Effect of dulaglutide injection on weight beyond glycemic control: real-world observational study

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Abstract

Dulaglutide is an effective Glucagon-like Peptide-1 (GLP-1) Receptor Agonist (RA) in optimizing weight and glycemic control in obese patients with Type 2 Diabetes Mellitus (T2DM). The study's objective was the real-world evaluation of the metabolic effect of Dulaglutide on weight and glycemic control in patients with T2DM from Southern Iraq. This study is a six-month observational prospective longitudinal evaluation of 185 obese individuals with T2DM. They were initiated on Dulaglutide as an add-on drug with Oral Antidiabetic (OAD) or insulin therapy. General characteristics of the patients, glycated hemoglobin (HbA1c), blood glucose, lipid profile, and side effects profile were evaluated at the enrollment and the end of the study. The enrolled 185 obese patients with T2DM, had a T2DM duration (2 -14 years) and initial HbA1c range (6 - 19.5%), with different treatment modalities, including insulin, OADs, or both. The study showed a significant reduction in weight, HbA1c, and serum cholesterol, with minimal hypoglycemic events in 5% of patients (n=9). The gastrointestinal side effects were mild to moderate and self-limited in >96% of patients (n=178), while they were so severe in 4% (n=7) and caused discontinuation of Dulaglutide. Therefore, the insulin regimen was either stopped (n=28), changed (n=7), or reduced (n=9). No change on oral medications was performed in 141 patients. In conclusion, Dulaglutide 1.5 mg administered once a week significantly reduced the weight, HbA1c, Self-Monitoring of Blood Glucose (SMBG), and cholesterol levels with minimal hypoglycemic risk.

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Informed consent: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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Introduction

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) are effective therapies for the treatment of type 2 diabetes.[1] Recent guideline placed GLP-1 RA as second-and third-line therapy.[2]

The most popular GLP1-RA, Dulaglutide, acts by increasing glucose-dependent insulin secretion, decreasing glucagon release, inhibiting hepatic gluconeogenesis, slowing gastric emptying, and centrally suppressing appetite. These effects are dose-dependent, which makes Dulaglutide more beneficial in individuals who need better control of their glycated hemoglobin (HbA1c), Fasting Plasma Glucose (FPG), and Postprandial Plasma Glucose (PPG) excursions, along with weight reduction, with its minimal hypoglycemic effect.[3-5]

Dulaglutide as monotherapy reduces HbA1c levels by 0.5% to 0.8%. Higher dosages do not provide a further significant decrease in HbA1c,[6] the combination with metformin and dulaglutide lowers HbA1c levels by 0.7% to 1.0%; greater reduction in HbA1c values was observed among patients with higher HbA1c values at baseline.[7]

Clinical trials reported gastrointestinal-related side effects

(e.g., nausea, vomiting, and diarrhea) as the most frequent adverse effect, ranging in severity from being self-limited to the degree that may cause drug discontinuation due to intolerance of the drug.[8]

In this study, we tried to evaluate the effectiveness of Dulaglutide in real-world and assess its metabolic effects in obtaining glycemic control and weight reduction; the side effect profile was studied as well.

Materials and Methods

This study involved the observational prospective longitudinal evaluation of a cohort of individuals with T2DM who attended Thi Qar Specialized Diabetes Endocrine and Metabolism Center (TDEMC) from March to September 2021.

The inclusion criteria in this study included individuals with poorly controlled T2DM who were overweight or obese, who received therapy with single or multiple Oral Antidiabetics (OADs), with or without insulin, and with or without microvascular complications. One hundred ninety-one individuals fulfilled the aforementioned criteria and agreed to start dulaglutide with weekly checking in TDEMC.

Six patients were considered defaulters and were excluded from the study, of whom four individuals received only a single injection of Dulaglutide. They discontinued it without explaining their choice, and two individuals discontinued it due to the cost. The final number of individuals in the study was 185 individuals.

Individuals with type 1 diabetes mellitus, pregnant women, individuals with T2DM with any stage of chronic kidney diseases or liver diseases, any patient with any overt thyroid dysfunction, and any patient with poorly controlled diabetes who refused the injectable medications were excluded from the study.

The HbA1c shows the patient's average blood glucose level over the past 2 or 3 months, and was measured at the enrollment visit and the end of the study using High-Performance Liquid Chromatography (HPLC) by BioRad D-10. All enrolled individuals were advised to bring their daily Self-Monitoring of Blood Glucose (SMBG) (at least twice daily) during their weekly visits.

We considered the patient has diabetes if the blood glucose level is 200 mg/dL or higher. We used HbA1c also to measure the patient's average blood glucose level over the past 2 or 3 months. An HbA1c below 5.7% is normal, between 5.7 and 6.4% indicates the patient has prediabetes, and 6.5% or higher indicates diabetes.[9]

All the enrolled individuals agreed to sign an informed consent, which indicated the study objectives and the possible management interventions, and a detailed description of possible investigation protocol in the center. The ethical review committee approval number is (TDEMC/D/2021/9/6).

For statistical analysis, we used IBM SPSS Statistics for Windows, Version 26.0. (Armonk, NY: IBM Corp.) for analysis of different variables. The study used the mean ± Standard Deviation (SD) or frequency (%) for data expression. We used the standard error of the mean in variables with multiple statistical outliers. Graphical representation of the data was done by bar and pie charts. The arithmetic log of the test variable was used to ensure the minimal aberration from normality distribution, which was further tested using Kolmogorov–Smirnov test (KS test) and Shapiro-Wilk test with Lilliefors correction. Paired sample t-test was used to assess the changes in different parameters and their arithmetic log at enrolment and the end of the study. A 2-sided significance (p-value) ≤0.05 was considered statistically significant at a 95% confidence interval.

Table 1. General characteristics of the 185 patients with T2DM.

Variable		Results
Women n (%)		122 (65.9)
Age (Years) Mean±SD	All	51±10
	Age range	25-75
	Men	51±10
	Women	51±10
Weight (Kg)	Mean±SD	106.16±6.01
Body Mass Index (Kg/m^2)	Mean±SD	40.70±6.01
	BMI range	28.72-60.77
	Overweight n (%)	6 (3.24)
	Obesity class I n (%)	23 (12.43)
	Obesity class II n (%)	64 (34.60)
	Obesity class III n (%)	92 (49.73)
Duration of T2DM (Years)	Mean±SD	6.52±2.94
	Range	2-14
SMBG mean±SD mg/dL		285.25±94.21
Glycated Hemoglobin	Mean±SD	10.76±2.21
	Range	6-19.5
Serum Total Cholesterol (mg/dL)	Mean±SD	228.0±53.44
Serum Creatinine (mg/dL)	Mean±SD	0.77±0.14
Modalities of Treatment (%)	Insulin Alone	7 (3.8)
	OAD Alone	141 (76.2)
	Combination	37 (20)
Number of Dulaglutide Shots	Mean±SD	8±3
	Range	4-17

Abbreviations: BMI, body mass index; OAD, oral antidiabetic; SD, standard deviation; SMBG, Self-Monitoring of Blood Glucose; T2DM, type 2 diabetes mellitus.

Results

We enrolled 185 patients with T2DM, about 66% were women (n=122). The overall mean age and gender-specific mean age were similar. Approximately 97% of patients (n=179) were obese of different classes. The duration of T2DM ranges from two to fourteen years. The initial HbA1c readings were uncontrolled and ranged (from 6 - 19.5%), with a mean of (10.76 ± 2.21%), with different treatment modalities, including insulin, OADs, or both. The enrolled patients had normal mean serum creatinine (0.77 ± 0.14 mg/dL) and elevated serum cholesterol (228.0 ± 53.44 mg/dL).

Figure 1 shows the total number of Dulaglutide shots during the study, which were affected by Gastrointestinal (GI) side effects. These side effects were severe enough to cause the drug discontinuation in seven patients, while they were mild to moderate and self-limited in the rest (Figure 2).

The variables of interest in this study, namely body weight, Body Mass Index (BMI), HbA1c, mean SMBG, total serum cholesterol, did not show the normal distribution for their values in presentation or at the end of the study (Table 2). The normality distribution was assured using Kolmogorov-Smirnov and Shapiro-Wilk with Lilliefors correction for the native and arithmetic log of some of the variables above (body weight, BMI, and initial HbA1c). The distribution of other variables (HbA1c at the end of the study, mean SMBG, and total serum cholesterol) did not show normality distribution even after log conversion due to multiple outliers (Table 2).

In Table 3, we used Paired Sample T-Test to evaluate the reduction of body weight, BMI, HbA1c, mean SMBG, and total serum cholesterol during the study. All the test variables showed a marked and significant reduction in their enrollment and the final values. The pattern of significant reduction was not affected by the normality distribution.

The insulin regimen in 44 patients was changed either in the form of stopping the insulin entirely (n=28), shifting to another insulin type instead of what was previously used (n=7), and the reduction of the insulin dose (n=9), as seen in Figure 3. There was no change in the OADs during the study.

In the course of the initiation of the study during the first four

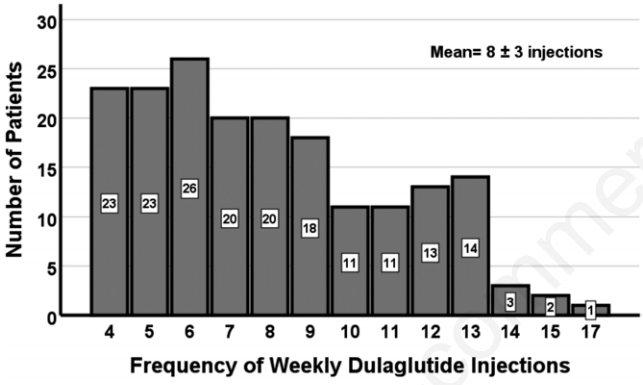

Figure 1. Frequency of weekly Dulaglutide injection in 185 patients with T2DM.

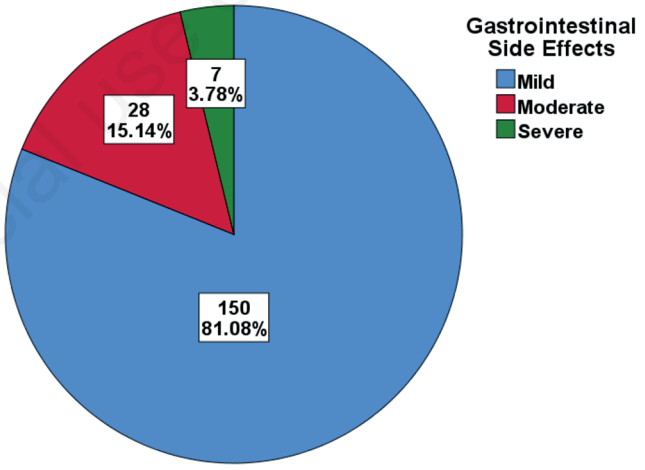

Figure 2. Severity of gastrointestinal side effects in 185 patients with T2DM after treatment with Dulaglutide 1.5 mg/week.

Table 2. Significance levels (p-value) of normality testing using Kolmogorov-Smirnov and Shapiro-Wilk with Lilliefors correction for the variables in the final testing.

Variables	Kolmogorov-Smirnov Significance		Shapiro-Wilk Significance	
	For native values	For log (variable)	For native values	For log (variable)
Weight at enrollment	0.038	0.200	0.008	0.209
Weight at end of study	0.002	0.200	0.005	0.077
Body Mass Index at enrollment	0.042	0.200	0.026	0.761
Body Mass Index at end of study	0.040	0.200	0.029	0.880
Glycated Hemoglobin at enrollment	<0.0001	0.006	0.001	0.122
Glycated Hemoglobin at end of study	0.002	<0.0001	0.004	<0.0001
Mean SMBG at enrollment	<0.0001	0.004	<0.0001	0.029
Mean SMBG at end of study	<0.0001	<0.0001	<0.0001	<0.0001
Total Cholesterol at enrollment	<0.0001	<0.0001	<0.0001	<0.0001
Total Cholesterol at end of study	<0.0001	0.002	<0.0001	<0.0001

Abbreviations: SMBG, Self-Monitoring of Blood Glucose.

weeks, nine individuals described mild to moderate hypoglycemic attacks, which were self-limited. These attacks were confined to patients on insulin and Dulaglutide together. Yet, these attacks contributed to the cessation of insulin in four patients and adjustment in three patients only. We did not change the insulin regimen in the remaining two patients as the attacks were minimally effective.

Discussion

To the extent of our knowledge, this is the first study that dealt with Dulaglutide use in Iraq; the agent, which was launched to use in Iraq in early 2020 for patients with T2DM, is not registered yet to be used in public hospitals and centers, with the cost issues for the patients with T2DM as the main hurdle for its common use in the clinical private practice setting.

The age distribution in this study was (25 - 75 years), which was similar to the age ranges in many randomized controlled trials like AWARD trials.[9,10] However, AWARD-4 showed nonconfirmatory results regarding using this agent in the young age group.[11]

Although our results regarding the mean duration of T2DM, mean fasting SMBG readings, and HbA1c levels were somewhat similar to the results in AWARD trials,[9-12] minor differences could be attributed to the selection criteria of the patients in the studies, their add-on medications, and their general characteristics.

The study lasted six months, and the number of Dulaglutide injections (Figure 1) differed from one patient to another depending on personal factors like the severity of the adverse events. The cost of Dulaglutide is not included in the assessment because we did not have any objective tool to assess the financial level of the enrolled individuals in this study.

Obesity in individuals with poorly controlled T2DM represents the main motive for using Dulaglutide as a monotherapy or combination, whether their initial treatments included insulin or OADs.[12,13]

This study showed significant weight and BMI reduction following Dulaglutide injection in a similar pattern to AWARD trials.[9,10] We could not conclude whether this reduction is dose-dependent because the study was short real-life study with no comparator group, unlike the lengthy AWARD trials and other studies, which used different comparators.[11,12]

This study described a higher weight reduction than what was shown in other AWARD studies because the enrollment criteria were different.

The patients receiving Dulaglutide injections significantly reduced the mean HbA1c and SMBG to more than 25% and 42% of their original values, respectively. These reduction trends were similar to or slightly more than that of AWARD's and other studies, which described dose-dependently reduced glycemic parameters.[9-11,14-16]

The effect of Dulaglutide on glycemic level may be evident in the first weeks of treatment initiation due to its 12 – 72 hours of peak activity after injection, followed by the 2 – 3 weeks steady-state.[17]

The differences between the mean reduction in HbA1c and SMBGs between this study and the AWARD trials could be attributed to the tolerability of the selected GLP-1 RA, background therapy, and the baseline HbA1c.[18]

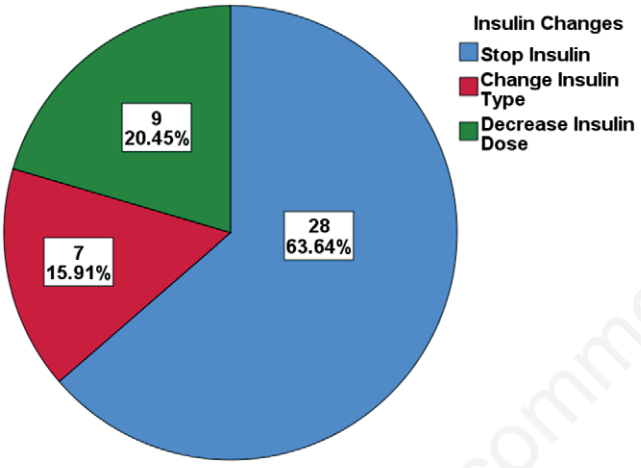

Figure 3. Manipulation of daily insulin injection in 44 patients on different insulin-containing therapeutic regimens. Nine patients described self-limited mild to moderate hypoglycemic attacks.

Table 3. Mean reduction in different variables in the study using paired sample T-test.

Variables	At the start of the study	At the end of the study	Paired Difference	95% C.I. of the difference		p
				Lower	Upper	
Weight (kg) Mean (SE)	106.16 (1.13)	99.27 (1.10)	6.89 (0.44)	6.03	7.75	<0.0001
Log Weight Mean (SE)	2.02 (0.01)	1.99 (0.01)	0.03 (0.002)	0.03	0.03	<0.0001
BMI (kg/m2) Mean (SE)	40.70 (0.44)	38.08 (0.42)	2.62 (0.16)	2.30	2.95	<0.0001
Log BMI Mean (SE)	1.61 (0.01)	1.58 (0.01)	0.03 (0.002)	0.026	0.033	<0.0001
HbA1c Mean (SE)	10.76 (0.16)	8.00 (0.11)	2.76 (0.13)	2.50	3.02	<0.0001
Log HbA1c Mean (SE)	1.02 (0.01)	0.90 (0.01)	0.12 (0.01)	0.12	0.14	<0.0001
SMBG (mg/dL) Mean (SE)	285.25 (6.93)	163.98 (2.20)	121.27 (6.80)	107.88	134.67	<0.0001
Log SMBG Mean (SE)	2.43 (0.01)	2.21 (0.01)	0.22 (0.01)	0.21	0.25	<0.0001
TC (mg/dL) Mean (SE)	227.96 (3.93)	182.20 (3.01)	45.76 (4.48)	36.93	54.60	<0.0001
Log TC Mean (SE)	2.35 (0.01)	2.25 (0.01)	0.1 (0.01)	0.08	0.11	<0.0001

Abbreviations: BMI, body mass index; C.I., confidence interval; HbA1c, glycated hemoglobin; SE, standard error; SMBG, Self-Monitoring of Blood Glucose; TC, Total Cholesterol.

In Figure 3, we described the pattern of insulin adjustment for the 44 patients with T2DM with add–on Dulaglutide. The minimal contribution of the hypoglycemia to the adjustment and obtaining acceptable SMBGs results were the main motives for adjustment or stopping the insulin therapy in this subgroup of patients.

The insulin-induced hypoglycemic risk is lower with GLP-1RAs, due to the complex interaction between glucose-dependent insulin release from pancreatic beta cells and glucagon suppression.[11]

Accordingly, in patients who are obese with poorly controlled T2DM on a basal insulin regimen, with or without OADs, the GLP–1 RA may provide a logical option to adjust their weight and the complex multidose insulin regimen.[2] In the current study, such adjustment and stringent titration of insulin therapy may contribute to the lower levels of SMBG and HbA1c.

The total serum cholesterol was lowered and somewhat normalized after Dulaglutide 1.5 mg therapy for our enrolled patients, similar to what was shown in the AWARD trials' lipid profile, which could contribute to weight reduction and change of some dietary habits.[10,11]

Our enrolled patients reported less severe gastrointestinal side effects attributed to Dulaglutide, which led to the discontinuation of the presumed therapy in less than 4% of the cohort (n=7) in the first four weeks of initiation of therapy. AWARD-5 showed a similar figure of (3%) of patients who discontinued Dulaglutide, although the selection criteria and sample size differed.[19]

This figure was far less than Jiang *et al*., which was 16% of cases due to the same reasons.[20] The rest of the cohort completed their injection despite mild to moderate GI side effects, which were described as self-limited. These adverse events could be managed conservatively by consuming smaller portions regularly.[21]

AWARD trials related these transient GI side effects with the transient elevation of the concentration of pancreatic enzymes through a GLP-1-based mechanism.[9,16,22]

Conclusions

Dulaglutide at a dose of 1.5 mg per week was associated with a significant reduction in weight, HbA1c, SMBGs, and cholesterol levels with minimal risk of hypoglycemia in this sample of 185 patients with T2DM in this real-world longitudinal data from Southern Iraq.

A larger population in a longitudinal and prospective evaluation of patients with more diverse characteristics is needed to better illustrate Dulaglutide's effect in patients with T2DM for better generalization of the results.

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