WEEKLY TRELAGLIPTIN IMPROVES QUALITY OF LIFE IN TYPE 2 DIABETIC PATIENTS OF HYDERABAD, SINDH, PAKISTAN

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Abstract
Introduction
Type 2 diabetes is alarmingly increasing all over the globe. The oral anti diabetics are facing compliance problems, cost and limited improvement in quality of life. The DPP4 inhibitors increase incretin levels and have no chances of hypoglycemia thus improve overall quality of life.
Objective
To assess improvement in quality of life in type 2 diabetes mellitus, pre and post use of weekly trelagliptin attended OPD of Liaquat University Hospital Hyderabad / Jamshoro Sindh Pakistan
Study Design& duration. Quasi-experimental.
Study Setting; OPDs of Liaquat University Hospital Hyderabad / Jamshoro and
Duration of Study; July 2023 to October 2023
Methodology: 340 patients with type 2 diabetes for at least 2 years duration, already on metformin with or without glimepiride, age limit from 25-60 years of either gender were selected by nonprobability consecutive method. All patients had under gone for estimation of BMI, HbA1c and inquired for health related quality of life by LUMHS designed questionnaire. That questionnaire was designed after searching data base. 5 items calibrated from good to poor life quality such as finance, diet, sexual active, energy level and memory. Pre and post trelagliptin weekly given for 3 months and mean of pre and post response was assessed. The change of mean > 1.3 or Rubric > 10 score signified

better health related life. Reduction in HbA1c of at least ≥0.5% from the baseline and at 3 months was considered as secondary outcome achieved by weekly trelagliptin.

Results; 340 patients were selected, the mean age was 47 ±4.89 years. There were 220 males (65%) and 120 (35%) males. There is a significant proportion of males aged 47-60 years (61%) compared to females (37.5%). A higher percentage of females are married (79%). Females have a slightly higher mean BMI (25 ± 1.4) compared to males (24 ± 1.2). The values indicate that males have a higher average HbA1c level 0.5 compared to females 0.3. The pre and post Trelagliptin showed the variables Finance, Diet, Energy Level, and Sexual Activity showed statistically significant differences between males and females, with P-values less than 0.05. Memory, however, does not show a significant difference.

Conclusion: Weekly trelagliptin improved quality of life as well as HbA1c and it also better tolerated.

Keywords: Trelagliptin, weekly, Hyderabad, Diabetes

INTRODUCTION
Diabetes mellitus is an emerging metabolic problem with dysregulation of insulin and over secretion of anti-insulin hormones leads to hyperglycemia, dyslipidemia, vasculopathy and immune incompetency. Now diabetes accounts more than two thirds of cases of renal failure and retinopathy. Pakistan shows worst situation of diabetes , here , more than one third population is diabetic, making the total number of patients with diabetes are more than 3 crores.[1]

In Diabetes, problem of noncompliance of treatment is a serious issue and it increased when doctors are prescribed sub therapeutic doses .[2]

The treatment for type 2 diabetes focused on release of insulin or reducing peripheral resistance. Since 2 decades these pathophysiologies have been changed and more concentration on other physiological mechanism for example incretin, glucagon like peptides, amylin derivate or long biosimiliar insulin use. The past 30 years, concept to reduce sugar level and reduction of only HbA1c is significantly changed and now more emphasis on quality of life, prevention of major adverse coronary events and reducing foot ulcers.

Therefore any anti diabetic drug is not offering these mentioned targets, is no more under consideration for treatment by major diabetic societies guide lines.

In diabetics, the sensitivity to insulin is linked to intake of meal and counter regulatory hormones level. . The cessation of DPP-4 not only increases the post meal GLP-1 levels but also alters the 24-h pattern of GLP-1 levels, including fasting levels

Literature has shown that cessation of DPP4 enzyme promotes weight loss and stable control of diabetes. [3.] The use of DPP4 does not lead to hypoglycemia, drug interactions or renal damage. Sitagliptin was first drug of DPP4 group and studied in various aspects of diabetes including reduction in coronary events, fasting g in Ramadan , elder diabetics and add on treatment with insulin .

Trelagliptin, new molecule with once weekly dosing ,dipeptidyl peptidase-4 inhibitor, is highlighted for its better compliance and few side effects recently in Pakistan.

A single dose of trelagliptin , the median time to reach peak concentration was 1.0–1.5 h, and the elimination half-life in the elimination phase was 38.44–54.26 The inhibition of DPP-4 activity was maintained for 7 days.

In multiple studies using once-weekly trelagliptin at different doses in patients with poorly controlled type 2 diabetes , showed improvement in glycemic control than the placebo group, with good tolerability and acceptability .[5]

Health related Quality of life (HRQoL) is defined as a person's perceived quality of life representing satisfaction in the areas likely to be affected by health status. The assessment of HRQoL is important as it identifies health-related needs of a particular population and delivers quality care especially in populations with chronic diseases. [6]

Hence the improvement in HRQoL not only benefits the patients but also reduces social, financial and psychological burden related to chronic diseases. In recent past, HRQoL is emerging as an important assessment tool in caring the diabetics .

In one study concluded that HRQoL had a statistically significant relationship with gender, income, education, location, and duration of disease.

Quah *et al*. reported that higher HRQoL in diabetic patients is associated with young age, male gender, and a higher education level. Similarly, few others reported that patients having diabetes for more than 5 years had lower scores in all domains of quality of life except in blood pressure.[7]

At least 17 different scale are being used for assessment of quality of life in diabetics. Some are mentioned below

The appraisal of diabetes scale (ADS)

Audit of Diabetes-Dependent QOL measure (ADDQOL)

Diabetes Health Profile (DHP), and Problem Areas in Diabetes (PAID) are more suitable for single-scale questionnaires when investigating one or more specific aspects of diabetes-specific quality of life (QOL).

The ADDQOL, Diabetes Impact Measurement Scales (DIMS)

Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ-R

Iranian Diabetes Quality of Life (IRDQOL), Brief Clinical Inventory

The Asian Diabetes Quality of Life Asian DQOL

The Chinese Short Version of DQOL,

Elderly Diabetes Burden Scale (EDBS), Malay Version of Diabetes Quality of Life (DQOL), are relevant measures of HRQOL for diabetic type 2 patients.

The management of diabetes in Pakistan is challenging due to limited resources, poor access to health care, and a lack of awareness among the general population. Patients with diabetes in Pakistan are managed with a combination of lifestyle modifications and pharmacological interventions.[8]

According to the available data, a notable proportion of patients, specifically 18.7%, were found to have been prescribed with inaccurate dose or inappropriate dosage forms. [9]

The rationale of this study is to determine health related quality of life in diabetics in relation to weekly trelagliptin, which is comparatively new molecule.

METHODS

Three hundred and forty, out patients type 2 diabetics attending diabetic /medical OPDs of Liaquat university hospital Hyderabad / Jamshoro were fulfilling the inclusion criteria enrolled in this study by using 30% prevalence of type 2 diabetics are on insulin from 20th July 2023 to October 2023. The purpose, procedure, risks and benefits were explained, and written consent was obtained from patients on Proforma written in Urdu and Sindhi.

The data was collected on pre-designed Proforma including age, gender, BMI and duration of Diabetes. Baseline HBA1c level were noted .The BMI calculated by dividing the weight in kg with height in m^2. This study was quasie experimental. The sampling technique was nonprobability consecutive.

Three age groups were made from sample. Each patients already taken metformin with or without Glimepiride since diagnosis of diabetes. All groups were stopped other oral anti diabetics after trelagliptin use during study.

Base line HbA1C noted and final A1C was done after 3 months of weekly trelagliptin 100mg, which was supplied by authors with sub subsidiary rate.

The health quality related to the degree of people's life and their overall well-being, as well as their life satisfaction levels as either good or bad.

We have made Liaquat University of medical &health science questionnaire by using multiple data base and the search terms for example quality of life diabetes, quality of life, survey and measurements. The database searched included PubMed, Science Direct, CINAHL, PsycINFO, Medline and Pak medinet.

Finally 5 item and 3 sub items questionnaire was structured, started from high quality of life score 30 to lowest quality of life score 10. This questionnaire was filled before weekly trelagliptin and 3months after trelagliptin use.

LUMHS quality of life in diabetes

Finance		Diet		Energy level		Sexual active		Memory	
Manage well	6	enjoyment	6	Active	6	Active	6	Easy recall	6
Manage with difficulty	4	Diet dissatisfy	4	Fatigue after routine	4	1/ month	4	Impaired recall	4
Non manageable	2	Skip meals	2	Regular fatigue	2	Not even year	2	Unable to recall	2

30 Good
20 Moderate
10 Poor

The difference in between mean increase of 1.2 (10 rubric) in score of 5 item statically signifies improvement of quality of life. The reduction HbA1c of at least ≥0.5% from the baseline and reduction of BMI > 3% after 3 months of trelagliptin was considered secondary out comes.

Inclusion criteria
All patients with type 2 DM for at least 2 years duration, already taking metformin with or without Glimepiride.
● HbA1c > 7.5%
● Age limit from 25-60 years of either gender.

Exclusion criteria
● Type 1 Diabetes mellitus
● Patients with end stage renal disease on dialysis
● Patients with inflammatory conditions; i.e. with raised CRP levels
● Patients with frequent abdominal pain or recurrent Pancreatitis
● Patients with other endocrinopathies like thyroid, Addison's disease
● patients with pregnancy
● Patients on GLP1 agonists

Data analysis procedure
The data was analyzed by using SPSS version 22. The categorical variables such as gender, marital status, hypertension and efficacy were computed as numbers and percentages.
 The numerical data such as age, height, weight, BMI, baseline HbA1C and duration of diabetes were computed as mean and standard deviation or median (IQR) on the basis of normality.
The Pearson correlation was used for quality of life score and HbA1c and residence of patient and diabetes.
The stratification of questionnaire was done. The post stratification Chi-square test was applied on categorical variables at 95% confidence interval and the P-value ≤ 0.05 considered as statistically significant. The student t test was applied pre and post trelagliptin for responses.

RESULTS
The study was enrolled 340 patients from OPDs of Liaquat university hospitals of Hyderabad and Jamshoro blocks.

Results of Table 1
Sex Ratio was 1.8, indicating a higher proportion of males in the sample. Age distribution showed significant proportion of males aged 47-60 years (61%) compared to females (37.5%). The ratio of 3 indicates that older males are more prevalent in the sample. There was higher percentage of females are married (79%) compared to males (68%), with a statistically significant p-value of 0.03, indicating a meaningful difference in marital status distribution between genders.

The urban to rural ratio is similar between males and females, with no significant difference as indicated by the p-values (0.07 and 0.09).

Females have higher mean fasting sugar levels (127 ± 6.5) compared to males (115 ± 10).The

The mean duration of diabetes is the same for both genders (2 years), with a slightly higher standard deviation in females. The p-value of 0.05 suggests borderline statistical significance

Females have a slightly higher mean BMI (25 ± 1.4) compared to males (24 ± 1.2), with a p-value of 0.04, indicating statistical significance .Females have higher mean systolic blood pressure (140 ± 5.5) compared to males (125 ± 6.6), but the p-value of 0.8 indicates no significant difference. Males have slightly higher HbA1c levels (7.5 ± 1.7) compared to females (7 ± 1.5), but the p-value of 0.7 suggests no significant difference.

A higher proportion of males (91%) responded to all questions compared to females (83%), with a ratio of 2.(table 1)

Results of Table 2

Males generally score higher in finance (mean score of 4) compared to females (mean score of 3), with a relatively similar spread of responses (standard deviations of 1 and 1.2, respectively).

Both genders score high on diet, with females scoring slightly higher (mean score of 5) compared to males (mean score of 4.5). The standard deviation is the same (1), indicating a similar variation in responses.

Males have a higher mean score for memory (5) compared to females (4), with males having a smaller standard deviation (0.5) indicating less variability in responses compared to females (1.4).

 Both genders have the same mean score for energy level (4) with identical standard deviations (1), suggesting similar responses and variability.

There is a significant difference in the mean scores for sexual activity, with males scoring much lower (mean score of 2) compared to females (mean score of 5). The standard deviation for males (1.4) indicates greater variability in their responses compared to females (1).

Results of Table 3

Finance: The score difference shows a significant male dominance (1:3 ± 1.0).

The P-value (0.02) indicates a statistically significant difference between males and females in finance scores.

Diet. The score difference indicates equal variability for males and females (1 ± 1:1 ± 1).

The P-value (0.04) suggests a statistically significant difference between males and females in diet scores. The score difference shows males have slightly less variability compared to females (1 ± 0.5:1 ± 1.4).

Memory: The P-value (0.5) suggests no statistically significant difference in memory scores between males and females. The score difference indicates equal scores for males and females (1 ± 1:1).

Energy Level: The P-value (0.03) indicates a statistically significant difference in energy levels between males and females.

Sexual Active: The score difference shows a slightly higher male dominance (1.4:1).The P-value (0.04) suggests a statistically significant difference between males and females in sexual activity scores.

Results of Table 4

The values indicate that males have a higher average HbA1c level (0.5) compared to females (0.3). The p-value of 0.05 suggests that the difference in HbA1c levels between males and females is statistically significant at the 5% significance level. This means there is a 5% chance that the observed difference is due to random variation, and a 95% chance that it reflects a real difference between the sexes

Males have a higher BMI (2.1) compared to females (1.0). The p-value of 0.07 indicates that the difference in BMI between males and females is not statistically significant at the conventional 5% level but is close to it. This means there is a 7% chance that the observed difference is due to random variation. Males have higher systolic blood pressure (5) compared to females (3).

Table 1. Demographic characteristics of 340 patients

Variable	Male	Female	Percentage/ratio	P value
Sex (M /F)	220(65%)	120(35%)	1.8	
Age year 25 – 35	35(15%)	25(21%)		
36- 46	60(27%)	50(42%)	1.2	
47- 60	135(61%)	45(37.5%)	3	
Married	150(68%)	95(79%)	1.5	0.03
Un married	70(32%)	25(21%)	2.8	
Residence Urban	130(59%)	70(58%)	1.8	0.07
Rural	90(41%)	50(42%)	1.8	0.09
Sugar(mean) Fasting	115±10	127±6.5		
Duration of diabetes years(mean)	2 ±1.2	2±1.7		0.05
BMI(mean)	24±1.2	25±1,4		0.04
BP(mean) systolic	125±6.6	140±5.5		0.8
HbA1c	7.5±1.7	7±1.5		0.7
Respondents to all questions	200(91%)	100(83%)	2	

Table 2. Response rate of 340 respondents before weekly trelagliptin

Variable / question	MALE (220)	FEMALE(120)	Mean score M:F
FINANCE	190	100	4±1:3±1.2
DIET	200	110	4.5±1:5±1
MEMORY	180	110	5±0.5:4±1.4
ENERGY LEVEL	210	115	4±1:4±1
SEXUAL ACTIVE	170	90	2±1.4:5±1

Table 3. Improvement in Response of 340 patients after weekly trelagliptin

Variable	MALE	FEMALE	Score difference M:F	P value
Finance	200	110	1:3±1.0	0.02
DIET	200	110	1±1:1±1	0.04
MEMORY	190	110	1±0.5:1±1.4	0.5
ENERGY LEVEL	215	110	1±1:1	0.03
SXUAL ACTIVE	200	100	1.4:1	0.04

Table 4. Secondary endpoints of 340 patients after weekly trelagliptin

Variables	MALE	FEMALE	P value
HbA1c (%)	0.5	0.3	0.05
BMI	2.1	1.0	0.07
HTN (systolic)	5	3	0.06

DISCUSSION

This study is unique one in medical literature because previous all studies done on trelagliptin were few patients and focused just aspect of compliance. Our study has been focused the quality of life as well as secondary end points also for instance BMI and weight loss

Diabetes needs a holistic care, multiple drug treatment , proper and timely assessment of complications. Mishandling of any of these components result worst quality of life and serious life threating events in patients with type 2 diabetes.[10]

Our study have included those subjects who were on metformin or combination of metformin and glimepiride. Before initiation of weekly trelagliptin, treatment of metformin or combination was stopped and our approach is matched to a study has shown that trelagliptin was better to once-daily alogliptin in lowering hemoglobin A1c in patients with type 2 diabetes. [11]

A small study of Asian origin patients with type 2 diabetes were kept on once weekly trelagliptin, showed better glycemic control than vidagliptin daily [12]. Our study shown decrease in HbA1c after 3 months of trelagliptin and p-value of 0.05 suggested that the difference in HbA1c levels between males and females is statistically significant. That showed over all stable or better glycemic profile of patients

In our study patients were selected with HbA1c over 7% and age limit was 25 to 60 years which is better selected than a study has shown patients aged more 20 years with Type 2 diabetes with HbA1c $\geq 6.5\%$ and $< 10.0\%$ at the start of screening.[13]. This study also created bias because author have selected newly diagnosed patients and kept on DPP$ which is against guide lines

There were also no major changes in the other efficacy parameters, such as HbA1c and FPG. Regarding safety, we previously demonstrated that trelagliptin shows a similar safety profile as an once-daily DPP-4 inhibitor, alogliptin[14].

Our study was conducted over 3 months and HbA1c was assessed 2 times 0 and at 3 months which is similar to Ishii et al [15] consisted of one month screening period and 3 months treatment period. Patients were assessed during screening at one month, and at weeks and 3 months of the treatment period by that researcher.

The main areas of quality of life improved were finance, sexual activity and memory.

The variables Finance, Diet, Energy Level, and Sexual Activity show statistically significant differences between males and females, with P-values less than 0.05. Memory, however, does not show a significant difference

There is a significant difference in the mean scores for sexual activity, with males scoring much lower (mean score of 2) compared to females (mean score of 5). The standard deviation for males (1.4) indicates greater variability in their responses compared to females (1).

Males generally score higher in finance (mean score of 4) compared to females (mean score of 3), with a relatively similar spread of responses (standard deviations of 1 and 1.2, respectively).

There is a notable difference in fasting sugar levels and systolic blood pressure between genders, although only BMI and marital status differences are statistically significant.

These all above observation could be partly due to better compliance as one study showed that patients with diabetes are more adherent to medications that are dosed less frequently.

During 3 months study period, we didn't report any serious side effects which is match able to study showed Trelagliptin has a similar safety profile to daily DPP-4 inhibitors.[17]

In our study , primary end points were change in quality score or their means and secondary end points were BMI and Hba1c which is similar to study published in Diabetes [18] shown same end points and secondary out comes which was only BMI . While we have shown 3 secondary end points BMI, BP and HbA1c.

CONCLUSION
This study concluded significance of right choice of treatment in diabetes. Many oral anti diabetics are good in controlling sugar but not improving in quality of life. The selection of oral therapy for diabetes should focus in prevention of complications, compliance and improve standards of life.

More studies are needed for exploring health related quality of life in chronic conditions like diabetes in Pakistan.

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