)	7.280	0.570	< 0.0001	0.268	0.020	< 0.0001
Using antidepressant medications (yes vs. no)	6.283	0.719	< 0.0001	0.258	0.025	< 0.0001
PHQ-9 score	1.311	0.040	< 0.0001	0.050	0.001	< 0.0001
PHQ-9 score ≥ 10 (yes vs. no)	13.357	0.566	< 0.0001	0.559	0.019	< 0.0001
Using oral hypoglycemics only (yes vs. no)	–1.879	0.512	0.000	–0.086	0.018	< 0.0001
Using insulin (yes vs. no)	2.447	0.527	< 0.0001	0.111	0.018	< 0.0001
Using thiazides (yes vs. no)	–0.238	0.574	0.678	–0.010	0.020	0.620
Using β-blockers (yes vs. no)	1.614	0.552	0.005	0.038	0.019	0.051
Using ACE inhibitors (yes vs. no)	–0.743	0.509	0.145	–0.030	0.018	0.091
Using statins (yes vs. no)	–0.229	0.529	0.666	–0.008	0.019	0.679

previous studies.[18–21] This suggests that aversive symptoms (such as pain from neuropathy), depression, and health behaviors associated with mood regulation (such as smoking and eating) exist in a mutually reinforcing pattern that exerts a significant effect on patients' overall health state, as indicated by the feeling thermometer findings.

This pattern of reciprocal interactions between symptom severity, depression, and quality of life has been found in other chronic diseases such as asthma[22]

Table 3. Multivariable Relationships With Symptom Burden and Distress

Characteristic	Total Symptom Count			Mean Distress		
	β	SE	*P*	β	SE	*P*
Age (years)	–0.0223	0.0388	0.5658	–0.0003	0.0013	0.7909
Sex (female vs. male)	2.2421	0.5181	< 0.0001	0.0612	0.0169	0.0003
Post-secondary education (yes vs. no)	0.5286	0.4683	0.2591	0.0077	0.0153	0.6149
Living alone (yes vs. no)	–0.0112	0.5607	0.9841	0.0211	0.0183	0.2479
Caucasian (yes vs. no)	–0.5190	0.5092	0.3082	–0.0251	0.0166	0.1311
Duration of diabetes (years)	0.0168	0.0322	0.6021	–0.0003	0.0011	0.7396
Baseline A1C (%)	0.0060	0.2199	0.9784	0.0148	0.0072	0.0393
History of neuropathy (yes vs. no)	3.7069	0.5373	< 0.0001	0.1042	0.0175	< 0.0001
Foot amputation or MNSI score > 2 (yes vs. no)	0.8031	0.4757	0.0915	0.0219	0.0155	0.1572
History of eye disease (yes vs. no)	–0.2710	0.5299	0.6091	–0.0050	0.0173	0.7726
BMI (kg/m^2)	0.1395	0.0443	0.0017	0.0072	0.0014	< 0.0001
Systolic blood pressure (mmHg)	0.0110	0.0167	0.5093	0.0004	0.0005	0.478
Diastolic blood pressure (mmHg)	0.0067	0.0277	0.8091	0.0001	0.0009	0.892
Total cholesterol (mg/dl)	0.0031	0.0072	0.6701	0.0001	0.0002	0.7111
LDL cholesterol (mg/dl)	0.0077	0.0232	0.7415	0.0011	0.0008	0.163
Triglyceride level (mg/dl)	0.0038	0.0018	0.0328	0.0002	0.0001	0.0006
History of depression (yes vs. no)	2.1388	0.6303	0.0007	0.0517	0.0205	0.0118
Using antidepressant medications (yes vs. no)	0.6774	0.7454	0.3636	0.0488	0.0243	0.0446
PHQ-9 score ≥ 10 (yes vs. no)	11.1252	0.6105	< 0.0001	0.4804	0.0199	< 0.0001
Using oral hypoglycemic only (yes vs. no)	0.9480	0.9195	0.3026	0.0416	0.0300	0.1656
Using insulin (yes vs. no)	1.5094	0.9896	0.1274	0.0774	0.0322	0.0165
Using thiazides (yes vs. no)	–0.3656	0.5111	0.4744	–0.0085	0.0167	0.6084
Using β-blockers (yes vs. no)	1.1790	0.5056	0.0198	0.0275	0.0165	0.0949
Using ACE inhibitors (yes vs. no)	–0.9374	0.4524	0.0384	–0.0403	0.0147	0.0064
Using statins (yes vs. no)	–0.1261	0.5001	0.801	0.0010	0.0163	0.951

and chronic kidney disease requiring hemodialysis.[23] Our study adds to these other studies in supporting the idea that diabetes-specific symptoms are more significantly shaped by factors such as depression and obesity than by severity and duration of diabetes per se.

Our analysis has some important limitations. First, the cross-sectional study design precludes causal inference. Longitudinal data are necessary to prove causality. Because we posit reciprocal relationships between diabetes symptoms and their determinants, multiple waves of data will be necessary to fully understand these complex relationships.

Second, our sample is not representative of the entire population of patients with type 2 diabetes. ACCORD participants had diabetes for a mean of 10 years, were at high

risk for cardiovascular events, and were willing to undergo intensive treatment to control glucose, including frequent clinic visits and the use of insulin.

Third, although we assessed a broad range of factors for their associations with diabetes symptoms, there are many other factors that could have been examined in metabolic (C-reactive protein), physiological (nerve conduction velocities), behavioral (exercise), and psychosocial (anxiety) domains that may have affected the final multivariable models.

In summary, our study demonstrates strong associations between diabetes symptoms and distress and female sex, BMI, neuropathy, and depression. These factors likely reinforce each other, although precise specification of these relationships awaits longitudinal data.

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