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Original Research Article

Fatigue and diabetes mellitus: a prospective study

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ABSTRACT

Background: Fatigue is a common complaint among patients with diabetes mellitus (DM) that can undermine the daily functional activities of a person. The objectives of the study were to assess the fatigue in patients of newly diagnosed type 2 DM and to relate fatigue with blood glucose parameters (BGP) and glycemic control.
Methods: A total 50 patients of type 2 DM, diagnosed as per American Diabetes Association 2011 criteria, were enrolled in the study group. Each subject was evaluated two times for fatigue using Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) scale. 1st assessment was at the time of enrollment and 2nd was done after achieving target control of type 2 DM. Values of Fasting blood glucose (FBG), postprandial blood glucose (PPBG), blood glucose variability (BGV) and glycosylated hemoglobin (HbA1c) were obtained for each subject at each assessment. Data collected was analyzed statistically.
Results: Mean age of study group was 50.7±8.9 years with male to female ratio of 1.17:1. Mean values of MFSI-SF score at 1st and 2nd assessment were 14.10±17.97 and 4.64±14.06, respectively indicating a statistically significant improvement in fatigue ($p<0.05$) after achieving target control. Overall fatigue, general fatigue, emotional fatigue, and vigor score correlated significantly with glycemic control (HbA1c) with correlation coefficient (r) of 0.337, 0.351, 0 .339, and - 0.281, respectively (all $p <0.05$).
Conclusions: Fatigue had a positive correlation with FBG, PPBG and BGV and HbA1c. A significant improvement in all the parameters of fatigue was noted after control of diabetic status.

Keywords: Blood glucose parameters, Blood glucose variability, Diabetes Mellitus, Fatigue, HbA1c, MFSI-SF

INTRODUCTION

Diabetes mellitus (DM) comprises of a group of common metabolic disorders that share the phenotype of hyperglycemia, caused by absolute or relative lack of pancreatic hormone i.e. insulin.[1] This chronic disease is associated not only with an increased risk of cardiovascular diseases, strokes, kidney failure and related pathologies, but also with a higher incidence of neuropsychiatric symptoms, including fatigue and cognitive dysfunction[1]. Fatigue is a common complaint among patients with DM and is likely to be multidimensional, encompassing physiological, psychological, and lifestyle factors.[2] Fatigue in diabetes may be associated with physiological phenomena, such as hypo- or hyperglycemia or wide swings between the two as described in various studies. Fatigue is a subjective experience that can be described as 'extreme and

persistent tiredness, weakness, and exhaustion-which can be mental, physical or both.[3] Fatigue produces negative affect on self-rated health and quality of life.[4] It acts as a barrier to their health-promoting behaviors, such as participating in diabetes self-care regimens, following a healthy eating plan or participating in regular exercise. Hence, it is associated with decreased physical functioning and decreased ability to manage routine daily activities.[2,5] Measuring the fatigue is very challenging as it is of multidimensional nature.[2]

The prevalence of fatigue in diabetes has been found as high as 61% in an epidemiological study of type 2 diabetes patients.[6] Despite this elevated frequency and the impact of fatigue on the patient's wellness and treatment efficacy, only few studies worldwide are available on fatigue in diabetes and on its relation to blood glucose parameters and many of them are limited to nonspecific symptoms of fatigue.[7] To our knowledge no study has been done in Indian subcontinent till now. We performed an observational study in this regard to assess fatigue in patients of newly diagnosed type 2 diabetes (without evidence of co-morbidities and complications) and to evaluate its relationship with blood glucose parameters.

METHODS

A total of fifty newly diagnosed patients of Type-2 diabetes mellitus diagnosed as per American Diabetic Association (ADA) 2011 criteria[8], age group of 18 to 60 years and who were able to read, write and understand English/ Hindi were enrolled in the study prospectively from August 2013 to July 2014. The study was done at our institute. Those patients who had anemia, hypothyroidism, and renal, cardiac, liver or pulmonary disease; patients on antidepressant/antipsychotics; subjects taking drugs known to produce fatigue (e.g. statins, β blockers, calcium channel blockers); other co morbid conditions known to cause fatigue (hypertension, dyslipidemia, smoking, alcoholism, peripheral vascular disease) were excluded from the study group.

A written and informed consent was taken from all patients enrolled in the study as subjects. All enrolled subjects were admitted in the ward, evaluated for detailed clinical history and clinical examinations (including fundus examination). Depression was ruled out of all patients by subjecting them to complete the Patient Health Questionnaire -9 (PHQ-9) score.[9] PHQ-9 is a depression assessment-screening tool consisting of nine questions. The questionnaire is designed to assess patient's mood over last two weeks. Any patient scoring greater than a score of 'four' will be considered having depression. Patients having evidence of depression as per PHQ-9 was excluded from the study. Each subject was then assessed (i.e. first assessment) for fatigue by using Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). MFSI-SF is a 30-item self-report measure designed to assess the principal manifestations of fatigue.[10] It encompasses 5 subscales i.e. general fatigue (GF), physical fatigue (PF), emotional fatigue (EF), mental fatigue (MF) and vigor. Each subscales contains 6 items. Items are rated on a 5-point scale indicating how true each statement was for the respondent during the last week (0 indicates not at all; 4 indicates extreme). The score of each subscale ranges from 0 to 24; and MFSI-SF total score ranges from -24 to 96; with higher scores indicating more fatigue except for the Vigor subscale, where a higher score indicates less fatigue (i.e. more Vigor).[10]

HbA1c value for glycemic control and Blood glucose parameters (BGP) i.e. FBG, PPBG and BGV were obtained for each subject. For blood glucose variability (BGV) a fasting, pre and postprandial and a 3 a.m. blood glucose value was obtained for each patient by using glucometer.

All subjects were then put on drug therapy (oral hypoglycemic agents with or without insulin) for control of diabetes. Subjects who achieved the target glycemic control (i.e.HbA1c $\leq$7.0) and target BGPs (FBG <126mg/dl and PPBG <200mg/dl) were again evaluated (i.e. second assessment) for the fatigue using the same fatigue assessment scale i.e. MFSI-SF. Significant fall in the score ($p<0.05$) was considered as having relief in fatigue.

Data collected was analyzed statistically by using Pearson correlation coefficient and paired sample t test. Correlation between fatigue and various BGPs was measured by calculating the Pearson's correlation coefficient (r) that ranges from -1 to +1. Values of coefficient (r) interpreted were as follows: $r = 0$ no correlation; $0<r \leq 0.3$ weak correlation; $0.3<r<0.7$ moderate correlation and $r \geq 0.7$ strong correlation.

RESULTS

The patients in the study group, 27 (54%) were men and 23 (46%) were women with male to female ratio of 1.17:1 [Table 1]. Mean age of study population was 50.7±8.9 years [Table 1].

Table 1: Demographic profile of study group

Demographic parameters	Observations
Total number of subjects	50
Mean age ±SD (years)	50.72±8.95
Male/Female	27/23

SD- standard deviation

Mean values of blood glucose parameters (BGP) at both assessments are summarized in table 2. At first assessment (i.e. pre-treatment or baseline) mean values for FBG (mg/dl), PPBG (mg/dl), BGV (mg/dl) and HbA1c (%) were 174.76±37.67, 273.48±31.84, 52.55±17.00 and 9.97±2.08, respectively whereas mean values at second assessment (i.e. post treatment after achieving target) were 112.40±14.00, 166.24±25.96,

32.55±7.52 and 6.76±0.31, respectively [Table 2]. There was a significant improvement noted in BGPs with treatment (all p <0.05) [Table 2].

Table 2: Mean values with standard deviations for blood glucose parameters before and after treatment

Parameters	Pre-treatment (baseline)	Post-treatment	p value
FBG (mg/dl)	174.76±37.67	112.40±14.00	<0.01
PPBG (mg/dl)	273.48±31.84	166.24±25.96	<0.01
HbA1c (%)	9.97±2.08	6.76±0.31	<0.01
BGV (mg/dl)	52.55±17.00	32.55±7.52	<0.01

FBG-Fasting blood glucose; PPBG-post prandial blood glucose; HbA1c-Glycosylated hemoglobin; BGV-blood glucose variability; p value <0.05 significant; p value >0.05 non significant

Mean values of fatigue parameters at both assessments are summarized in Table 3. It was 6.76±5.52, 6.74±5.05, 5.92±5.04, 4.92±4.22, 10.08±2.17 and 14.10±17.97 for General fatigue (GF), Physical fatigue (PF), Emotional fatigue (EF), mental fatigue (MF), Vigor score (VS), and Overall fatigue (OF), respectively at first assessment [Table 3]. After achieving target at second assessment, the mean values for the same parameters were 4.98±3.86, 4.90±4.02, 3.88±3.72, 3.38±3.23, 12.56±3.94 and 4.64±14.06, respectively [Table 3]. Significant improvement in MFSI-SF fatigue subscales as well as in overall fatigue score was noted at second assessment (all p <0.05) [Table 3].

Four subscales namely GF, PF, EF, and MF were correlated positively with FBG (p value >0.05) whereas negative significant correlation was found between vigor score (VS) and FBG (r = -0.472; p =0.001) [Table 4]. GF, PF, EF and MF had positive correlation (r= 0.108, 0 .123, 0 .271, 0.179, respectively; p>0.05) with PPBG but VS had negative correlation (r= -0.039; p >0.05). BGV was positively correlated with all fatigue parameters (p<0.05 for GF only) [Table 4]. HbA1c was correlated significantly with GF (r= 0.351), EF (r= 0.339), VS (r= -0.281) and non-significantly with PF (r= 0.274) and MF (r=0.128) [Table 4]. Total MFSI-SF score was correlated positively with HbA1c (r= 0.337; p<0.05) and BGPs (p>0.05) [Table 4].

Table 3: Mean values with standard deviation for various MFSI-SF subscales at Baseline and post treatment.

Fatigue parameters	Pre-treatment (baseline)	Post-treatment	p value
General score	6.76±5.52	4.98±3.86	0.000
Physical score	6.74±5.05	4.90±4.02	0.000
Emotional score	5.92±5.04	3.88±3.72	0.000
Mental score	4.92±4.22	3.38±3.23	0.000
Vigor score	10.08±2.17	12.56±3.94	0.000
Overall fatigue score	14.10±17.97	4.64±14.06	0.000

MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form; p value <0.05 significant; p value >0.05 non-significant

Table 4: Correlation of fatigue subscales with various blood glucose parameters.

Fatigue parameter	FBG		PPBG		BGV		HbA1c	
	(r)	p value	(r)	p value	(r)	p value	(r)	p value
General fatigue	0.043	0.766	0.108	0.456	0.325	0.021	0.351	0.013
Physical fatigue	0 .157	0.275	0 .123	0.394	0 .246	0.084	0 .274	0.055
Emotional fatigue	0 .207	0.149	0 .271	0.056	0 .236	0.102	0 .339	0.016
Mental fatigue	0.155	0.284	0.179	0.214	0.234	0.102	0.128	0.377
Vigor score	-0.472	0.001	-0.039	0.785	0.070	0.631	- 0.281	0.048
Overall fatigue score	0.216	0.133	0.201	0.168	0.256	0.073	0.337	0.017

FBG- Fasting blood glucose; PPBG- post prandial blood glucose; BGV- blood glucose variability; HbA1c- Glycosylated hemoglobin; (r)-Correlation coefficient; p value <0.05 significant; p value >0.05 non-significant, Note: significant p values are shown in bold letters.

DISCUSSION

Fatigue is a common and distressing complaint among people with diabetes, and likely to hinder their ability to perform daily diabetes self-management tasks.[7] Patients with diabetes who neglects their health because of fatigue put themselves at greater risk for complications associated with diabetes. The successful self-management of diabetes requires physical, psychological and cognitive tasks (e.g. exercise participation, management of hypoglycemia and hyperglycemia, and calculation of insulin doses) that are likely to be affected by fatigue.[7] Very few studies have explored this symptom dimension in patients with diabetes, and most have been limited to nonspecific symptoms of fatigue.[7] Fatigue in diabetes is attributed to various physiological (hypoglycemia,

hyperglycemia, blood glucose fluctuations), psychological factors (emotional distress and depressive symptoms) and life style variables (increased body mass index, reduced physical activity). Only one study has examined the role of these factors, but that was limited to female gender only.[7] Other studies exploring fatigue have been conducted, but either with subjects having co morbidities[11] or with subjects having the additional burden of maintaining their employment status.[12] Therefore, the purpose of this study was to investigate the presence and severity of fatigue in patients with type 2 Diabetes (without evidence of comorbidities and complications) and to identify the relationship between fatigue and glycemic control.

Though fatigue has been reported to be more common in females than males[13] but we recruited comparable number of patients (males- 27 and females- 23) [Table 1] in our study to obviate the effect of gender. All the patients achieved good control of diabetes post treatment [Table 2]. The five parameters (i.e. subscales) of MFSI-SF fatigue score were calculated before and after achieving the target blood glucose control and were compared with each other [Table 3]. There was a significant difference ($p<0.01$) in all the parameters of fatigue indicating improvement in fatigue after blood sugar control [Table 3]. Similar observation was achieved by de Sonnaville JJ, et al who found improvement in fatigue levels after control of diabetes, whereas Fritschi et al reported no improvement in fatigue parameters with the control of diabetic status.[14,7]

As fatigue can be influenced by various blood glucose parameters i.e. FBG, PPBG, HbA1c and BGV, so Pearson correlation coefficient was used to study the correlation between fatigue and blood glucose parameters (BGPs). A statistically non-significant ($p>0.05$) positive correlation was observed between FBG and general fatigue score ($r=0.043$); physical fatigue score ($r=0.157$); emotional fatigue score ($r=0.207$); mental fatigue score ($r=0.155$) and total fatigue score ($r=0.138$) [Table 4]. There was a negative correlation between FBG and Vigor score ($r= -0.472$) and the relation was statistically significant ($p<0.01$) proving that the vigor score improves with control of FBG [Table 4]. Similar were the observations made by Drivsholm et al and Bulpitt et al, who found the association of fatigue with the elevated fasting blood sugar levels.[6,15]

Fatigue has been found to be associated with high PPBG in various studies.[16,17] However we found non-significant correlation between fatigue and PPBG ($p>0.05$ for all fatigue subscales) [Table 4], which is supported by Fritschi et al observation.[7] Many researchers have correlated fatigue with the long-term glycemic control in term of HbA1c. Nielsen et al and Fritschi et al have found that there is no correlation of fatigue with HbA1c whereas Vander Does FE et al found positive correlation of fatigue with HbA1c which is also supported by our study as we also found a good correlation between HbA1c and fatigue subscales [Table 4].[18,7,19]

A statistically significant correlation was observed between daily Blood sugar variability with General Fatigue score ($r=0.325$) and statistically non-significant positive correlation was observed for other subscales [Table 4].

Thus, present study showed that fatigue was positively correlated with blood glucose fluctuations and fatigue improved after control of blood glucose fluctuations. This means that blood glucose fluctuations are a variable that influences fatigue which is similar to the observations made by Sommerfield et al who found that fatigue is associated with blood sugar fluctuations, i.e. higher the fluctuations, more the fatigue.[17]

However, Cynthia Fritchi et al reported that there is no correlation of fatigue with blood sugar fluctuations.[7] Recent evidence suggests that these glucose fluctuations during the postprandial period may act as strong triggers for inflammatory markers and oxidative stress which is thought to play a key role in the development of diabetic vascular complications.[20] Diabetes and its related effects represent a potential archetype for fatigue, with abundant potential for future research.

This study had several limitations. The study was performed in a single center within a relatively small region. Fatigue is a complex symptom and it is difficult to quantify it. However, fatigue was evaluated on 5 scale parameters only. Also, the study is based on the questionnaire without any objective evidence, hence, can have many flaws; therefore physician must exercise their clinical acumen in the light of our observations while evaluating fatigue.

CONCLUSION

Fatigue had positive correlation with poor glycemic control and there was a significant improvement in all the parameters of fatigue after control of diabetic status. Health care professionals should assess fatigue in their patients and should educate them on fatigue management in term of achieving good control of diabetes. Our findings are just preliminary and they have to be confirmed on a large-scale study.

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