Time With Diabetes Distress and Glycemia-Specific Distress: New Patient-Reported Outcome Measures for the Psychosocial Burden of Diabetes Using Ecological Momentary Assessment in an Observational Study

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OBJECTIVE

To estimate time with diabetes distress using ecological momentary assessment (EMA) in people with type 1 diabetes and analyze its associations with glycemic management based on continuous glucose monitoring (CGM).

RESEARCH DESIGN AND METHODS

We used EMA to assess diabetes distress in a sample of recently hospitalized adults with type 1 diabetes once a day for 17 consecutive days in an ambulatory setting. Additionally, participants were asked daily about hypoglycemia distress (<70 mg/dL [3.9 mmol/L]), hyperglycemia distress (>180 mg/dL [10 mmol/L]), and variability distress (glucose fluctuations). Per person, the percentage of days with elevated distress was calculated (time with distress). Multilevel regression was used to analyze daily associations of distress ratings with CGM-derived parameters. EMA-derived associations between diabetes distress and glycemic outcomes were compared with questionnaire-derived associations.

RESULTS

Data of 178 participants were analyzed. Participants spent a mean (SD) of days in a state of diabetes distress, 54.6 ± 26.0% in hyperglycemia distress, 45.2 ± 27.5% in variability distress, and 23.0 ± 19.3% in hypoglycemia distress. In multilevel analyses, higher daily ratings of diabetes distress were significantly associated with hyperglycemia (β = 0.41). Results showed high between-person variability as explanation of variance of the models ranged between 22.2 and 98.8%. EMA-derived diabetes distress showed a significant association with mean glucose (r = 0.25), while questionnaire-based diabetes distress did not (r = 0.10). Prospectively, time with diabetes distress was associated with HbA_{1c} at the 3-month follow-up (r = 0.27), while questionnaire-based distress showed no association (r = 0.11).

CONCLUSIONS

Time with distress as assessed with EMA showed a comparative advantage over distress as determined by questionnaire-based assessment of diabetes distress regarding associations with glycemic management.

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Patient-reported outcomes (PRO) have become increasingly important in clinical practice and diabetes research (1). In type 1 diabetes, one of the most frequently assessed PRO is diabetes distress (2). Diabetes distress refers to the emotional impact of diabetes on the life of a person. Elevated diabetes distress occurs when stress associated with diabetes tends to chronically exceed a person's coping skills (3). There are well-validated questionnaires for assessing diabetes distress, such as the Problem Areas in Diabetes (PAID) questionnaire and the Diabetes Distress Scale (DDS), with which diabetes distress has been established as an important PRO (2,4,5). The prevalence of elevated diabetes distress is estimated at 20–40% for people with type 1 diabetes (2). It is a key factor in diabetes therapy, as it is associated with worse diabetes self-management, depression, and lower quality of life (2,3).

However, the association between glycemic management and diabetes distress is not entirely clear. Validation studies of PAID (r = 0.30) and DDS (r = 0.01) have not unequivocally shown a substantial association between diabetes distress and glycemic management (4,5). Schmitt et al. (6) found rather small associations between HbA_{1c} values and PAID (r = 0.06) and DDS (r = 0.16). Furthermore, little is known about associations between diabetes distress and continuous glucose monitoring (CGM)-derived parameters of glycemic management, such as time in range and glucose variability (7,8). A meta-analysis of intervention studies targeting elevated diabetes distress showed a moderate effect on reduction of diabetes distress (Cohen d = 0.48), whereas the simultaneous effect on glycemic management was rather small (Cohen d = 0.20) (9). In addition, intervention studies of CGM and automated insulin delivery systems have demonstrated inconclusive and generally much smaller effects of these devices on PRO as assessed by questionnaires—in stark contrast to larger effects on CGM-derived parameters of glycemic management (8,10–14).

This equivocal evidence regarding associations between diabetes distress and glycemic management might indicate that diabetes distress is an emotional response that is partially independent from glycemic management, at least in certain subgroups. For these specific subgroups, other factors such as the experience of living with a chronic condition might be more important than glycemic management alone.

Methodological issues could further explain the equivocal evidence regarding associations between glycemic management and diabetes distress. For glycemia, associations are mainly based on HbA_{1c}, which provides only retrospective information about the mean glucose level in the past 8–12 weeks. In contrast, CGM provides a more detailed picture and could allow for more granular analyses. For PRO, questionnaires mainly provide a retrospective summary rating. Questionnaires are, therefore, prone to bias (such as response bias or recall bias), with people remembering only certain problematic aspects of living with diabetes, or peak effects when selective attention is given to the most salient problems in the recall period, regardless of duration or frequency (15,16). Therefore, questionnaires may not be optimal for recording emotional experiences, which are more responsive to the current context and situations. As such, questionnaires might not fully account for the variability in experiences of diabetes distress and therefore do not mirror the day-to-day experiences of people living with diabetes.

A methodology that could overcome the shortcomings of traditional questionnaires is ecological momentary assessment (EMA). EMA allows the repeated daily sampling of participants' responses in their everyday life, usually via smartphone (17). Thus, the daily level of diabetes distress can be assessed, allowing for the estimation of time spent with diabetes distress and the daily variation of distress. This momentary assessment would provide a more comprehensive picture of diabetes distress because it complements the assessment of a rather stable (trait-like) experience of increased diabetes distress, via retrospective questionnaire, with an assessment of the contextually varying emotional experience of diabetes burden.

Using EMA in combination with CGM offers interesting possibilities; both increase the temporal resolution in assessment compared with HbA_{1c} and questionnaires. This combination might provide a clearer picture of how different aspects of glycemic management are associated with diabetes distress. Furthermore, with EMA, intensive longitudinal data for each person can be generated (17). These data enable the analysis of "n of 1" trials regarding idiosyncratic associations between glycemic management and diabetes distress. These analyses would help identify people who show a stronger association between glycemic management and diabetes distress and could contribute to the development of individualized approaches (i.e., precision monitoring and precision medicine) (18,19).

In this observational study, we assessed diabetes distress on a daily level using EMA and analyzed the relationship between glycemic management and diabetes distress by combining EMA and CGM. To provide a subjective counterpart to CGM-derived parameters (20), we assessed EMA-derived parameters of glycemia-specific distress regarding hypoglycemia, hyperglycemia, and glucose fluctuations. In subsequent n-of-1 analyses, the idiosyncrasies of these associations between EMA-derived distress and glycemic management were investigated. We also analyzed whether daily assessment of diabetes distress with EMA had a comparative methodological advantage over questionnaire-based assessment. In doing so, we propose new context-sensitive PRO measures, called "time with diabetes distress" and "time with glycemia-specific distress."

RESEARCH DESIGN AND METHODS

The DIA-LINK1 Study was a noninterventional, prospective observational study in people with type 1 diabetes. The present analysis focuses on a 17-day EMA period in which diabetes distress and glycemia-specific distress were assessed daily; the full study protocol is available from ClinicalTrials.gov (clinical trial reg. no. NCT03811132).

Recruitment

Participants were recruited at the Diabetes Clinic Mergentheim, Bad Mergentheim, Germany. This is an inpatient facility to which people with diabetes are referred because of sustained hyperglycemia, occurrence of complications, or psychosocial issues complicating the treatment and course of diabetes. After recruitment in the inpatient setting and then discharge from the clinic, the data collection began. Recruitment took place

between March 2019 and March 2020. Thus, data collection was completed before the beginning of the coronavirus disease 2019–related lockdown measures in Germany. The recruitment goal was to include 200 people with type 1 diabetes. Participants were grouped based on elevated versus nonelevated levels of diabetes distress and depressive symptoms (i.e., stratified recruitment). Elevated diabetes distress was determined with use of PAID (4) with a cutoff score of ≥40 (21). Elevated depressive symptoms were determined with use of the Center for Epidemiological Studies–Depression (CES-D) scale with a cutoff score of ≥22 (22). Four groups with 50 participants each were established, including those with *1*) neither elevated diabetes distress nor depressive symptoms, *2*) elevated diabetes distress but no elevated depressive symptoms, *3*) no elevated diabetes distress but elevated depressive symptoms, and *4*) elevated diabetes distress and elevated depressive symptoms.

The following inclusion criteria were applied: type 1 diabetes, diabetes duration ≥1 year, age 18–70 years, sufficient German language skills, compatible smartphone, and informed consent. People were excluded if any of the following exclusion criteria were present: inability to consent, significant cognitive impairment, severe somatic illness or mental disorder, terminal illness, or being bedridden.

Participants were provided with information about the study, both orally and in writing. Written informed consent was obtained. The study was approved by the Ethics Committee of the German Psychological Society (NH082018).

Study Phases

After inclusion, participants completed a baseline assessment. They were then equipped with an unblinded, intermittently scanned CGM system (FreeStyle Libre 2) for the whole study period. For EMA, a smartphone application (mEMA, Ilumivu Software for Humanity, Asheville, NC) was installed on participants' personal smartphones. During the inpatient stay, the EMA procedure was tested to ensure proper functioning. The EMA was done in an outpatient, ambulatory setting. Beginning on the first Saturday after discharge from the hospital, the EMA period started, with questions prompted daily over 17 consecutive days. Twenty-six days after EMA initiation, participants completed PAID. Three months after baseline, follow-up assessment took place, with glucose data over 14 days collected and participants completing the questionnaires described below. An overview of the design and analytic strategy can be found in Fig. 1.

Assessments

At baseline, we obtained demographic and medical data with case report forms using medical files and personal interviews. HbA_{1c} was measured in a central laboratory at baseline and at a 3-month follow-up. Participants completed the following questionnaires at baseline and at a 3-month follow-up:

- Diabetes distress: PAID consists of 20 items for assessing emotional problems and diabetes-specific burdens (4). A total score was calculated, with higher scores indicating more distress.
- Depressive symptoms: the CES-D contains 20 items for assessing depressive symptoms over the past week (22). A total score was calculated, with higher values indicating more depressive symptoms.
- Fear of hypoglycemia: the short form of the Hypoglycemia Fear Survey II (HFS-II-SF) was used (23). A sum score was calculated, with higher scores indicating greater fear of hypoglycemia.
- Fear of complications: a short form of the Fear of Complications Questionnaire – Short Form (FCQ-SF) was used containing six items (24). A sum score was calculated, with higher scores indicating greater fear of complications.

For assessment of diabetes distress at a daily level, five questions from PAID were adapted for use in daily surveys and asked every evening (prompted at 8:00 P.M.). Those five questions related to the following: *1*) feelings of deprivation/restriction, *2*) feeling overwhelmed by diabetes management, *3*) feeling left alone with diabetes, *4*) diabetes taking up too much mental and physical energy, and *5*) feeling guilty or anxious when getting off track with diabetes management. For each day, a sum score of daily diabetes distress was calculated and transformed to a scale from 0 to 100. A cutoff score of ≥40, as in the original PAID (21), was applied to indicate days with elevated diabetes distress.

For assessment of glycemia-specific distress, the following questions were asked daily at the evening prompt: How much were you distressed. . .

- by low glucose values (<70 mg/dL, <3.9 mmol/L) today?
- by high glucose values (>180 mg/dL, >10 mmol/L) today?
- by fluctuations of your glucose today?

Responses were given on a scale from 0 (not at all) to 10 (very much). For comparability with the daily diabetes distress scores, responses to each question were transformed to a scale from 0 to 100 and the PAID cutoff score of ≥40 was applied to indicate elevated glycemia-specific distress.

For each participant per day, 24-h glucose data were extracted, and the following parameters were calculated: % time in range (70–180 mg/dL [3.9–10 mmol/L]), % time in a state of hypoglycemia (<70 mg/dL [<3.9 mmol/L]), % time in a state of hyperglycemia (>180 mg/dL [>10 mmol/L]), and glucose fluctuations as coefficient of variation (CV).

Statistical Analyses

According to CGM guidelines, a minimum of 10 days should be used in assessing CGM-derived parameters of glycemic management (20). Thus, the same time frame was used for EMA-derived distress measures: only participants who completed EMA ratings on at least 10 days were included in the present analysis. For assessment of the associations between daily distress ratings and CGM-derived parameters on a daily level, multilevel modeling with participant as nesting factor was used. Dependent variables were the respective daily distress ratings. Within-level predictors were daily % time <70 mg/dL (3.9 mmol/L), daily % time >180 mg/dL (10 mmol/L), daily glucose CV, and daily number of glucose scans. The following variables were included as between-level predictors: female sex, baseline PAID and CES-D scores, interaction between PAID and CES-D scores, and the 17-day person-averages of glucose parameters and number of scans. In each analysis, we controlled for study day and first autoregressive parameter.

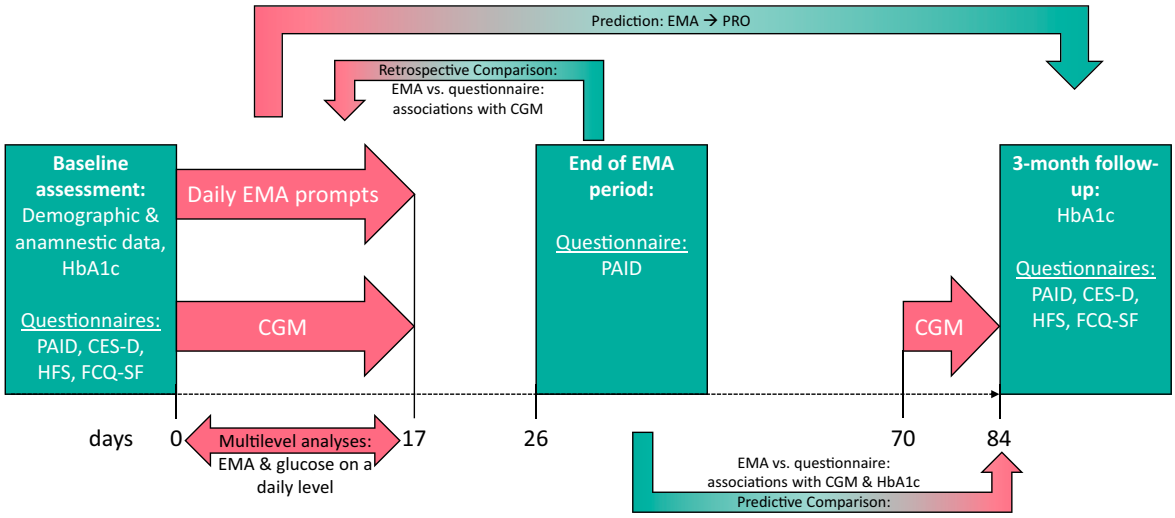

Figure 1—Design of the DIA-LINK1 Study and analytic strategy for EMA-based distress ratings. Multilevel analyses: Two-level regression analysis with participant as nesting factor and daily distress ratings as dependent variable. CGM-derived parameters as within-level predictors; demographic and anamnestic data as between-level predictors. Retrospective comparison: Comparison of correlations between EMA-based diabetes distress and glucose (EMA-phase) to correlations between questionnaire-based diabetes distress and glucose (EMA phase). Predictive comparison: Comparison of correlations between EMA-based diabetes distress and glucose (follow-up phase) to correlations between questionnaire-based diabetes distress and glucose (follow-up phase). Prediction: Correlations between EMA-based diabetes and glycemia-specific distress ratings and questionnaires at 3-month follow-up. CES-D, Center for Epidemiological Studies – Depression; CGM, continuous glucose monitoring; EMA, ecological momentary assessment; FCQ-SF, Fear of Complications Questionnaire – Short Form; HFS, Hypoglycaemic Fear Survey; PAID, Problem Areas in Diabetes.

Bayes estimation was used, and raw estimates and standardized coefficients (β) are reported.

Furthermore, data were aggregated over the 17-day EMA period for each participant. For each person, mean and median distress ratings were calculated, as were the percentages of days with elevated diabetes distress ("time with diabetes distress") and elevated glycemia-specific distress (times with hypoglycemia, hyperglycemia, and variability distress). Mean ratings and time with distress variables were then correlated with questionnaire data and CGM-derived parameters at different time points (Fig. 1). Missing data were not imputed. Additionally, we determined reliability for these new measures by following multilevel approaches from Geldhof, et al. (25) and from Bolger and Laurenceau (26). (See Supplementary Tables 1 and 2.) The level of significance was set to 0.05 due to the exploratory nature of the analyses. All analyses were performed with SPSS 26 (IBM, Armonk, NY) and Mplus 8.6 (27).

RESULTS

Baseline Characteristics

A total of 203 people with type 1 diabetes participated in the study. Full sample characteristics are displayed in Table 1. Participants were relatively young, with a mean age of 38.6 years. They were highly experienced with CGM systems; 86% had a CGM system prior to study inclusion. Because of stratified recruitment, mean PAID and CES-D scores were rather high. Overall, participants had rather suboptimal glycemic management over the 17 days, with mean ± SD % time in hyperglycemia of 41.9 ± 18.6.

Daily EMA prompts were answered on an average ± SD of 13.4 ± 3.4 days per person. Across all participants, this resulted in a high mean response rate, of 79%, for responses to daily prompts. Overall, 87.7% of all participants gave answers on at least 10 of 17 days. For the following analyses, only those participants were included (n = 178) (Table 1).

Time With Diabetes Distress and Glycemia-Specific Distress

Table 2 shows the mean and median values of daily distress ratings over the 17-day EMA period. The highest ratings were seen for hyperglycemia distress (mean ± SD 42.4 ± 18.4) and glucose variability distress (34.7 ± 17.9). On average, participants spent 24.1% of days in diabetes distress, 23% in hypoglycemia distress, 54.6% in hyperglycemia distress, and 45.2% in glucose variability distress. The cumulative distribution of participants' time with diabetes distress and glycemia-specific distress is shown in Fig. 2 and demonstrates, for example, that nearly 10% of participants had high diabetes distress on >80% of days (Fig. 2*A*). Supplementary Fig. 1 shows the course of the mean daily distress ratings over the 17 days. The corresponding course of CGM-derived glucose parameters is shown in Supplementary Fig. 2.

The reliability of the daily diabetes distress assessment was high, with an ω reliability score of 0.76 (Supplementary Table 1). Reliability of the single items assessing glycemia-specific distress averaged across all days ranged between 0.81 and 0.90 (Supplementary Table 2).

Associations of EMA-Derived Distress and Glycemic Management on a Daily Level

Table 3 shows the associations of CGM-derived parameters of glycemic management with daily experiences of distress (within-person effects) as well as the impact of between-person differences on the experiences of daily distress (between-person effects). Within persons, increased daily exposure to hyperglycemic values was significantly associated with higher daily diabetes distress, higher

Table 1—Baseline characteristics for the total sample and the sample used for analysis

	All (*N* = 203)	Participants included in analyses (*n* = 178)
Age (in years)	38.6 ± 12.8	39.0 ± 12.6
Female sex	119 (59)	103 (58)
BMI, in kg/m^2	26.1 ± 5.2	26.2 ± 5.1
Years of education	13.1 ± 2.6	13.2 ± 2.6
Duration of diabetes, years	18.6 ± 11.7	19.0 ± 11.7
HbA_{1c}, % (mmol/mol)	8.7 ± 1.9 (72 ± 21)	8.6 ± 1.9 (70 ± 21)
Insulin pump therapy	118 (58)	104 (58)
CGM use prior to inclusion#	174 (86)	152 (85)
Long-term complications (mean per person)+	0.69 ± 0.85	0.71 ± 0.85
PRO (baseline assessment)		
Diabetes distress (PAID sum score, range 0–100)	39.9 ± 18.1	39.9 ± 18.1
Depressive symptoms (CES-D sum score, range 0–60)	21.3 ± 11.4	21.0 ± 11.6
Hypoglycemia fear (HFS-II-SF sum score, range 0–44)	15.2 ± 9.3	15.0 ± 9.2
Fear of complications (FCQ-SF sum score, range 0–18)	9.5 ± 4.9	9.4 ± 4.9
CGM-derived parameters of glycemic management (17-day EMA phase)		
Glucose (mg/dL)	177.2 ± 38.5	175.3 ± 38.6
% time with glucose <70 mg/dL (3.9 mmol/L)	3.8 ± 3.9	3.8 ± 4.0
% time with glucose 70–180 mg/dL (3.9–10 mmol/L)	54.4 ± 17.0	55.2 ± 17.2
% time with glucose >180 mg/dL (10 mmol/L)	41.9 ± 18.6	41.0 ± 18.8
Glucose fluctuations (CV)	32.2 ± 4.9	32.0 ± 4.8

Data are means ± SD or *n* (%). #CGM use: real-time CGM or intermittent-scanning CGM. +List of complications: retinopathy, neuropathy, nephropathy, diabetic foot syndrome, cardiovascular disease, apoplexy, arterial vascular disease.

hyperglycemia distress, higher glucose variability distress, and lower hypoglycemia distress. Greater daily glucose variability was significantly associated with higher daily diabetes distress and glucose-specific distress. Increased exposure to hypoglycemic values was significantly associated with higher daily hypoglycemia distress and lower daily hyperglycemia distress within persons. Higher frequency of daily glucose scans of a person was significantly associated with higher daily diabetes distress and higher daily hypoglycemia and glucose variability distress. Between persons, higher baseline levels of diabetes distress as assessed via questionnaire led to higher daily ratings of diabetes distress and hyperglycemia distress. Interestingly, depressive symptoms at baseline had no effect on daily distress ratings.

n-of-1 Analyses: Idiosyncrasies of the Associations Between Distress and Glycemic Management

The variance explained by the model regarding the distress ratings ranged between 22.2 and 98.8%, illustrating the high between-person variability in associations between daily distress ratings and glycemic predictors. Supplementary Fig. 3 shows the cumulative distribution from the *n*-of-1 analyses and illustrates that, for 25% of participants, the model explained >64% of the variation in daily diabetes distress (Supplementary Fig. 3*A*), indicating a rather high dependency of daily distress ratings from glucose. In Supplementary Fig. 4, three prototypical persons are presented to show different levels of associations. Person A showed a high association between daily hyperglycemia distress and hyperglycemic exposure, indicating a high psychosocial reactivity to glucose levels (or high metabolic reactivity to distress). Person B showed varying levels of hyperglycemia distress that were independent of actual exposure to hyperglycemic values. Person C showed no hyperglycemia distress, but hyperglycemic exposure varied across the study days.

Table 2—Person level: mean and median ratings of daily distress ratings and time with diabetes distress/glycemia-specific distress over the 17-day EMA period

	Average of daily distress ratings (range 0–100)		Time with distress: % of days with elevated ratings (≥40)	
Type of daily distress	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Diabetes distress	25.4 ± 17.4	23.3 (11.5–35.6)	24.1 ± 29.7	9.5 (0–40.3)
Hypoglycemia distress	20.7 ± 12.8	19.3 (10.7–29.5)	23.0 ± 19.3	19 (7–38)
Hyperglycemia distress	42.4 ± 18.4	42.9 (29.8–55.1)	54.6 ± 26.0	57.5 (33–76)
Glucose variability distress	34.7 ± 17.9	34.9 (21.3–47.0)	45.2 ± 27.5	44.0 (23–65)

n = 178. IQR, interquartile range.

Cross-sectional Comparison of EMA-Assessed Distress and Questionnaire-Assessed Distress (17-Day EMA Period)

For comparison of EMA-derived diabetes distress with questionnaire-based diabetes distress, correlations with glycemic

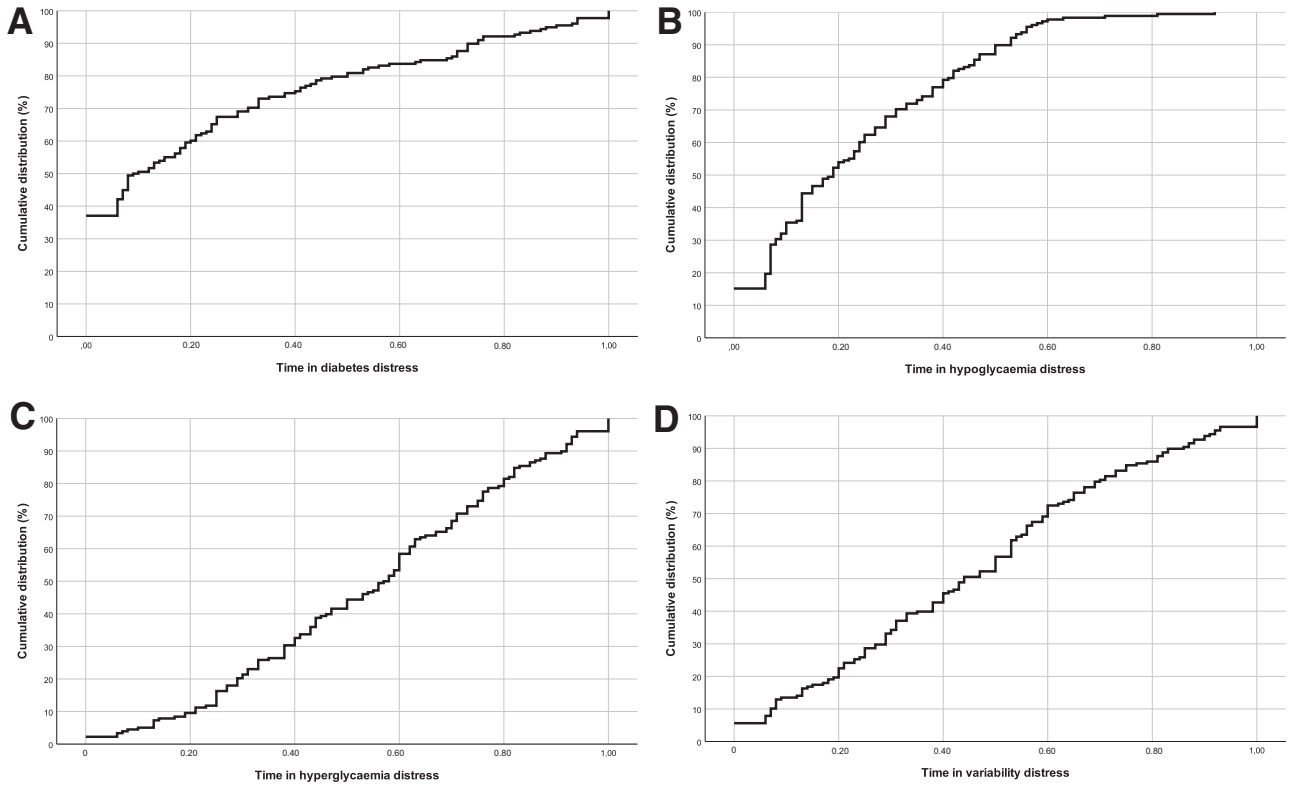

Figure 2—Cumulative distribution of time with diabetes distress (*A*), time with hypoglycemia distress (*B*), time with hyperglycemia distress (*C*), and time with variability distress (*D*). Each person's percentage of days in respective distress (*x*-axis) was used for the cumulative distribution.

management over the 17-day EMA period were analyzed. EMA-derived (mean) diabetes distress was significantly associated with mean glucose, time in range, and time in a state of hyperglycemia (Table 4). In contrast, diabetes distress assessed via questionnaire at the end of the EMA period showed no significant associations with glycemic management (except for % time <70 mg/dL [3.9 mmol/L]) (Table 4). All EMA-derived measures were significantly associated with questionnaire-based diabetes distress at the end of the EMA period, with the highest correlation for daily diabetes distress (r = 0.64) (Supplementary Table 3).

Longitudinal Comparison of EMA-Derived Distress and Questionnaire-Based Distress (3-Month Follow-up)

All EMA-derived distress measures were significantly associated with questionnaire-based diabetes distress, depressive symptoms, hypoglycemia fear, and fear of complications 2 months later at the 3-month follow-up (Supplementary Table 3). Time with hypo- and hyperglycemia distress was significantly associated with glycemic parameters at the 3-month follow-up (Supplementary Table 3). Higher EMA-derived diabetes distress was significantly associated with higher mean glucose levels (r = 0.27), lower time in range (r = −0.20), higher time in hyperglycemia (r = 0.20), and higher HbA_{1c} (r = 0.23) at the 3-month follow-up (Supplementary Table 4). In contrast, questionnaire-based diabetes distress (assessed at the end of the EMA period) showed no significant associations with glycemic management at the 3-month follow-up (Supplementary Table 4).

Sensitivity Analyses

Dropout analyses showed no substantial differences between participants included in analysis and those with low adherence to the EMA signals (Supplementary Table 5). Furthermore, level of adherence was not associated with the level of questionnaire- or EMA-derived distress or other psychosocial issues (Supplementary Table 6). Multilevel analyses were separately repeated for those with no prior CGM use before the study (n = 26) and for those who had already used a CGM system (n = 152). Standardized coefficients were highly comparable between the two groups (Supplementary Table 7), indicating that both groups showed a comparable level of association between CGM-derived parameters of glycemic parameters and EMA-derived distress ratings. Interestingly, the daily assessments did not seem to result in increased motivation for diabetes management, as the number of scans decreased over the study period (Supplementary Table 8). Furthermore, a sensitivity analysis showed that the daily number of scans can also be predicted by daily distress ratings and CGM-derived parameters of glucose management (Supplementary Table 8). Elevated diabetes distress at baseline did not substantially moderate the results, indicating comparable associations for those with and without elevated questionnaire-based diabetes distress (Supplementary Table 9).

CONCLUSIONS

The study introduced EMA-derived measures of diabetes and glycemia-specific distress to reflect the contextual and time-varying daily experiences of people with diabetes. This approach can be seen

Table 3—Daily level: estimates and standardized regression coefficients from two-level regression analysis predicting daily distress ratings from daily glucose parameters

	Daily diabetes distress (range 0–100)		Daily hypoglycemia distress (range 0–100)		Daily hyperglycemia distress (range 0–100)		Daily glucose variability distress (range 0–100)	
Predictor	Estimate (SD)	Std. coefficient (95% CI)	Estimate (SD)	Std. coefficient (95% CI)	Estimate (SD)	Std. coefficient (95% CI)	Estimate (SD)	Std. coefficient (95% CI)
Within-level predictors (daily assessment)								
% time with glucose <70 mg/dL (<3.9 mmol/L)+	0.79 (0.49)	0.04 (−0.01 to 0.09)	**8.78 (0.92)**	**0.26 (0.20–0.31)**	**−2.34 (0.90)**	**−0.06 (−0.09 to −0.01)**	1.07 (0.93)	0.03 (−0.02 to 0.08)
% time with glucose >180 mg/dL (>10 mmol/L)+	**2.23 (0.13)**	**0.41 (0.36–0.44)**	**−0.67 (0.25)**	**−0.07 (−0.13 to −0.02)**	**6.64 (0.26)**	**0.58 (0.54–0.61)**	**3.24 (0.23)**	**0.33 (0.29–0.38)**
Glucose CV+	**1.89 (0.34)**	**0.13 (0.09–0.18)**	**3.36 (0.57)**	**0.14 (0.09–0.19)**	**5.53 (0.57)**	**0.18 (0.14–0.22)**	**5.36 (0.59)**	**0.21 (0.16–0.25)**
Number of glucose scans	**0.07 (0.04)**	**0.06 (0.01–0.11)**	**0.39 (0.07)**	**0.20 (0.13–0.27)**	0.09 (0.07)	0.04 (−0.02 to 0.09)	**0.30 (0.06)**	**0.14 (0.08–0.20)**
Study day	−0.01 (0.05)	−0.004 (−0.03 to 0.03)	−0.09 (0.09)	−0.02 (−0.05 to 0.02)	**−0.21 (0.10)**	**−0.04 (−0.07 to −0.003)**	**−0.24 (0.09)**	**−0.05 (−0.08 to −0.02)**
Between-level predictors (baseline assessment or person-average of the 17-day period)								
Female sex	2.49 (2.26)	0.07 (−0.07 to 0.19)	−0.48 (1.79)	−0.02 (−0.16 to 0.13)	3.19 (2.57)	0.09 (−0.05 to 0.23)	0.50 (2.77)	0.01 (−0.14 to 0.14)
Diabetes distress (PAID sum score, range 0–100)	**0.37 (0.13)**	**0.38 (0.11–0.63)**	0.04 (0.11)	0.06 (−0.27 to 0.36)	**0.34 (0.15)**	**0.37 (0.07–0.66)**	0.01 (0.17)	0.01 (−0.30 to 0.32)
Depressive symptoms (CES-D sum score, range 0–60)	0.02 (0.23)	0.01 (−0.30 to 0.29)	0.03 (0.18)	0.03 (−0.31 to 0.35)	0.10 (0.26)	0.07 (−0.30 to 0.41)	−0.12 (0.26)	−0.07 (−0.38 to 0.22)
Interaction PAID × CES-D	0.002 (0.005)	0.10 (−0.36 to 0.57)	0.003 (0.004)	0.22 (−0.27 to 0.72)	−0.005 (0.006)	−0.26 (−0.71 to 0.29)	0.01 (0.01)	0.33 (−0.12 to 0.77)
Person-average % time with glucose <70 mg/dL (<3.9 mmol/L)+	1.14 (3.92)	0.02 (−0.15 to 0.17)	**−9.71 (3.36)**	**−0.31 (−0.47 to −0.11)**	−2.01 (4.17)	−0.05 (−0.22 to 0.13)	−9.17 (4.67)	−0.19 (−0.36 to 0.03)
Person-average % time with glucose >180 mg/dL (>10 mmol/L)+	−0.66 (0.74)	−0.07 (−0.24 to 0.08)	−1.26 (0.61)	−0.20 (−0.36 to 0.01)	**−3.21 (0.87)**	**−0.37 (−0.54 to −0.19)**	**−3.46 (0.94)**	**−0.35 (−0.50 to −0.20)**
Person-average glucose CV+	1.47 (2.82)	0.04 (−0.12 to 0.21)	3.79 (2.29)	0.16 (−0.04 to 0.32)	−3.90 (2.79)	−0.12 (−0.27 to 0.05)	2.90 (2.94)	0.08 (−0.12 to 0.20)
Person-average number of scans	0.14 (0.13)	0.08 (−0.05 to 0.23)	**−0.28 (0.19)**	**−0.24 (−0.42 to −0.04)**	0.21 (0.15)	0.13 (−0.04 to 0.32)	−0.21 (0.15)	−0.12 (−0.30 to 0.02)

N = 178. Two-level regression analysis using Bayes estimation with participant as nesting factor, respective daily distress rating as criterion, and within-level and between-level variables as predictors. Each analysis was controlled for study day and first autoregressive parameter as well as the person-average of glucose parameters for the 17-day period. Significant findings ($P < 0.05$) appear in boldface type. Std., standardized. +Unit of glucose parameters in increments of 10%.

Table 4—Comparison of associations between diabetes distress (questionnaire versus EMA) and glycemic management

CGM-derived glycemic parameters during the 17-day EMA period	Questionnaire assessment at the end of the EMA period		EMA (17-day EMA period)	
	Diabetes distress (20-item PAID sum score)	Diabetes distress short form (5 PAID items used in the EMA period)	Mean daily diabetes distress ratings (over the whole EMA period)	Time with diabetes distress (over the whole EMA period): % of days with elevated ratings (≥40)
Mean glucose	0.10 (P = 0.208)	0.13 (P = 0.085)	**0.25 (P = 0.001)**	**0.26 (P < 0.001)**
Glucose variability (CV)	−0.07 (P = 0.346)	−0.07 (P = 0.390)	0.03 (P = 0.744)	−0.002 (P = 0.979)
% time with glucose <70 mg/dL (3.9 mmol/L)	**−0.18 (P = 0.018)**	**−0.21 (P = 0.007)**	−0.14 (P = 0.058)	−0.14 (P = 0.064)
% time with glucose 70–180 mg/dL (3.9–10 mmol/L)	−0.07 (P = 0.385)	−0.10 (P = 0.214)	**−0.21 (P = 0.005)**	**−0.22 (P = 0.004)**
% time with glucose >180 mg/dL (10 mmol/L)	0.10 (P = 0.194)	0.13 (P = 0.086)	**0.22 (P = 0.003)**	**0.23 (P = 0.002)**

Depicted are Pearson correlation coefficients. N = 174.

as a measurement complementary to existing well-validated questionnaires to achieve a more comprehensive picture of diabetes distress. Measurement of diabetes and glycemia-specific distress on a daily basis showed that time with hyperglycemia distress was most prevalent among participants, followed by glucose variability distress, general diabetes distress, and hypoglycemia distress. Multilevel regression analyses also demonstrated that daily ratings of diabetes distress and glycemia-specific distress were significantly associated with actual glucose levels on that day. As expected, findings of the correlation analysis showed that EMA-based daily diabetes distress was more highly associated with glycemic management than questionnaire-based assessment of diabetes distress. That higher association held during the 17-day EMA period and at the 3-month follow-up. This difference is important, especially when one considers that diabetes distress as assessed by questionnaire at the end of the EMA period related to the same time frame as diabetes distress as assessed with EMA. This finding indicates that there was a benefit of daily assessment of distress with EMA because it was more sensitive to CGM-assessed glycemic management.

The psychometric properties of the proposed measures indicated reliable and valid assessment of daily diabetes distress and glycemia-specific distress. Sensitivity analyses indicate that the results were not dependent on level of engagement with the EMA prompts, prior CGM experience, or presence of elevated diabetes distress at baseline. The associations between distress as assessed with EMA and CGM data were highly comparable for those with and without elevated distress as assessed by questionnaire. This demonstrates the additional value of the daily distress ratings because associations of EMA-assessed distress seem not to be influenced by questionnaire-assessed diabetes distress.

Time with diabetes distress and time with glycemia-specific distress are additional PRO measures assessed by EMA in a person's daily life. These measures provide intuitive insights because mental well-being can be mapped as a percentage of days with elevated distress. This perspective on mental well-being can also be useful for intervention studies where effects of an intervention could be expressed as the reduction in number of days spent with elevated distress. The clinical usefulness of the proposed PRO measures can further be seen in the significant associations with questionnaire-based PRO measures at the 3-month follow-up, such as diabetes distress, depressive symptoms, fear of hypoglycemia, and fear of long-term complications. Furthermore, repeated daily assessment of these new measures allowed for analysis of associations between mental health variables and glycemic management at an individual level. These *n*-of-1 analyses can provide interesting insight for clinical practice with regard to individualized precision medicine and precision mental health (18,19,28). Three prototypical examples demonstrate how these *n*-of-1 patterns can help to better understand the associations within and between individuals. In the presented cases, the distress ratings of Person A may be reduced by improving glycemic management, while this interventional approach seems not to be promising for Person B, for whom distress and glycemia were independent. These examples demonstrate how the *n*-of-1 patterns could help to find potential starting points for individualized interventions. The suggested PRO measures could be included in just-in-time adaptive intervention strategies as tailoring variables for developing a precision mental health approach (19). The need for such intervention strategies became visible in this study because mere monitoring induced by the EMA approach did not lead to substantial changes in the distress ratings.

In interpreting these results, the following limitations must be considered. First, participants were recruited from an inpatient setting and had suboptimal glycemic management and likely other issues with diabetes management. These factors may have introduced a selection bias. Second, a stratified recruitment strategy was used based on elevated levels of distress and depressive symptoms. Thus, psychosocial problems at baseline might be overrepresented in this sample, potentially limiting generalizability. Third, amount of time in

a state of hypoglycemia was extremely small, possibly limiting associations and estimations of time with hypoglycemia distress. However, as all participants were equipped with an unblinded CGM, time in a state of hypoglycemia was representative of rates reported in previous studies with unblinded CGM use (29). Fourth, there could be bias due to reactivity introduced by the daily assessments. However, we found little evidence for such bias, as the EMA-derived measures did not change much over time and were not associated with the participants' level of adherence. Furthermore, participants' scan frequency decreased over the study days, also indicating little bias related to the daily assessments. Lastly, results are not generalizable to type 2 diabetes.

Taken together, daily ratings of diabetes distress and glycemia-specific distress showed significant cross-sectional associations in multilevel regression analyses as well as longitudinal associations with CGM-derived parameters of glycemic management. These associations hold promise for use of these EMA-based distress measures as more sensitive outcomes in intervention studies with analysis of the glucose-lowering effect of new treatment options, possibly resulting in higher effect sizes than those seen with questionnaires (10). This higher sensitivity to change via EMA has already been demonstrated in other conditions (30). However, it must be considered that this study did not include an intervention, so changes over time were not expected and could not be analyzed.

In sum, EMA-based distress measures offer additional, intuitive, and detailed insight into the daily experiences of people with diabetes. They complement the traditional assessment of a more stable, trait-like concept of diabetes distress via questionnaires with more responsive measures that are sensitive to contextual and time-varying effects. Questionnaire-based assessment of diabetes distress offers valuable clinical insights into possible problem areas and sources of distress that can be addressed in clinical practice (31) and can serve as a screening tool for depressive symptoms (21). Complimentary to this, assessment of distress via EMA can be used to identify the frequency, intensity, and variation of distress. The combination of EMA with CGM is particularly intriguing as a combination of daily measurement of glucose with daily assessment of PRO. That combination also made it possible to illustrate the idiosyncrasies of the associations between distress and glycemic management in *n*-of-1 analyses. Based on these results, we propose a new set of EMA-derived PRO measures: time with diabetes distress, time with hyperglycemia distress, time with hypoglycemia distress, and time with variability distress. In future research investigators could also implement a more "in the moment" analysis to possibly provide relevant information related to momentary fluctuations of glucose. More research is needed to further validate these measures and show their sensitivity in intervention studies.

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