Journal of Clinical & Translational Endocrinology 34 (2023) 100328

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Utilizing a quality of life tool to examine the presence of fatigue in subjects with diabetes mellitus

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ARTICLE INFO

Keywords:
Quality of Life
Fatigue
Diabetes mellitus
Diabetic neuropathy
Cognitive fatigue
Physical fatigue

ABSTRACT

Introduction: The prevalence of fatigue in patients with diabetes mellitus (DM) can be as high as 50 %. Physical, mental, and psychosocial components of fatigue negatively impact quality of life (QOL), morbidity and mortality. Several tools have been developed to address fatigue, but none specifically for measuring fatigue in DM. The aim of this study was to assess the impact of diabetes and neuropathy on fatigue using the Norfolk QOL-Fatigue (QOL-F) survey.

Methods: 605 adult participants from *[Anonymous]* were recruited (400 subjects with type 1 or type 2 DM and 205 subjects without diabetes (controls)). All subjects completed the Norfolk QOL-F. Demographics, weight, BMI, and duration of diabetes were obtained. The Norfolk QOL-F, a 35-item validated questionnaire, assesses five domains: subjective fatigue, physical and cognitive fatigue, reduced activities, impaired activities of daily living, and depression.

Results: Subjects with DM reported significantly higher fatigue total scores (52.63vs33.89, $p < 0.0001$) and in all five domains when compared to controls. Patients with DM with neuropathy were significantly more fatigued than those without (59.72vs27.83, $p < 0.0001$). Fatigue scores in patients with DM without neuropathy were similar to controls (27.83vs33.89, $p = NS$). In multivariate analysis, age, gender, and presence of neuropathy significantly impacted fatigue scores.

Conclusions: The Norfolk QOL-F questionnaire can potentially identify the impact of chronic diseases such as diabetes on fatigue. Assessing the different components of fatigue is important for clinicians in improving disease management and outcomes. Further investigations are needed to confirm these observations in specific cohorts with other comorbidities.

Introduction

Diabetes mellitus is a leading cause of adult disability and is a significant global health problem. According to the CDC, over 37 million Americans, or 11 % of the US population, has diabetes, and the prevalence continues to steadily increase annually. Furthermore, diabetes was the seventh leading cause of death in the United States in 2019 [1]. Patients with diabetes suffer from a variety of symptoms and complications that have negative impacts on quality of life (QOL) and are associated with increased morbidity and mortality. A patient's health-related QOL is a subjective assessment of their ability to function in a satisfactory manner that aligns with their needs and values in relation to their perceived physical, mental, and social well-being that may be affected by the presence of disease or treatment. Fatigue has consistently been identified as one of the most distressing complaints in patients with diabetes. Prevalence of fatigue in diabetes varies between 23 % and 50 % [2,3], has been associated with numerous contributing factors, and can have a profound impact on QOL [4]. Physiological, psychological and social/situational factors can influence the development and progression of fatigue. As a result, these factors can cause a vicious cycle of downstream effects such as deterioration in diabetes self-management, decreased physical activity and function, worsened eating behaviors,

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https://doi.org/10.1016/j.jcte.2023.100328
Received 7 March 2023; Received in revised form 12 June 2023; Accepted 20 October 2023
Available online 10 November 2023

and ultimately increased severity of disease and decreased QOL [4]. Despite this knowledge, few studies have tried to elucidate the multidimensional aspects of fatigue in diabetes in a comprehensive way.

Fatigue is a word that is often used in casual conversation and is considered as a normal occurrence in everyday life. It is commonly described by patients as feelings of "tiredness," "weakness" and "malaise," and is one of the most common complaints in primary care with prevalence rates of 4 to 45 % depending on settings and methods used to assess fatigue [6–8]. Despite its commonality, it should still be acknowledged as a major, multidimensional symptom in medicine that is encompassed by physical, mental, and psychosocial components that can affect all aspects of QOL ranging from mood and physical functioning to activities of daily living (ADLs) [5]. Due to its complexities and subjectivity, fatigue has historically been difficult to translate into a quantifiable measure. To date, there are a number of fatigue scales that have been validated as adequately measuring fatigue and QOL, such as the nine-item Fatigue Severity Scale (FSS) [9], the Fatigue Assessment Scale (FAS) [10], and the Visual Analog Fatigue Scale (VAFS) [11]. Several studies have demonstrated the ability for these scales to be applicable to chronic diseases, such as diabetes [2,12,13,14]. However, limited tools are sensitive to capturing the multidimensional aspects of fatigue in patients with diabetes and its impact on QOL and disease management [4,15].

The Norfolk Quality of Life-Fatigue (QOL-F) is a recently validated tool that measures the cognitive, physical, and emotional aspects of fatigue [16]. It includes 35 items divided into 5 domains as follows: 1) subjective fatigue, 2) physical and cognitive problems due to fatigue, 3) depression, 4) reduced activities, and 5) impaired ADLs. The aim of this study was to investigate the utility of the Norfolk QOL-Fatigue to detect the impact of diabetes and neuropathy on different aspects of fatigue and identify associated factors. We hypothesize that cognitive and physical measures of fatigue will be influenced by the presence of diabetes and diabetic neuropathy when compared to subjects without diabetes.

Material and methods

Study design and recruitment

This study utilized a population-based, cross-sectional study design, in order to examine different factors as they relate to the presence of fatigue at one point in time. Study subjects consisted of voluntary participants from *[Anonymous]*. Inclusion criteria included male and female subjects, between the ages of 18 and 79, of any ethnic and racial backgrounds, with and without type 1 or type 2 diabetes mellitus (T1DM; T2DM). Exclusion criteria included women who were pregnant or had recently given birth and were lactating.

All study participants completed the Norfolk Quality of Life-Fatigue (QOL-F) questionnaire concerning their physical and cognitive responses to fatigue. Additionally, participants with T1DM or T2DM also completed the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire, a validated, 35-item, self-administered questionnaire that investigates the presence of diabetic peripheral neuropathy (DPN) based on reported symptoms [17]. Participants with Norfolk QOL-DN scores $\geq$ 10 were classified as DM with DPN, based on prior studies showing good correlations between Norfolk QOL-DN scores and clinical/electrophysiological diagnosis of PN. Demographics including age, gender, race and ethnicity, weight, height, BMI and duration of diabetes (if applicable) were obtained from all participants. Participants were identified and recruited from the *[Anonymous]*, the *[Anonymous]* campus, local primary care and family medicine clinics, and by using approved system-wide e-mail announcements, database searches, and web-based advertising in public groups on social media platforms. Participants were also recruited from local gyms, community centers, health fairs, and community events via approved paper fliers that contained scannable QR codes using a mobile device. Questionnaires were completed in person with pencil and paper (pre-COVID-19 pandemic) or online (after COVID-19 pandemic) as described below. The protocol was approved by the *[Anonymous]* Institutional Review Board and performed in accordance with the Declaration of Helsinki, with informed consent obtained from all participants before study participation.

Changes in methodology post-COVID-19 pandemic

Following the COVID-19 pandemic, participants had the option of completing the questionnaires either on site or online via the REDcap platform.

Norfolk QOL-Fatigue questionnaire

The Norfolk QOL-Fatigue questionnaire is a 35-item validated tool that was originally designed to assess and distinguish between physical, cognitive, and emotional aspects of fatigue in different age groups [17]. Item development was conducted and distilled through Delphi method, structured interviews and focus groups, pooling questions from several different sources including the Norfolk QOL-DN, the SF-36 (Short Form 36) self-reported functional and well-being measures, the CES-D (Center for Epidemiologic Studies Depression Scale), and the PROMIS (Patient Reported Measurement Information System) item bank from the NIH for measuring QOL with an item-response theory approach. The distilled tool was validated through exploratory and confirmatory factor analysis (encompassing validation of its construct, convergent and face validation, and reliability testing) in 400 + disease-free, multiethnic participants ranging from 30 to 79 years old (51 % female). The tool's validation showed good internal consistency and strong inter-factor correlations, ranging from 0.690 to 0.830. Thirty-five items loaded clearly (0.617 or higher) on each of the five factors that were designated as constituents of five scales: 1) subjective fatigue, 2) physical & cognitive problems due to fatigue, 3) depression, 4) reduced activities, and 5) ADLs. It is a self-administered questionnaire with a 7-day recall time. Responses are graded from 0 (never/none of the time/not a problem) to 4 (always/all of the time/severe problem) with higher scores indicating higher degree of fatigue symptoms, problems or functional limitations with a total score ranging from 0 to 140 (Appendix 1).

Data analysis

Normal distribution of each continuous and categorical variable was confirmed by a normality test to ensure all appropriate assumptions were met for each statistical test. Parametric (Student's T-test) and non-parametric tests (Wilcoxon signed-rank test) were used to compare differences between groups, depending on sample size and distribution. Pearson Correlation Coefficient and simple linear regression were initially used to assess potential associations between variables. Multivariate regression models (e.g., OLS regression) were then used incorporating confidence intervals so that point estimate results were not over-interpreted. Regression models included covariates (e.g., age, gender, race, weight, DM duration, DPN) as appropriate and were correlated with measures of fatigue. All statistical analyses were performed using JMP v10.0 (SAS Institute Inc., NC), with the risk of Type I error set at $\alpha = 0.05$.

Results

Demographic characteristics of the cohort

Complete and validated survey responses were received from 605 adult subjects (400 patients with DM, 205 controls). Of the patients with diabetes, 72 (18 %) and 328 (82 %) adults were diagnosed with T1DM and T2DM respectively, and of all adults with DM, 311 (78 %) reported having DPN symptoms.

Demographic characteristics are provided in Table 1. Participants with diabetes were older, and had significantly higher BMI compared to those in the control group (32.28 ± 0.87 vs 29.25 ± 1.1, p < 0.0001). Mean duration of diabetes in years was 13.67 ± 1.12.

QOL-F scores

Subjects with DM reported significantly higher fatigue scores in all five domains when compared to the control group (Table 2). Subjects with T1D had a similar Total Fatigue Score to subjects with T2D (54.5 ± 24.7 vs 52.2 ± 27.3, p = 0.505). However, the T1D cohort had higher scores in the cognitive & physical (17.1 ± 8.6 vs 14.5 ± 8.8, p = 0.0233) and ADLs domains (4.4 ± 3.9 vs 3.4 ± 3.7, p = 0.0288) in comparison to the T2D cohort. Of note, the T1D cohort was significantly younger (39.4 ± 15.3 vs 58.2 ± 12.5 years, p < 0.0001), leaner (161.6 ± 35.9 vs 211.5 ± 52.8 lbs, p < 0.0001), had a higher percentage of White Americans (79 % vs 35 %, p < 0.0001) and more frequent DPN symptoms (89 % vs 75 % p = 0.00068).

Subjects with DM with DPN were significantly more fatigued than those without DPN in all five domains as well (Table 3).

Associations between fatigue scores and demographic & metabolic factors

On bivariate linear regression analysis, significant negative linear correlations were observed between age and fatigue scores with younger participants reporting more fatigue in both cohorts (Table 4). No significant correlations were detected between weight or duration of diabetes and reported fatigue in the diabetes and control cohorts (Table 4). Females were significantly more fatigued than males in the control group. Female participants with DM showed higher fatigue scores, although these were not statistically significant (Fig. 1). No significant differences in fatigue scores were observed between African Americans (AA) and non-AA in both cohorts except for non-AA having higher ADLs sub-scores in the diabetes cohort (Fig. 1).

Table 1
Demographic characteristics in subjects with diabetes and controls.

	Diabetes Mellitus (n = 400)	Controls (n = 205)	p-value*
Age *(years)*	54.84 (53.37–56.31)	50.20 (48.11–52.28)	**0.0004**
Sex			
Female	229 (57)	135 (66)	0.0533
Male	170 (43)	70 (34)	
Race			
African American	206 (52)	85 (41.5)	
White	171 (43)	111 (54)	0.0455
Native American	6 (1)	1 (0.5)	
Asian/Pacific Area	17 (4)	8 (4)	
Ethnicity			
Non-Hispanic	392 (98)	194 (95)	0.0453
Hispanic	8 (2)	11 (5)	
BMI *(kg/m^2)*	32.22 (31.36–33.07)	28.61 (27.75–29.46)	**<0.0001**
Weight *(lbs)*	202.5 (197.2–207.8)	179.9 (174.2–185.7)	**<0.0001**
Waist circ *(inches)*	40.47 (39.55–41.40)	34.51 (33.19–35.84)	**<0.0001**
Duration of DM *(years)*	13.67 (12.55–14.79)	N/A	N/A
T1DM/T2DM	72/328 (18/82)	N/A	N/A
DN *(Y/N)*	311/89 (78/22)	N/A	N/A

Data presented as mean (95 % CI) or n (%); *Student's *t*-test for continuous variables and Fisher's Exact test for categorical variables. BMI = Body Mass Index; DM = diabetes mellitus; DN = diabetic neuropathy; lbs = pounds; T1DM = Type 1 Diabetes; T2DM = Type 2 Diabetes; Y = yes; N = no.

Table 2
QOL-F scores in subjects with diabetes vs controls.

	Diabetes Mellitus (n = 400)	Controls (n = 205)	p-value*
Total Fatigue	52.63 (49.99–55.27)	33.89 (30.40–37.38)	**<0.0001**
Subjective Fatigue	16.98 (16.18–17.77)	12.62 (11.49–13.74)	**<0.0001**
Cognitive & Physical Problems	14.95 (14.08–15.81)	9.14 (7.99–10.29)	**<0.0001**
Depression	10.53 (9.95–11.11)	7.26 (6.45–8.07)	**<0.0001**
Reduced Activities	6.60 (6.21–6.99)	3.97 (3.47–4.46)	**<0.0001**
ADLs	3.57 (3.20–3.94)	0.89 (0.56–1.23)	**<0.0001**

Data presented as mean (95 % CI); * Student's *t*-test or Wilcoxon signed-rank test depending on distribution. ADLs = activities of daily living.

Table 3
QOL-F scores in subjects with diabetes with and without diabetic neuropathy vs controls.

	DM with DN (n = 311)	DM without DN (n = 89)	Controls (n = 205)	p-value*
Total Fatigue	59.72 (56.98–62.47)	27.83 (23.93–31.74)	33.89 (30.40–37.38)	**<0.0001**[#]
Subjective Fatigue	18.64 (17.79–19.45)	11.17 (9.67–12.67)	12.62 (11.49–13.74)	**<0.0001**[#]
Cognitive & Physical Problems	17.20 (16.29–18.10)	7.09 (5.79–8.70)	9.14 (7.99–10.29)	**<0.0001**[#]
Depression	11.87 (11.24–12.49)	5.87 (4.91–6.82)	7.26 (6.45–8.07)	**<0.0001**[#]
Reduced Activities	7.55 (7.14–7.96)	3.28 (2.70–3.86)	3.97 (3.47–4.46)	**<0.0001**[#]
ADLS	4.47 (4.05–4.89)	0.43 (0.20–0.66)	0.89 (0.56–1.23)	**<0.0001**[#]

Data presented as mean (95 % CI); *ANOVA or Wilcoxon signed-rank test depending on distribution with post-hoc Turkey ([#]DM with DN vs DM without DN and Controls). ADLs = activities of daily living; DM = diabetes mellitus; DN = diabetic neuropathy.

Impact of COVID-19 pandemic and in-person vs web-based questionnaires completion

Within the DM group (n = 400), 252 participants were recruited pre-COVID-19 pandemic and 148 participants were recruited post-pandemic. Within the control group (n = 205), 79 participants were recruited pre-COVID-19 pandemic and 126 participants were recruited post-pandemic. Subjects who were recruited post-pandemic had significantly higher total fatigue scores than those recruited pre-COVID-19 pandemic in both cohorts as seen in Fig. 2.

Sixty percent of participants completed questionnaires in person (n = 360) and 40 % completed them virtually through the RedCap platform. In the DM cohort, 70 % completed questionnaires in person versus 39 % in the control group. Table 5 shows differences in fatigue scores in subjects completing the questionnaires in person versus virtually for both cohorts.

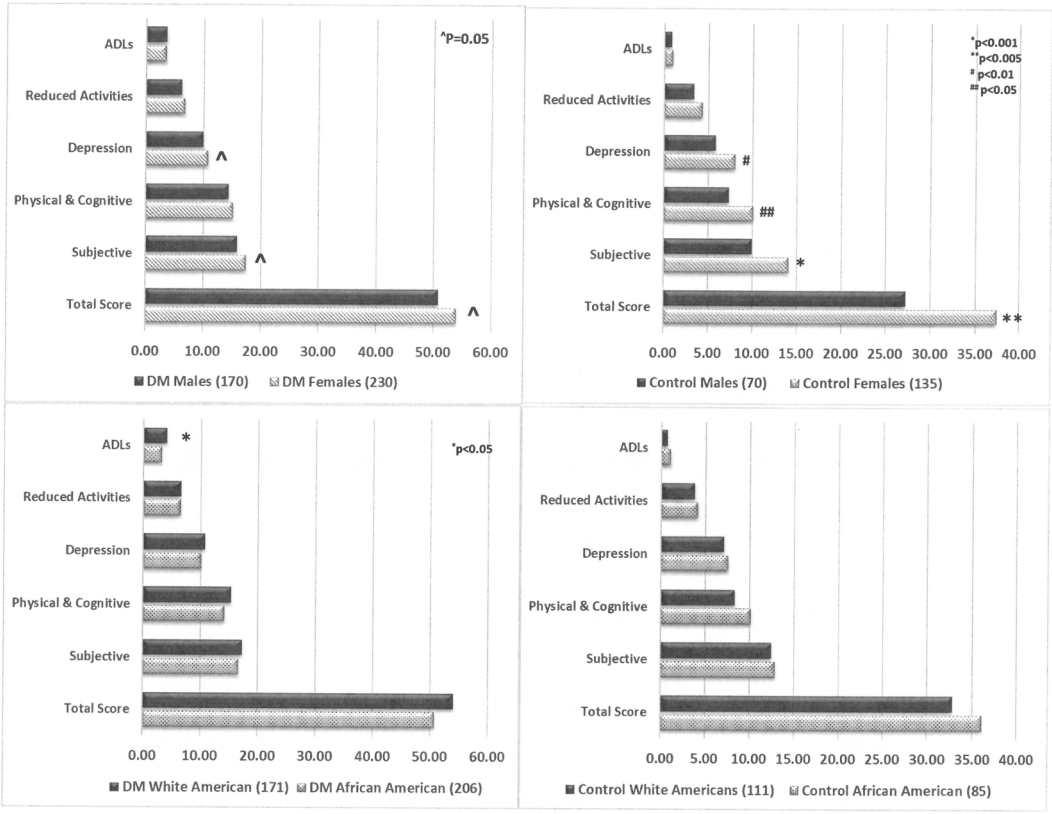
Multiple regression analysis to identify factors influencing fatigue in both cohorts

Multivariate regression models were created for both DM and control groups, consecutively adding predictor variables to the model one at a time (forward selection) and assuring all assumptions were met at every step. Tables 6 & 7 show the models for each cohort. For the DM group, younger age, presence of DPN, and female sex were correlated with worse fatigue scores. For the control group, female sex, younger age, and completing the questionnaires post-COVID pandemic were correlated with higher fatigue scores.

Table 4
Bivariate correlations between fatigue scores and demographic and metabolic factors in the diabetic and control cohorts.

QOL-F Scores (DM)	Age		BMI		Weight		DM Duration	
	r*	p-value	r*	p-value	r*	p-value	r*	p-value
Total Fatigue	−0.2683	**<0.0001**	0.0734	0.1642	0.0037	0.9419	−0.0437	0.4386
Subjective Fatigue	−0.1135	**0.0234**	0.1053	0.0875	0.1137	**0.0236**	0.001	0.9917
Cognitive & Physical Problems	−0.339	**<0.0001**	0.0184	0.727	−0.0758	0.1319	0.0723	0.199
Depression	−0.316	**<0.0001**	0.0555	0.2926	−0.0085	0.8659	0.0955	0.0897
Reduced Activities	−0.1322	**0.0198**	0.0886	0.0927	0.0548	0.2764	0.0473	0.4012
ADLS	−0.2514	**<0.0001**	0.0204	0.6999	−0.0594	0.2382	0.0434	0.4412
QOL-F Scores (controls)	**Age**		**BMI**		**Weight**			
	r*	p-value	r*	p-value	r*	p-value		
Total Fatigue	−0.2798	**<0.0001**	0.1522	**0.031**	0.0565	0.4245		
Subjective Fatigue	−0.2579	**0.0002**	0.1018	0.1203	0.0066	0.9261		
Cognitive & Physical Problems	−0.3174	**<0.0001**	0.1934	**0.0059**	0.1053	0.1357		
Depression	−0.1953	**0.005**	0.1359	0.0543	0.0997	0.1582		
Reduced Activities	−0.1573	**0.0243**	0.0971	0.1701	−0.0088	0.9015		
ADLs	−0.1913	**0.006**	0.0154	0.8287	−0.0405	0.5671		

*r = Pearson's r or Spearman's rho Correlation Coefficient depending on distribution. ADLs = activities of daily living; BMI = body mass index; DM = diabetes mellitus; QOL-F = Quality of Life-Fatigue.



p-values calculated using Student's t-test or Wilcoxon signed-rank test depending on distribution. ADLs=activities of daily living; DM=diabetes mellitus

Fig. 1. Effect of Gender and Race on Fatigue Scores in subjects with diabetes and controls.

Discussion

This study shows that individuals with diabetes are significantly more fatigued than their healthy counterparts, as evidenced in all five domains of the Norfolk QOL-F, which included subjective, physical and cognitive fatigue, depression, reduced activities, and ADLs. Fatigue scores were predominantly driven by subjects with DPN in all domains. Participants without DPN had similar fatigue scores to controls. Several studies have indicated an association between diabetes and fatigue utilizing other tools to measure fatigue [2,3,12,13,14]. Systematic reviews and *meta*-analyses have also demonstrated that fatigue in adults with DM is related to multiple physiologic, psychologic and social factors. Of all physiologic factors, having more diabetes-related complications (such as DPN, nephropathy or CVD) are most often related to the presence and severity of fatigue. Factors that chronically impact sleep quality will manifest itself as frequent tiredness or fatigue. Specifically in patients with diabetes, neuropathic pain can be extremely debilitating and worsen at night, causing impaired quality and duration of sleep and lowered mood, and thus fatigue. Poor glycemic control or fear of nighttime episodes of hypoglycemia, especially in those with T1DM, may also impact sleep quality, leading to presentations of fatigue. This confirms our current findings [4,6,7,8,15]. However, it is important to note that the presence of other chronic complications of diabetes (nephropathy, retinopathy) that can contribute to fatigue were

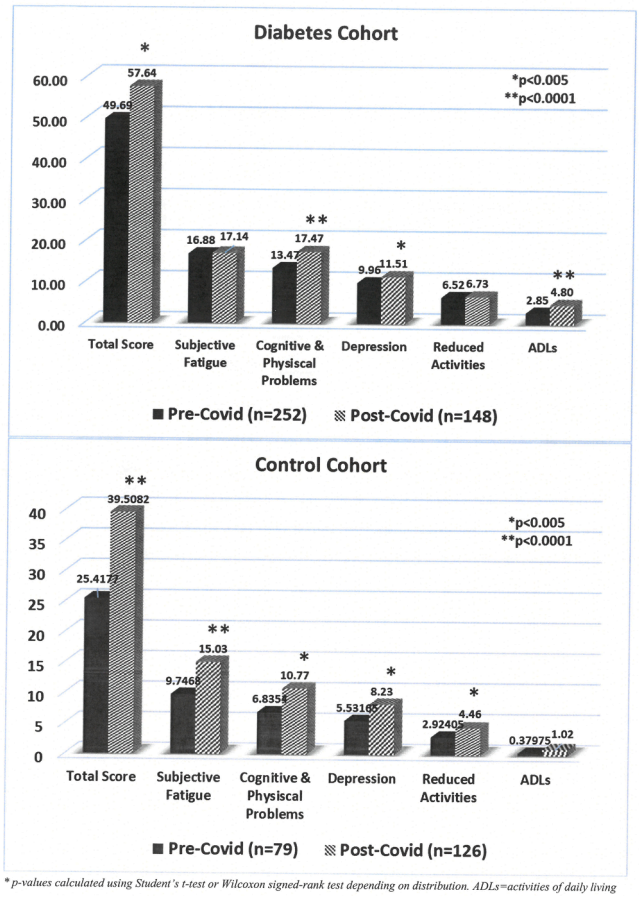


Fig. 2. Impact of COVID-19 pandemic on Fatigue Scores in the diabetic and control cohorts.

not assessed in this study.

Additionally, this study revealed worsened fatigue scores reporting in younger individuals which has been observed in other cohorts [2,3,4,8,12,13]. Several hypotheses have been proposed to explain this phenomenon. Namely, individuals who have experienced fatigue for a longer period of time may have developed coping mechanisms or becoming desensitized, thus perceiving symptoms as less severe. Moreover, generational differences exist in association with everyday responsibilities and life stressors. Those in middle life are usually in the peak of their careers and/or raising families with increased levels of perceived stress, exhaustion, and subsequent increased levels of fatigue, as compared to those in post-retirement age.

In our study, we found that females were significantly more fatigued than males in both groups. These findings are consistent with the literature in various populations [4,8]. Females displayed higher fatigue scores within the subjective, physical & cognitive, and depression domains. It has been proposed that women and men with DM perceive and communicate symptoms of fatigue differently, and measuring different dimensions of fatigue is relevant when addressing fatigue in females. It has also been suggested that common life stressors experienced in middle life populations may also be experienced differently based on gender, race/ethnicity, and socio-economic factors. However, on our multivariate regression analysis we did not observe individual associations between age and gender in relation to fatigue scores (multicollinearity), as has been shown in other studies [4,18]. This could be related to differences in the populations studied or simply to sample size variations. Furthermore, other tools used to assess fatigue don't capture the multidimensional aspects of fatigue and its different components/domains. Our tool might be more specific in detecting fatigue within these different domains and this may also account for some of the different results seen in comparison to previous studies.

Body weight, race, and duration of diabetes were not shown to significantly impact fatigue scores in this study. This differs from what the literature has shown. However, our results did show a trend between body weight/BMI and different fatigue domains, especially subjective fatigue and cognitive/physical fatigue. This signals the potential need for a larger study population. Several studies have established a directly proportional relationship between fatigue and diabetes-related physiologic factors such as increased BMI and longer duration of diabetes [4,8].

Situational factors that encompass an individual's psychosocial environment include social support, socioeconomic status, education, and cultural differences related to race and ethnicity. In patients with diabetes, having low socioeconomic status, poor social support (i.e. living alone), and low education levels are all known to influence higher levels of fatigue. Very few studies have been done to investigate the relationship between race/ethnicity and fatigue [3,12,13,14]. Our cohort had a significant representation of individuals self-reported as AA (40 to 52 %) and no differences in fatigue scores were found between different race/ethnicity backgrounds in both the diabetes and control groups. However, we did not investigate other situational factors and social determinants of health (socio-economic status, education level, social support) that could have influenced our results. Future studies should ensure that underrepresented minorities are reflected proportionately within their study populations.

Subjects who were recruited post-COVID-19 pandemic were significantly more fatigued than those who were recruited pre-COVID-19 pandemic. This is expected considering the tremendous impact that

Table 5
Fatigue scores differences based on in-person vs virtual questionnaire completion in diabetes vs control cohorts.

	Diabetes Mellitus			**Controls**		
	In-person (n = 281)	Virtual (n = 119)	p-value*	In-person (n = 79)	Virtual (n = 126)	p-value*
Total Fatigue	50.02 (46.66–53.38)	58.78 (54.95–62.61)	**0.0012**	25.52 (21.09–29.75)	39.20 (34.39–44.01)	**<0.0001**
Subjective Fatigue	16.96 (15.94–17.99)	17.02 (15.85–18.18)	0.9501	9.75 (8.21–11.29)	14.43 (12.92–15.94)	**<0.0001**
Cognitive & Physical Problems	13.57 (12.51–14.65)	18.19 (16.93–19.44)	**<0.0001**	6.84 (5.36–8.31)	10.59 (8.99–12.18)	**0.0016**
Depression	10.06 (9.31–10.81)	11.63 (10.82–12.44)	**0.0153**	5.53 (4.59–6.47)	8.35 (7.20–9.50)	**0.004**
Reduced Activities	6.53 (6.03–7.02)	6.77 (6.20–7.35)	0.5664	2.92 (2.31–3.54)	4.62 (3.93–5.31)	**0.0009**
ADLs	2.89 (2.47–3.32)	5.18 (4.50–5.85)	**<0.0001**	0.40 (0.10–066)	1.21 (0.70–1.73)	**0.0303**

Data presented as mean (95 % CI); *Student's *t*-test or Wilcoxon signed-rank test depending on distribution. ADLs = activities of daily living; n = number of participants.

Table 6
Multivariate Regression Model – Diabetes Group.

Diabetes Mellitus							
Model Summary[a]							
Rsquare[b]							0.30255
Rsquare Adj							0.286595
Root Mean Square Error							23.01899
Mean of Response							52.07325
Observations (or Sum Wgts)							314
ANOVA[a]	**DF**	**Sum of Squares**		**Mean Square**		**F Ratio**	**Sig**
Model	7	70335.97		10,048		18.963	**<0.0001[b]**
Error	306	162141.35		529.9			
Total	313	232477.32					
Coefficients	**Beta-coefficient**	**Std Error**	**t-Ratio**	**Sig**	**Lower 95%**	**Upper 95%**	**Collinearity (VIF)**
Intercept	55.643728	7.180541	7.75	**<0.0001**	41.514242	69.773214	
Age *(years)*	−0.279239	0.103684	−2.69	**0.0075**	−0.483263	−0.075215	1.3296683
Race *(AA)*	−0.655583	1.414427	−0.46	0.6433	−3.438817	2.1276503	1.1807357
Sex *(F)*	3.318024	1.394696	2.38	**0.018**	0.5736163	6.0624317	1.1320765
Weight *(lbs)*	0.0183572	0.026423	0.69	0.4877	−0.033637	0.0703511	1.1655295
DM Duration *(years)*	−0.120919	0.135938	−0.89	0.3744	−0.388411	0.1465729	1.1050416
DN *(No)*	−16.40967	1.626279	−10.09	**<0.0001**	**−19.60977**	−13.20956	1.0970154
COVID *(Post)*	−1.476815	1.660659	−0.89	0.3745	−4.744571	1.7909401	1.4188369

a: Dependent variable (Norfolk QOL-F total score); b: Predictors (age, race, gender, weight, DM duration, DPN & COVID-19 pandemic). AA = African American; Adj = adjusted; DF = degrees of freedom; DM = diabetes mellitus; DPN = diabetic peripheral neuropathy; F = female; lbs = pounds; Sig = significance; Wgts = weights.

Table 7
Multivariate Regression Model – Control Group.

Controls							
Model Summary[a]							
Rsquare[b]							0.147033
Rsquare Adj							0.125274
Root Mean Square Error							23.25149
Mean of Response							33.56436
Observations (or Sum Wgts)							202
ANOVA[a]	**DF**	**Sum of Squares**		**Mean Square**		**F Ratio**	**Sig**
Model	5	18265.86		3653.17		6.7572	**<0.0001[b]**
Error	196	105963.81		540.63			
Total	201	124299.66					
Coefficients[a]	Beta-coefficient	Std Error	t-Ratio	Sig	Lower 95%	Upper 95%	Collinearity (VIF)
Intercept	38.45009	9.890598	3.89	**0.0001**	18.944434	57.95576	
Age *(years)*	−0.349443	0.114594	−3.05	**0.0026**	−0.575439	−0.123446	1.1218494
Race *(AA)*	1.1156808	1.760036	0.63	0.5269	−2.355359	4.5867206	1.124635
Sex *(F)*	3.8421964	1.845723	2.08	**0.0387**	0.2021695	7.4822233	1.1529548
Weight *(lbs)*	0.0592066	0.042283	1.4	0.163	−0.024182	0.1425952	1.1462783
COVID *(Post)*	4.8777268	1.795577	2.72	**0.0072**	1.3365953	8.4188583	1.1474861

a: Dependent variable (Norfolk QOL-F total score); b: Predictors (age, race, gender, weight, DM duration, DPN & COVID-19 pandemic). AA = African American; Adj = adjusted; DF = degrees of freedom; F = female; lbs = pounds; Sig = significance; Wgts = weights.

the COVID-19 pandemic had in everyday life and stress, affecting all populations. Furthermore, fatigue has recently been elucidated as one of the most common symptoms (up to 90 %) in patients with long-COVID syndrome [19]. However, it is important to note we also implemented a change in methodology post-pandemic with data collection switching to virtual surveys, which could have introduced user bias. Additionally, we observed differences in demographics between the pre-pandemic and post-pandemic participants within both cohorts. In the group with diabetes, participants recruited post-pandemic were of younger age, predominantly white, had a higher participation of males, and were leaner individuals. In the control group, participants recruited post-pandemic were also of younger age, predominantly African American, and had a higher participation of females. This could have impacted reported levels of fatigue. Similarly, data on whether subjects had ever been diagnosed with COVID-19 before or during the study and suffered from long-COVID syndrome was not collected, which could have also impacted reported fatigue. Future longitudinal studies should explore the impact of long-COVID syndrome on fatigue and its effect on chronic disease outcomes.

Several limitations must be considered when interpreting the findings of this study. The cross-sectional design of the study and limited information on sociodemographic factors preclude the identification of causality. Information is also lacking on the presence of other chronic complications of diabetes such as retinopathy or nephropathy, and other comorbidities (cancer, cardiovascular disease, etc) which can also influence the degree of fatigue experienced by patients with diabetes. Furthermore, information on diabetes control becomes relevant as poor diabetes management at baseline could contribute to higher prevalence of fatigue symptoms. Additionally, use of insulin and other diabetes medications were not assessed in these participants. Injection burden may contribute to increased fatigue, and as such is also a limitation to this study. BMI in patients with diabetes was higher than controls and could be a confounder, as increased BMI is related to increased levels of fatigue. As stated previously, another major limitation was the change in methodology post-COVID-19 pandemic introducing potential user bias, especially on self-reported variables such as weight, waist

circumference, and duration of diabetes. Due to these limitations, the results of this study cannot be extrapolated to other populations. A larger sample size and appropriate matching is needed to confirm these observations in specific cohorts with other comorbidities.

Conclusions

This study shows that the Norfolk QOL-F survey is a useful tool that can identify the presence of fatigue and its different domains in chronic diseases, such as diabetes and its complications. Fatigue is a multifactorial experience in patients with diabetes and in particular, in those with DPN, that has debilitating consequences on QOL and self-management, contributing to worsening of diabetes control and severity of disease. Consequently, healthcare providers should investigate the presence of fatigue and its different components in order to address these implications and improve disease outcomes. Additional studies are needed to further investigate the utility of this survey in populations with other chronic diseases and as an outcome measure on interventions to reduce fatigue and its consequences.

Funding Source

Eastern Virginia Medical School [Internal Funds] for participants' stipend.

CRediT authorship contribution statement

Catherine Nguyen: Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft. **Henri K. Parson:** Conceptualization, Methodology, Validation, Data curation, Supervision, Project administration, Funding acquisition, Writing – review & editing. **Jordan Pettaway:** Methodology, Investigation, Resources, Data curation, Writing – review & editing. **Amber Ingram:** Methodology, Investigation, Resources, Data curation, Writing – review & editing. **Taneisha Sears:** Methodology, Investigation, Resources, Writing – review & editing. **Jason T. Bard:** Methodology, Investigation, Resources, Writing – review & editing. **Steven Forte:** Methodology, Investigation, Resources, Writing – review & editing. **Jennifer A. Wintringham:** Methodology, Investigation, Resources, Writing – review & editing. **Etta Vinik:** Conceptualization, Methodology, Validation, Data curation, Writing – review & editing. **Elias S. Siraj:** Conceptualization, Methodology, Validation, Supervision, Writing – review & editing. **Carolina M. Casellini:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Visualization, Supervision, Project administration, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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