

Clinical and psychological characteristics of liraglutide treatment among patients with type 2 diabetes

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ABSTRACT

Aim: This study aimed to evaluate the glycemic control, quality of life (QOL), and sleep quality in type 2 diabetes mellitus (T2DM) patients who are treated with liraglutide and to investigate whether the QOL and sleep quality were correlated with the glycemic control of this population. **Methods:** A cross-sectional study was carried out on T2DM patients who were treated with liraglutide. Data on body weight and glycemic control were recorded while the QOL and sleep quality were assessed using the Short-Form Health Survey (SF-36), the 5-item World Health Organization Well-Being Index (WHO-5), and the Pittsburgh Sleep Quality Index (PSQI) questionnaires. **Results:** Eighty-four T2DM patients who initiated liraglutide with a mean age of 46.7 years were included in the study. The mean hemoglobin A1c (HbA1c) was 7.76% (standard deviation [SD] = 0.62), and about 88.1% of patients had HbA1c >7%. The PSQI score showed not too bad sleep quality (mean 4.3 ± 1.9). The mean WHO-5 score of the study population showed a “moderate” QOL (12.4 ± 3). Patients had lowest SF-36 score (mean = 52.3) in the subscale of “energy and fatigue.” There was a significant positive correlation between HbA1c and the “energy and fatigue” ($r = 0.232$, $P = 0.034$) but not with the other subscales. **Conclusion:** Patients with T2DM taking liraglutide have moderate sleep difficulty and QOL score. Nonetheless, none of these outcomes was significantly correlated with glycemic control. Further well-designed studies with long-term follow-up and larger population sizes are needed to confirm our findings.

Keywords: Diabetes mellitus, glycemic control, liraglutide, quality of life, sleep quality

Introduction

Diabetes mellitus (DM) bears a heavy economic burden worldwide. In 2015, it was estimated that the global economic burden of DM was \$1.31 trillion, and the number is expected to increase with the increasing prevalence of the disease worldwide.^[1] In 2018, type 2 DM (T2DM) affected about 500 million individuals around the world, and the number is expected to increase, especially in low-income countries.^[2] The prevalence of DM is increasing at an alarming rate in Saudi

Arabia—over 25% of the adult population is suffering and that figure is projected to be more than double by 2030.^[3,4] In fact, DM has approximately registered a 10-fold upsurge in the last three decades in Saudi Arabia.^[3,4] It is well-demonstrated that poorly managed diabetes leads to serious diabetes-related complications.^[5]

Rigorous research on DM has resulted in the development of several novel pharmacological agents that aim to improve the glycemic control of DM patients. Despite the recent advances in the treatment of DM, a substantial proportion of DM patients still suffer from poor glycemic control in real life.^[6]

Due to the increasing prevalence of DM, its impact on the QOL and well-being of the patients is of clinical and economic

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significance. The chronic nature of the disease and long-term treatment have significant effects on patients' well-being and QOL.^[7] In addition, T2DM patients tend to be older in age, more obese, have less physical activity, and suffer from DM complications that lead to lower QOL scores compared with nondiabetic controls.^[8,9] DM patients are likely to suffer from nocturia, which might affect their sleep quality and, therefore, affect their QOL.

Researchers have suggested that better glycemic control might improve the QOL of DM patients.^[10] Others suggest that clinical and educational interventions might improve the health status, and perceived ability to control their disease results in improved QOL.^[11] About 80% of DM patients have poor sleep quality.^[12] Poor sleep has been associated with poor glycemic control in DM patients.^[13] Therefore, sleep quality has recently gained more attention as an important outcome measure of the efficacy of the novel antidiabetic medications.

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that has shown efficacy in the management of T2DM.^[14-19] A recent study showed that after 12 weeks of treatment and follow-up, liraglutide could improve glycemic control and decrease weight without deteriorating the QOL in obese patients with T2DM.^[20] The drug has been recommended for the management of T2DM patients in primary care and a specialist setting.^[21,22] Therefore, we conducted this study to evaluate glycemic control, QOL and sleep quality in T2DM patients taking liraglutide and investigate whether the QOL and sleep quality were correlated with the glycemic control of this population.

Methods

We followed the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) statement guidelines when reporting this manuscript.^[23]

Institutional review board approval

The study was approved by the ethics committee on January 17 2018; institutional review board (IRB) approval number HAP -01-R-015. All patients received the informed consent form and signed it.

Ethical compliance with human/animal study

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The study was approved by the ethics committee on January 17, 2018; institutional review board (IRB) approval number HAP 01R015.

Study design, setting, and duration

We conducted a cross-sectional study on patients with T2DM who initiated liraglutide therapy in combination with their treatment regimens. All patients with T2DM attending our center

during the period from February to July 2019 were eligible for inclusion in this study.

Eligibility criteria of the study population

Study subjects were selected according to the following criteria:

- (1) T2DM patients between 30 and 70 years of age
- (2) Patients who were treated with liraglutide for at least 6 and up to 24 months prior to inclusion in the study
- (3) Individuals who gave informed consent

Study questionnaires

Pittsburgh Sleep Quality Index (PSQI) Arabic version^[17]

The Pittsburgh Sleep Quality Index (PSQI) global score can range from 0 to 21, with higher scores indicating worse sleep quality. As for the individual components on the PSQI scale, 0 indicates no difficulty and 3 indicates severe difficulty. The Arabic version of the PSQI is a reliable and valid instrument,^[23] with 98.3% sensitivity and 90.2% specificity.^[24]

Well-Being Index (WHO-5 Arabic version) questionnaire

The 5-item World Health Organization Well-Being Index WHO-5 scale has 5 items, with the raw scores ranging from 0–25—0 representing the worst possible and 25 representing the best possible QOL. The Arabic version of the WHO-5 questionnaire is a valid and reliable instrument to be used in this population.^[25]

Short-Form 36-item survey (SF-36) Arabic version

All Short-Form 36-item survey (SF-36) parameters are scored from 0–100, with 100 representing the highest level of functioning possible. The Arabic version of the SF-36 is a reliable tool that has been used before in the present population.^[1]

Statistical analysis

While continuous data were summarized using means, medians, standard deviation (SD), minimum, and maximum, categorical data were summarized using frequency counts and percentages. Correlations between outcomes and variables were also looked at using Pearson's correlation coefficients. Psychological outcomes and population characteristics were compared using independent sample t-tests and one-way analysis of variance (ANOVA). Finally, bivariate and multivariate linear regression models for each outcome variable were conducted. Variables with a $P < 0.2$ at the bivariate level were selected to continue to the multivariate level. Only significant associations with $P < 0.5$ remained in the final models. The outcome-dependent variables looked at included the WHO-5 total score, Global PSQI score, and all eight SF-36 scales. The independent variables looked at include:

- Age (continuous)
- Gender
- Weight (continuous)
- T-cholesterol
- Low-density lipoprotein (LDL)

- Triglycerides (TG)
- High-density lipoproteins (HDL)
- Sulphonylureas
- Dipeptidyl peptidases 4 inhibitors (DPP4-inhibitors)
- Thiazolidinediones
- Biguanides
- Insulin
- Fasting blood sugar (FBS)
- Number of insulin injections/day
- Hemoglobin A1c (HbA1c; cutoff and continuous scores)
- DM duration
- LiraRx duration
- Frequency of hypos
- Hypertension
- Dyslipidaemia
- Retinopathy
- Neuropathy
- Having any history of amputation

All analyses were done using the Statistical Package for the Social Sciences (SPSS) software (version 23, for Windows).

Results

Characteristics of the Study Population

This study included 84 patients with T2DMs who were on liraglutide treatment. The mean age of the study population ranged from 39 to 58 years old with a mean (SD) of 46.70 (5.2) years. About 52.4% of the study population were females. The characteristics of the study population are shown in Table 1.

Glycemic control

All patients in our study were treated with liraglutide (a dosage of 1.8 mg) as a part of the guidelines in clinical practice. The mean HbA1c was 7.76% (SD = 0.62). About 88.1% of patients had HbA1c >7%. The mean liraglutide treatment duration was 16.17 (SD = 3.12) months. The mean frequency of hypos was 1.39 (SD = 1.13) months.

Sleep quality and QOL score

The mean score of the global PSQI in our sample was 4.30 (SD = 1.91), which indicates not too bad sleep quality, thus, relatively good quality of sleep. All components of the PSQI had mean scores ranging from 0 to 1 except for the sleep latency (mean score of 1.33). The scores between 0 and 1 reflect the minimal difficulty in sleep quality, duration, efficiency, disturbance, etc., while for sleep latency, a mean score of 1.33 indicates the moderate difficulty of sleeping [Table 2]. The mean WHO-5 score of the study population was 12.36 (SD = 3), which indicates a “moderate” QOL. In terms of the SF-36 score, the highest functioning subscale among the eight parameters was the “role limitations due to physical health” (mean score of 79.76), followed by pain (mean score 77.35) and “role limitations due to emotional problems” (mean score 72.62). On the other hand, the

Table 1: The descriptive statistics for demographic variables

Variable	Descriptive statistic Mean (SD)
Age (years)	46.70 (±5.206)
Gender	
Males (%)	47.6%
Females (%)	52.4%
Weight (Kg)	95.27 (9.69)
Height (cm)	165.68 (7.80)
Waist Circumference (cm)	100.86 (10.33)
Total Cholesterol (mmol/L)	4.44 (1.13)
TG (mmol/L)	1.33 (0.64)
LDL (mmol/L)	2.04 (0.66)
HDL (mmol/L)	1.39 (0.68)
Medications	
Sulphonylurea	13 (15.5%)
DPP4_Inhibitors	27 (32.1%)
Thiazolidinediones	12 (14.3%)
Biguanides	66 (78.6%)
Insulin	61 (72.6%)
Number of Insulin Injections	
0	23 (27.4%)
1	22 (26.2%)
2	31 (36.9%)
3	5 (6.0%)
4	3 (3.6%)
HbA1c %	7.758 (0.6149)
DM Duration (years)	7.524 (0.6456)
LiraRx Duration (months)	16.167 (0.1233)
Frequency of Hypos (months)	1.393 (1.1303)

SD=Standard deviation, TG=Triglycerides, LDL=Low-density lipoprotein, HDL=High-density lipoproteins, DPP4=Dipeptidyl peptidases 4 inhibitors, DM=Diabetes mellitus

mean score on “energy and fatigue” is the lowest, with a mean score of 52.32; this indicates that patients are experiencing a loss of energy and some fatigue [Table 2].

Correlation between the population characteristics and the QOL and sleeping

The correlation analysis showed that glycemic control (HbA1C) significantly correlated with weight, component 5, and energy fatigue. While weight did not significantly correlate with any of the psychological outcomes but correlated negatively with the HbA1c ($r = -0.23, P = 0.034$). The results of the correlation analysis are shown in Table 3.

Discussion

Study findings and comparisons

Liraglutide, which is prescribed by primary care physicians as an additive for the management of T2DM, acts by increasing insulin secretion through the stimulation of GLP-1 receptors.^[18,21,22] Our study showed that patients with T2DM treated with liraglutide have not too bad sleep quality, thus, relatively good quality of sleep, as indicated by the PSQI score (mean = 4.3). In terms of sleep latency and QOL, they have moderate sleep difficulty and moderate QOL. Those patients scored moderately in the SF-36

Table 2: The sleep quality and QOL of the study population

Score	Subscale	Mean	SD
PSQI global and component scores	Sleep quality	0.31	0.54
	Sleep latency	1.33	0.57
	Sleep duration	0.27	0.52
	Sleep efficiency	0.44	0.86
	Sleep disturbance	0.93	0.30
	Sleep medic	0.61	0.66
	Day time dysfunction	0.40	0.52
	Global PSQI score	4.30	1.91
WHO-5 scale	Total Score	12.36	3.02
	Percentage Score	49.43	12.08
SF-36	Physical Functioning	63.99	18.31
	Role Limitations due to Physical Health	79.76	32.11
	Role Limitations due to Emotional Problems	72.62	40.13
	Energy and Fatigue	52.32	10.16
	Emotional Wellbeing	59.48	11.89
	Social Functioning	68.60	17.52
	Pain	77.35	17.16
	General Health	57.68	22.18

QOL=Quality of life, SD=Standard deviation, PSQI=Pittsburgh Sleep Quality Index, WHO-5=5-item World Health Organization Well-Being Index, SF-36=Short-Form Health Survey

subscales with the lowest scores achieved in the “energy and fatigue” subscale, which indicated those patients have a loss of energy and fatigue.

Previous studies

In addition to achieving glycemic control measured by HbA1C levels, improving the QOL, sleep quality, and other patient-reported outcomes have recently gained attention as therapeutic targets of DM treatment. Sleep quality is an important outcome in DM patients. A cross-sectional study by Barakat *et al.*^[12] showed that about 80% of diabetic patients had poor sleep quality, which leads to poor glycemic control.^[12]

An observational study of 158 obese patients with T2DM showed that liraglutide treatment was associated with significant reductions in excessive daytime sleepiness besides the improvements in blood glucose and body weight.^[26] A randomized controlled trial (RCT) comparing liraglutide with placebo showed that liraglutide significantly reduced body weight and improved the apnoea-hypoxia index in obese patients with obstructive sleep apnoea.^[27] Another study on 71 non-diabetic subjects showed that GLP-1 was significantly associated with sleep apnoea.^[28] Increasing the obstructive sleep apnoea was associated with reductions in GLP-1 which adversely affect glucose metabolism.^[28] In a prospective multicentre observational cohort study, researchers from Japan found that liraglutide could improve the levels of HbA1c and reduce weight without deteriorating the QOL score in obese patients with T2DM.^[29] In Saudi Arabia, a recent study showed that liraglutide achieved good glycemic control with no impact on body weight.^[26] Another study by Tonoike and colleagues showed that adding liraglutide to insulin in patients with T2DM could significantly improve glycemic control, body weight, and QOL.^[30]

Table 3: Correlation between both weight and glycemic control and the psychological scores

	Weight	HbA1c
Weight		
Pearson's Correlation	1	-0.231*
Sig. (2-tailed)		0.034
n	84	84
HbA1c		
Pearson's Correlation	-0.231*	1
Sig. (2-tailed)	0.034	
n	84	84
PSQI Component 1		
Pearson's Correlation	-0.035	-0.026
Sig. (2-tailed)	0.752	0.813
n	84	84
PSQI Component 2		
Pearson's Correlation	-0.030	0.058
Sig. (2-tailed)	0.787	0.603
n	84	84
PSQI Component 3		
Pearson's Correlation	-0.086	-0.069
Sig. (2-tailed)	0.435	0.533
n	84	84
PSQI Component 4		
Pearson's Correlation	0.039	0.028
Sig. (2-tailed)	0.724	0.797
n	84	84
PSQI Component 5		
Pearson's Correlation	0.118	-0.302**
Sig. (2-tailed)	0.286	0.005
n	84	84
PSQI Component 6		
Pearson's Correlation	0.076	0.111
Sig. (2-tailed)	0.495	0.316
n	84	84
PSQI Component 7		
Pearson's Correlation	-0.092	-0.090
Sig. (2-tailed)	0.405	0.414
n	84	84
PSQI Global score		
Pearson's Correlation	-0.005	-0.030
Sig. (2-tailed)	0.963	0.784
n	84	84
WHO-5 total score		
Pearson's Correlation	-0.038	0.002
Sig. (2-tailed)	0.729	0.988
n	84	84
Physical functioning		
Pearson's Correlation	-0.095	0.051
Sig. (2-tailed)	0.391	0.643
n	84	84
Role limitations physical health		
Pearson's Correlation	-0.116	0.146
Sig. (2-tailed)	0.295	0.185
n	84	84
Role limitations emotional problems		
Pearson's Correlation	-0.145	0.196
Sig. (2-tailed)	0.189	0.074

Contd...

Table 3: Contd...

	Weight	HbA1c
<i>n</i>	84	84
Energy Fatigue		
Pearson's Correlation	-0.153	0.232*
Sig. (2-tailed)	0.166	0.034
<i>n</i>	84	84
Emotional wellbeing		
Pearson's Correlation	-0.114	0.199
Sig. (2-tailed)	0.301	0.069
<i>n</i>	84	84
Social Functioning		
Pearson's Correlation	-0.116	0.153
Sig. (2-tailed)	0.292	0.166
<i>n</i>	84	84
Pain		
Pearson's Correlation	-0.169	0.075
Sig. (2-tailed)	0.124	0.497
<i>n</i>	84	84
General Health		
Pearson's Correlation	-0.166	0.022
Sig. (2-tailed)	0.131	0.843
<i>n</i>	84	84

*Significant (P<0.05), **Highly significant (P<0.01), HbA1c=Hemoglobin A1c, PSQI=Pittsburgh Sleep Quality Index, WHO-5=5-item World Health Organization Well-Being Index

Lau *et al.*^[31] conducted a study to assess the relationship between glycemic control and the QOL in patients in DM patients from four community clinics in California, the USA. They assessed the QOL using SF-36, which was also utilized in our study. They found a significant association between better HbA1c levels and better mental QOL scores but not physical QOL. These results are not in agreement with our findings; our results showed that neither emotional nor physical well-being was not significantly correlated with glycemic control. This could be explained by the relatively small sample size in our study. Another explanation is that only patients with liraglutide treatment were included in our study while in Lau *et al.*^[31] they included all DM patients irrespective of their treatment regimen.

In another study, on T2DM patients in Manipal, showed that better glycemic control (HbA1c) significantly correlated with a better QOL as assessed by the modified diabetes QOL questionnaire (MDQoL)-17.^[32] In a Russian study on type 1 DM patients, better glycemic control was associated with higher QOL and better emotional state.^[33]

In a cross-sectional study, based on the Sleep and Food Registry in Kanagawa, Sakamoto, *et al.*^[13] found that Japanese patients with T2DM had poor sleep quality, especially those with inadequate glycemic control. After adjusting for age, gender, BMI, smoking, and other confounders, they found that the global PSQI score was significantly higher and that sleep duration was significantly shorter in the subgroup of patients in the top HbA1c quartile (HbA1c ≥7.9%).^[13] Chang and colleagues reported a significant decrease in sleep quality

and frequent nocturia in women with T2MD; these findings highlighted the importance of improving the sleep quality of DM patients through non-pharmacological management and lifestyle modifications.^[34]

A meta-analysis of 20 published studies showed that DM patients with longer or shorter sleep duration had significantly lower glycemic control compared to those with normal sleep duration.^[35] These findings highlight the importance of studying sleep quality in DM patients; however, owing to the methodological limitations of observational studies, it is difficult to establish the temporal relationship between sleep quality and glycemic control in a short time frame. Therefore, we cannot emphasize whether sleep quality affects glycemic control or better glycemic control affects better sleep quality. Future well-designed studies with larger sample sizes, longer follow-up duration, and further evaluation of the patients at different time points will help to shed light on the nature of the relationship between QOL, sleep quality, and glycemic control in DM patients.

Strengths and limitations

Strengths:

- (1) We assessed three different scales in the study population
- (2) Our study population is a homogenous group of T2DM patients taking liraglutide compared to the previous study, which included patients on different treatment regimens.

Limitations:

- (1) The selection of patients taking liraglutide only led to a relatively small sample in the study.
- (2) The lack of pre-post evaluation; therefore, we could not associate any of the clinical and psychological outcomes with the treatment regimen in the absence of the baseline data

Generalizability and current knowledge

This study expands the literature by providing evidence that patients with T2DM have poor sleep quality and moderate QOL, which requires further management and attention in clinical practice.

Conclusion

Patients with T2DM who are treated with liraglutide have moderate sleep difficulty and moderate QOL scores. Nonetheless, none of these outcomes was significantly correlated with glycemic control. Further well-designed studies, with long term, follow up and larger population size, are needed to confirm our findings.

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None.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/

their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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