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Real-Time Associations Between Glucose Levels and Fatigue in Type 2 Diabetes: Sex and Time Effects

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Abstract

Objective: Fatigue is a pervasive and serious complaint among aging adults with type 2 diabetes. Anecdotally, hyperglycemia was thought to cause fatigue, but prior cross-sectional analyses failed to find any relationship between glucose levels and fatigue. However, study methodology may have caused this relationship to be missed. Our aim was to use concurrent and continuous data across 5 days to examine real-time momentary relationships between glucose and fatigue levels by week, day, and time of day. Additionally, we explored how these relationships differed by sex. **Method:** Participants ($N = 54$, 51% male, 54% non-White) wore continuous glucose monitors and wrist actigraphy into which they inputted fatigue ratings 6–8 times daily during waking hours across 5 days. Generalized estimation equation models were used to explore the relationship between glucose and fatigue when averaged by week, day, and time of day. Differences by sex were also explored. **Results:** HbA1c and baseline and real-time fatigue were higher in women than in men. Baseline HbA1c and self-reported general fatigue were unrelated. Fatigue levels averaged by day and time of day were higher in women than in men ($p < .05$). Glucose and fatigue were significantly related at all levels of data (weekly, daily, and time of day) in women but not men. **Conclusions:** Our findings suggest that, when measured concurrently, glucose excursions may affect fatigue levels in women.

Keywords

real-time data, continuous glucose monitoring, diabetes symptoms

Fatigue in adults with type 2 diabetes is common, potentially debilitating, and a serious impediment to self-care (Hernandez et al., 2019; Kirk et al., 2015; Laranjo et al., 2015). Studies have consistently cited fatigue as a major barrier to physical activity in these adults (Kirk et al., 2015; Laranjo et al., 2015; Thomas et al., 2004). Fatigue of this nature can best be defined as a subjective perception of a decreased capacity to perform physical and/or mental tasks. This construct of fatigue differs from muscle fatigability, which can be measured objectively through tests of strength or time to fatigue within a given bout of exercise (Egan et al., 2013; Kirk et al., 2015; McGuire et al., 2014; Miquelon & Castonguay, 2016).

The cause of fatigue in type 2 diabetes, however, remains unknown (Fritschi et al., 2012; Lasselin et al., 2012a; Sudore et al., 2012). In prior cross-sectional analyses among patients with type 2 diabetes, fatigue has been associated with depression, diabetes-related distress, nonfatigue diabetes symptoms, obesity, inflammation, and low levels of physical activity (Fritschi et al., 2012; Hernandez et al., 2019; Lasselin et al., 2012a, 2012b; Nguyen et al., 2015; Park et al., 2015; Seo et al., 2015; Singh et al., 2016). Anecdotally, fatigue is thought to result from abnormal glucose levels; however, findings from cross-sectional analyses have revealed no evidence in support of a relationship between glucose levels and fatigue in patients with type 2 diabetes (Fritschi et al., 2012; Lasselin et al., 2012a; Park et al., 2015; Singh et al., 2016) or type 1 diabetes (Goedendorp et al., 2014; Menting et al., 2016). Findings from prospective trials have revealed only indirect or weak associations between glucose levels and fatigue (Hajos et al., 2011; Menting et al., 2016). In one prospective trial of the effects of starting insulin glargine on health-related quality of life (HR-QOL), Hajos et al. (2011) reported that, after the initiation of insulin therapy, both HbA1c and fasting glucose levels improved and fatigue symptoms decreased over 6 months in patients with type 2 diabetes. The authors did not, however, report any

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evidence of a direct relationship between glucose levels and fatigue. In another prospective trial of predictors of persistent fatigue in adults with type 1 diabetes, cognitive, behavioral, and clinical factors were the strongest predictors of persistent fatigue; however, HbA1c was not associated with fatigue at baseline (Menting et al., 2016).

Sex has been strongly associated with fatigue in patients with diabetes (Kirk et al., 2015; Nguyen et al., 2015; Valentine et al., 2009), with males generally reporting very low levels of fatigue. Women with type 2 diabetes consistently report significantly higher levels of fatigue than do men (Kirk et al., 2015; Nguyen et al., 2015). In a study of aging adults, women reported 63% greater fatigue than men did, and the fatigue was related to physical activity ($r = -.26$), physical fitness ($r = -.41$), and inflammation (as measured with the biomarker C-reactive protein [CRP, $r = .29$]), but these findings were only significant in women (Valentine et al., 2011).

Advancing our knowledge of physiological factors that cause fatigue is the first step in designing interventions to treat fatigue. Traditional data collection methods, including retrospective report, are vulnerable to biases and lack of contextual framing. These methods may diminish the ability to reveal real-time interrelationships between glucose and fatigue. Thus, it is possible that prior cross-sectional studies missed existing interrelationships between fatigue symptoms and glucose levels. Wearable technology, including continuous glucose monitoring systems (CGMS) and real-time symptom monitoring using actigraphy, have made it possible to gather real-time and objective data under free-living conditions, thus overcoming the problems associated with traditional research methods. Thus, the aim of the present study was to use this technology to examine real-time momentary relationships between glucose and fatigue levels by week, day, and time of day in adults with type 2 diabetes. Additionally, we explored how these relationships differed by sex.

Method

Participants

We recruited participants from a large Midwestern city in the United States through flyer distribution and Internet-based bulletin boards between September 2010 and December 2014. Adults were eligible if they were aged 45 years or older and had been diagnosed with type 2 diabetes for ≥6 months. We excluded individuals who were unable to ambulate without assistance or had chronic illnesses known to affect fatigue levels, including coronary heart disease or heart failure, chronic obstructive pulmonary disease, fibromyalgia, chronic kidney disease, cancer, or any condition requiring medication known to cause fatigue. Prior to enrolling in the study, all participants provided written, informed consent. The institutional review boards of the participating institution approved all study methods.

Method

Participants completed three visits over 6 days to our diabetes and exercise laboratory, housed within the University of Illinois at Chicago, College of Nursing. During the first visit, we obtained baseline health and demographic information, anthropometric measurements (height, weight, and waist circumference), and HbA1c (A1CNow+™; Bayer Healthcare, Sunnyvale, CA). The A1CNow+ system has been certified by the National Glycohemoglobin Standardization Program, and research has shown that the results obtained from the A1CNow+ are comparable to laboratory methods using high-performance liquid chromatography (Bode et al., 2007). Participants completed a 6-min walk test (6MWT) for measurement of physical-function status according to established guidelines (ATS statement: Guidelines for the six-minute walk test, 2002; Enright, 2003).

We measured baseline symptoms (fatigue and depression) at the first visit using the National Institutes of Health–supported Patient-Reported Outcomes Measurement Information System (PROMIS) computerized adaptive testing (CAT). CAT is a flexible, computer-driven assessment that selects items from a large item bank of questions that all measure the same construct. Using item response theory, CAT selects only those items that refine the estimate of a respondent's score on the domain being measured. Participants respond to 1 item per tablet computer screen, and their response to a previously administered item guides selection of the next item. The content is tailored to each individual, so use of CAT means that individuals are not presented with questions that are not relevant to them. Measurement precision is calculated for each unique location along the continuum of a concept; thus, high measurement precision is achieved when each individual responds to a small set of tailored (individually calibrated) items. The CAT is brief; most respondents require only 4–12 items to achieve a precise score. All PROMIS assessments reflect the patient-reported outcome level from the prior 7 days and are not disease-specific. CAT scores are reported on a T-score metric (mean = 50; standard deviation [*SD*] = 10), which is aligned with the distribution of scores in the U.S. general population. The PROMIS measures (fatigue and depression) demonstrate strong validity across populations (Cella et al., 2016; Cook et al., 2016).

We measured real-time glucose using the Medtronic CGMS iPro®2 continuous glucose monitoring system (CGMS; Medtronic, Northridge, CA). We placed the CGMS sensor on the abdomen to collect samples from interstitial fluid over two 3-day periods. Participants performed three to four self-monitored blood glucose tests daily for CGMS calibration. We downloaded glucose data into the Medtronic CareLink® Management Software (Northridge, CA) as 5-min averages and then exported them as Excel data files for use in the analysis.

We collected real-time, self-reported fatigue data using a wrist accelerometer (Actiwatch-Score®; Philips Respironics, Bend, OR) placed on the nondominant wrist. We chose the Actiwatch-Score, which measures sleep and activity, for this

study because of its capability to record real-time, self-reported ratings of fatigue. We instructed participants to wear the watch continuously, except when they were bathing/showering. Participants entered self-reported fatigue scores from 0 (*no fatigue*) to 10 (*worst fatigue possible*) into the Actiwatch-Score, which was programmed to deliver vibratory reminders for scoring 6–8 times randomly during waking hours. We downloaded fatigue data from the Actiwatch-Score wrist accelerometer into Respironics Actiware software Version 5.70.1 (Philips Respironics, Bend, OR). Data epochs were recorded in 30-s intervals per the device specifications and then averaged for total wear time by week and day. We identified nonwear time as any bout of consecutive activity counts of 0 per min lasting $\geq$90 min that was not classified as sleep/rest time by the software. We considered data valid if wear time was $\geq$600 min/day.

Participants wore the CGMS and wrist accelerometer continuously starting Day 1 throughout the following 5 days. We replaced the CGMS after 3 days (per the manufacturer's instructions) during the second visit. No other data were collected during this visit. The iPro2 system does not provide visual reports of real-time blood glucose values, and we chose it to prevent participants from making aggressive changes in their diabetes management during the time that they were wearing the monitor. The participants returned to the lab for the third visit to return their devices.

Data Management and Statistical Analyses

Statistical analyses were conducted using IBM SPSS Version 24 (Chicago, IL). Descriptive data analyses (i.e., independent *t* test, Mann–Whitney *U* test, and χ^2 test) were conducted to present participant characteristics. Pearson correlation analyses were used to assess cross-sectional relationships between baseline measures of fatigue and glucose control and 5-day averages of fatigue and glucose scores. Generalized estimating equation (GEE) models were used to assess the real-time associations between fatigue and glucose levels by day and time of day. We chose GEE models over ordinary least squares regression models for several reasons. GEE models do not require independence of data and thus are able to overcome problems with correlated data arising from repeated fatigue measurements on the same individual. Additionally, GEE models are able to handle time-varying predictors and are more flexible for missing data than other models (Liang & Zeger, 1993). The fatigue scores and glucose levels were standardized by transforming them into *Z*-scores to account for differences in scale. Significant baseline variables were included as covariates in the models. To address our second aim, sex was treated as a moderating variable in separate GEE models. The required sample size for the daily repeated-measure GEE models of fatigue in this study was calculated with the power analysis software R longpower. The sample size of 94 subjects with 5 days of measurements satisfied the minimum power (.80; Donohue et al., 2013). Significance was set at $p < .05$.

Results

A total of 164 individuals inquired about the study. We screened 157 of these individuals for eligibility, finding that 6 were ineligible due to walking impairments, age range, or a diagnosis of type 1 diabetes (T1DM). Of the 151 eligible individuals, 49 potential subjects declined to enter the study, failed to attend the first scheduled appointment, or never called to schedule an appointment. In addition, one participant was enrolled twice, so we used only the first data set in the analyses. A total of 101 subjects completed the study; however, we excluded data from seven subjects due to failure of real-time data collection devices or failure to enter fatigue levels while wearing the devices. Data from 94 adults with type 2 diabetes met the criteria for inclusion in the analyses. The sample characteristics are detailed in Table 1.

Half of the participants were male (51%), and just over half were African American (54%). The mean duration of diabetes was 8.3 years; most (71%) were treated with metformin, and 32% were treated with insulin in combination with oral antihyperglycemic agents. In general, the participants were overweight or obese (mean body mass index [BMI] 33.1 $\pm$ 6.8 kg/m^2). Most participants had HbA1c values slightly higher than the recommended $\leq$53.0 mmol/mol (7%), with an average of 61 $\pm$ 23 mmol/mol (7.6% $\pm$ 2.0). We noted significant differences between men and women in HbA1c (54 mmol/mol [7.1%] vs. 65 mmol/mol [8.1%], respectively, $p = .009$) and BMI (30.8 $\pm$ 5.3 kg/m^2 vs. 35.4 kg/m^2 $\pm$ 7.4, respectively, $p = .001$).

Baseline PROMIS fatigue scores for the sample were higher than the U.S.-normed *T* score of 50, and scores for women were higher than those for men (52.9 $\pm$ 7.3 vs. 47.8 $\pm$ 8.7, respectively, $p < .01$). Fatigue levels averaged by week (across Days 2–6) were 2.5 $\pm$ 1.9 in men and 3.2 $\pm$ 1.6 in women ($p = .108$). Average daily fatigue scores were significantly higher in women than in men for Days 2–4 ($p < .05$) but not Days 5 and 6 (Figure 1).

When separated into categories by time of day (night [11:00 p.m.–5:59 a.m.], morning [6:00 a.m.–11:59 a.m.], afternoon [12:00 p.m.–5:59 p.m.], and evening [6:00 p.m.–10:59 p.m.]), fatigue scores during the night, afternoon, and evening were all significantly higher in women than in men ($p < .01$; Figure 2).

Neither weekly nor daily average sensor glucose levels differed between men and women. Average evening sensor glucose levels were significantly higher in women than in men (175.1 $\pm$ 58.7 vs. 163.7 $\pm$ 61.3 mg/dl [9.7 $\pm$ 3.3 vs. 9.1 $\pm$ 3.4 mmol/L], respectively, $p < .05$), but there were no other significant differences in time-of-day averages.

When we ran bivariate correlation analyses using baseline variables previously reported to be associated with fatigue (BMI, sex, depression, habitual activity, age) and added glucose control (HbA1c) into the analyses, we found that baseline fatigue (PROMIS) was significantly associated with depression ($r = .526$), BMI ($r = .315$), and female sex ($r = .306$; all *p* values < .01) but not with age, activity level, or HbA1c.

Table 1. Demographic and Disease Characteristics and Baseline Fatigue and Depression Scores of Participants.

Variable	All Subjects ($N = 94$)	Males ($n = 48$)	Females ($n = 46$)	p Value
Demographic				
Age (years), mean ± *SD*	58.3 ± 9.0	59.8 ± 10.4	56.7 ± 6.9	.089
Hispanic ethnicity, *n* (%)	11 (11.7)	4 (9.3)	7 (14.6)	.355
Race, *n* (%)				.026
White	31 (33.0)	21 (44)	10 (21.7)	
African American	51 (54.3)	22 (45.8)	29 (63)	
Asian American	3 (3.2)	2 (4.7)	1 (2.1)	
Native American/Pacific Islander	2 (2.1)	1 (2.1)	1 (2.1)	
Diabetes-specific				
DM duration (years), mean ± *SD* (range)	8.3 ± 6.9 (1–30)	8.4 ± 7.5 (1–30)	8.2 ± 6.3 (1–28)	.894
Metformin, *n* (%)	67 (71.3)	32 (66.7)	35 (76.1)	.590
Insulin therapy, *n* (%)	30 (32.0)	15 (34.9)	15 (32.6)	.834
HbA1c, mean ± *SD* mmol/mol	61 ± 23.0	54 ± 16.4	65 ± 24	.009
NGSP (%)	7.6 ± 2.0	7.1 ± 1.5	8.1 ± 2.2	
BMI (kg/m^2), mean ± *SD* (range)	33.1 ± 6.8 (20.1–67.3)	30.8 ± 5.3 (20.1–44.5)	35.4 ± 7.4 (24.6–67.3)	.001
Baseline PROMIS score				
Fatigue, mean ± *SD*	50.6 ± 8.3	47.8 ± 8.7	52.9 ± 7.3	.005
Depression, mean ± *SD*	50.1 ± 7.6	48.9 ± 7.6	51.0 ± 7.6	.255

Note. DM = diabetes mellitus; NGSP = National Glycohemoglobin Standardization Program; BMI = body mass index; PROMIS = Patient-Reported Outcomes Measurement Information Systems.

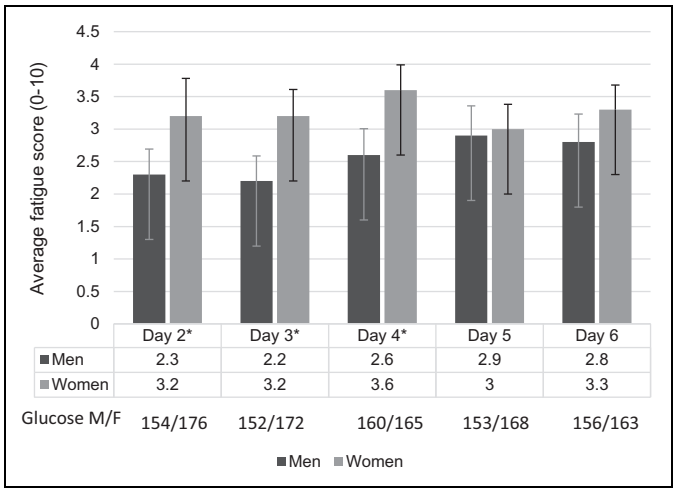

Figure 1. Daily average fatigue scores by sex. Error bars represent 95% confidence interval. *$p < .05$.

Momentary Associations Between Glucose Level and Fatigue by Week

We explored potential associations between fatigue scores and glucose levels averaged across 5 days using bivariate analyses. In all participants, average weekly glucose levels were unrelated to average weekly fatigue levels ($r = .203$, $p = .082$). When we analyzed subgroups based on sex, we found that the average weekly fatigue level in males was not associated with average weekly glucose levels ($r = .021$, $p = .905$); however, in women, we found that the average weekly fatigue level was significantly associated with average weekly glucose levels ($r = .378$, $p = .016$). We adjusted all analyses for BMI and depression.

Momentary Associations Between Glucose Level and Fatigue by Day

We used GEE models to explore potential relationships between daily averages of fatigue scores and glucose levels. We standardized fatigue and glucose data to account for scale differences. In the combined sample, daily average fatigue scores were modestly associated with daily average glucose level ($\beta = .160$, $p = .038$). When we looked at men and women separately, we found that daily average fatigue scores were related to daily average glucose level in women ($\beta = .226$, $p = .006$) but not in men ($\beta = .069$, $p = .571$). After controlling for depression and BMI, we found that only daily average glucose level significantly predicted daily average fatigue score in women ($\beta = .205$, $p = .012$), while only baseline depression was modestly associated with daily average fatigue score in men ($\beta = .051$, $p = .001$).

Momentary Associations of Glucose Level and Fatigue by Time of Day

In the combined sample, when we averaged fatigue values and glucose levels by time of day and controlled for BMI, sex, and depression, fatigue and glucose levels were associated at all times of day ($\beta = .123$, $p = .05$) except morning. When we analyzed data for women and men separately, however, fatigue was related to glucose ($\beta = .163$, $p = .011$) during the night, the afternoon, and the evening in women but was not related to glucose at any time of day in men ($\beta = .116$, $p = .313$). After controlling for depression and BMI, we found that only glucose levels significantly predicted fatigue in women ($\beta = .1431$, $p = .024$), while only baseline depression was modestly associated with fatigue in men ($\beta = .051$, $p = .001$).

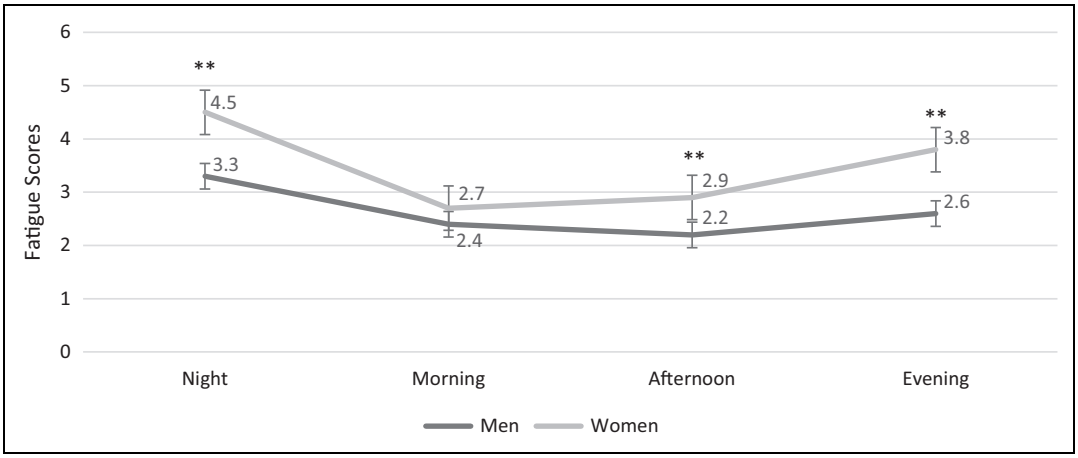

Figure 2. Average fatigue levels by time of day and sex.

Discussion

This study is the first to use ecological momentary assessment to study the real-time relationships between glucose levels and fatigue symptoms in adults with type 2 diabetes. The findings provide evidence that real-time glucose levels and fatigue symptoms are associated. In ecological momentary analyses, using CGM and real-time fatigue ratings, glucose and fatigue were related when the data were averaged by day and by time of day but not by week. When we ran separate analyses by sex, these relationships remained significant only in women. As we discussed above, there have been no reports of a cross-sectional relationship between fatigue levels and glucose control as measured by HbA1c (Fritschi et al., 2012; Park et al., 2015; Singh et al., 2016).

In the present study, 62% of women and 45% of men reported baseline fatigue scores higher than the U.S. adult population-normed *T*-score of 50. Women reported higher levels of fatigue than did men retrospectively at baseline and in real time for three of the five study days and for all times of day except for morning. Recent large descriptive trials have addressed patient-reported well-being and symptoms in aging adults. These studies provide strong evidence that women consistently report higher levels of fatigue than men (Hinz et al., 2018; Piepenburg et al., 2019; Sidani et al., 2019; Thakral et al., 2019). There are fewer reports of sex differences in fatigue symptoms among patients with diabetes. Findings from one cross-sectional study of the effects of diabetes symptoms on self-care behaviors, however, included similar sex differences, with women reporting higher levels of diabetes-related symptoms, including fatigue, than men (Kirk et al., 2015). Valentine and colleagues (2009) studied sex differences in predictors of fatigue among community-dwelling older adults and included CRP, activity levels, obesity, depression, and sleep in their model. Similar to our findings, women reported higher levels of fatigue than did men. Fatigue in women was related to percent body fat, CRP, self-reported physical activity, and depression, while only depression was significantly related to fatigue in men. The reason for these findings is not clear. As in Valentine's study, we found no significant difference in baseline depression symptoms between men and women in the present study, though men reported less depression than women (48.9 $\pm$ 7.6 vs. 51.0 $\pm$ 7.6, respectively). Fatigue is a symptom of depression, and studies have shown it to be associated with depression in patients with type 2 diabetes (Fritschi et al., 2012; Hernandez et al., 2019; Jain et al., 2015). Researchers have also found that depression mediated the relationship between glucose control and fatigue symptoms in adults with type 2 diabetes (Park et al., 2015) but did not assess sex differences in their studies. It is possible that men view fatigue as a sign of weakness and therefore do not report fatigue symptoms as frequently as women do. Further studies are thus needed that examine the deeper meaning of fatigue.

Recent studies of fatigue in patients with diabetes have revealed no significant relationships between retrospective self-reported fatigue symptoms and overall glucose control (HbA1c; Fritschi et al., 2012; Goedendorp et al., 2014; Lasselin et al., 2012a; Park et al., 2015; Singh et al., 2016) when studied cross sectionally. Ecological momentary assessment methods have been effective in describing the interrelationships between physical-activity behaviors and symptoms of fatigue and pain in osteoarthritis (Murphy et al., 2008; Murphy & Smith, 2010). By calculating weekly, daily, and time-of-day averages of real-time glucose levels and fatigue symptoms across multiple days for each participant, we were able to reveal momentary relationships between glucose and fatigue symptoms in adults with diabetes.

There were several limitations of the present study, including missing data due to participants not entering fatigue scores. The watch into which the fatigue scores were entered was programmed to vibrate and display lights as a reminder to enter a fatigue score. Participants may have become less responsive to signals as time went on. However, these missing data should not have posed a problem as we had $\geq$3,000 fatigue scores included in the models. The number of fatigue scores did decrease by the end of the week, which might explain the lack of a significant difference between men and women in average

daily fatigue scores for Days 5 and 6. Per the manufacturer's instructions, we replaced the CGMS sensor after 3 days of wear. During the interval between ending one sensor session and beginning the second, we lost some glucose data also.

The use of GEE models improved our ability to overcome the issue of missing data (Liang & Zeger, 1993). Additionally, by using a repeated-measures, within-subject design across multiple days, the amount of data was still greater than that of prior studies of fatigue in diabetes. In our final analyses, the β and *r* coefficients, though significant, were modest.

Our study was strengthened through use of real-time measures of glucose and fatigue across multiple days. Use of real-time momentary assessments to capture participant experiences or symptoms overcomes problems associated with retrospective data collection measures. Most pertinently, it avoids recall issues. Use of multiple and repeated assessments over time enhances reliability of the data by capturing biological or psychological phenomena as they occur in real time. Use of these data is more representative of participants' real-life experiences and allows for a more detailed analysis of contextual factors that surround the event or symptoms of interest (Schlicht et al., 2013; Shiffman et al., 2008). However, real-time momentary methods have been surprisingly underutilized in diabetes research. Prior studies of the relationship between glucose and fatigue used retrospective data and cross-sectional analyses, which may explain their lack of significant findings.

Fatigue is common in patients with diabetes, but further research is necessary to clarify the biological and behavioral mechanisms for this fatigue. The current understanding of fatigue in patients with diabetes is limited. Emerging evidence suggests that fatigue and other diabetes-related symptoms (sleep quality, neuropathic pain, and depression symptoms) are related to systemic chronic low-grade inflammation caused by the metabolic milieu in these patients (Lasselin & Capuron, 2014; Lasselin et al., 2012b). We were able to find a direct relationship between glucose levels and fatigue, but only a modest relationship and only in women. This finding is relevant for nursing practice as it suggests both the need to assess fatigue in the clinic setting and the possibility that effective interventions may differ by sex. Improving glucose levels across hours and days may improve fatigue levels in women, while in men the presence of fatigue symptoms may indicate the presence of underlying depression. Future studies should address momentary fatigue levels in relationship to the ability to carry out self-care activities in aging adults with type 2 diabetes.

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