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Liraglutide Effect on Blood Pressure, Lipids Profile, and Liver Enzymes in Arab Patients with Type 2 Diabetes Mellitus: A Prospective LIRA-BPL Study

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Abstract

Background: The pathogenetic mechanisms underlying type2 diabetes are quite complex and differ between different ethnic groups. This might results in different responses to medications. Data from LEAD trials showed that liraglutide was associated with significant reduction in weight HbA1c and blood pressure values. Unfortunately there are no enough data on Arab population.

Objectives: We aimed to assess the changes in blood pressure, lipids profile, and liver function test upon starting liraglutide and after 6 months of therapy in Arab patients with type 2 diabetes as primary objective.

Results: 365 agreed to sign an informed consent. 29% of the studied population was males (n=106) compared to 71% females (n=259). There was no significant change in systolic blood pressure, however average diastolic blood pressure improved significantly (74.4 ± 10 to 72 ± 9 mmHg at 6 months P<0.001). Significantly lower average diastolic BP was seen in Insulin users at both start and the end of the study (73+4 vs. 76+4 P=0.05, and (71+ 5 vs. 73+4.6) p=0.02, respectively). Mean AST and ALT was within normal range at baseline and despite that there was a highly significant reduction between baseline and end of study 29+18 to 25.7+ 13 and 25.1 + 20 to 22.2+ 16 for ALT and AST, respectively. Both of them showed highly significant P value (0.0000). There was a significant reduction in weight and HbA1c at 6 months. However the change in weight was more significant in insulin users compared to those who did not use insulin (96+3 to 93+5 vs. 93 +5 to 98+3.5, P-value at the end of the study was 0.02). The HbA1c reduction was significant irrespective of weight loss.

Conclusion: Liraglutide showed remarkable improvement in weight, HbA1c, liver enzymes, and diastolic blood pressure. Patients who used insulin at base line had better results in weight and lipids reduction.

Keywords: Liraglutide; Diabetes; Arab; Metabolic; UAE; ALT; AST; Blood pressure

Abbreviations:

ALT: Alanine Aminotransferase; AST: Aspartate Transaminase; GLP-1: Glucagon-Like Peptide; GFR: Glomerular Filtration Rate; SPSS: Statistical Program for Social Science

Introduction

Type 2 diabetes and obesity have become increasingly linked over the last decades; in fact as many as 80% of individuals with type 2 Diabetes are obese [1]. Therefore, efforts are being made to produce agents that act simultaneously to reduce weight and achieve Euglycemia. Glucagon-like peptides-1 (GLP-1) are physiological agents that are produced by the L- cells in the small intestine, the Jejunum specifically [2]. The GLP-1 agonists are a pharmacological preparation that is proved to control blood glucose and, to a considerable extent, reduce weight. The GLP-1 agonists' receptors have been found in different organs in the body including the pancreas, brain, stomach, heart, and intestine [3]. The physiological effects of the GLP-1 in various end organs are yet to be unveiled.

Liraglutide has been proved to be an efficacious agent among the GLP-1 agonists-its effect on glucose control, weight reduction, blood pressure reduction, and modulation of metabolic parameters [4-7]. But, to our best knowledge, it was not tested on the Arab population separately. Since many pharmacological agents showed different effects in different races, we conducted this study on patients from Arabic backgrounds looking into the efficacy of Liraglutide in modulating the blood pressure and metabolic parameters.

Patients and Methods

Aim of the study

We aimed to evaluate the efficacy of Liraglutide in modulation of different metabolic parameters in patients from Arabic descent with type 2 diabetes.

Primary objective

We aimed to assess the changes in blood pressure, lipids profile, and liver function test from the day of starting the Liraglutide and after 6 months of therapy.

Secondary objectives

We wanted to assess the same metabolic changes in insulin- and non-insulin-treated subjects before and after initiation of the Liraglutide and after 6 months.

Study design

The aim of this study was to assess the effect of Liraglutide in improving metabolic parameters in patients from Arabic descent with type 2 diabetes. The study adhered to the tenets of the Declaration of Helsinki. The protocol was compliant with the Health Insurance Portability and Accountability Act and approved by the Dubai Health Authority review board and given a reference number (MRC-08/2013_03).

In the first visit and after having an informed consent signed, we recorded the patients' demographics (age, sex, ethnic background), co-morbidities, current medications, weight, and blood pressure. Laboratory tests including fasting blood glucose, creatinine, and lipids profile (Total cholesterol, Low-density lipoprotein, Triglycerides). After 3 and 6 months respectively, we measured weight, blood pressure, creatinine, lipid profile, AST and ALT, as well as Insulin doses. Patients who did not complete the 6-month duration or who missed the follow-up and patients with contradicting results in medical files and the electronic database were excluded from the study.

Study population

We included 436 patients with type 2 diabetes mellitus who accepted to start Liraglutide (and willing to pursue the study for 6 months). The study was conducted in two main governmental diabetes centers in Dubai, United Arab Emirates, both of which provide tertiary-level diabetes service and follow the international guidelines of diabetes treatment. Both centers receive patients via the same referral pathway, ending up with seeing similar population. Inclusion criteria included Arab patients with an age range of 18 to 70 years, being diagnosed with type 2 diabetes mellitus, and being overweight or obese (BMI >30 kg/m^2) at the time of inclusion. We have excluded those with type 1 diabetes mellitus, renal impairment (creatinine clearance <60 ml/m^2) in the estimated GFR calculation, pregnant women, and those with history of pancreatitis.

Data analysis

Analysis of data was done using SPSS (statistical program for social science version 16) as follows:

Description of quantitative variables as mean, SD, and range

Description of qualitative variables as number and percentage

Chi-square test was used to compare qualitative variables between groups.

Unpaired t-test was used to compare quantitative variables in parametric data (SD<50% mean)

Mann Whitney test was used instead of unpaired t-test in non parametric data

(SD>50%mean)

Paired t-test was used to compare quantitative variable within the same group before and after in parametric data (SD<50%mean)

Wilcoxon test was used instead of paired t-test in non-parametric data (SD>50%mean).

P value <0.05 was considered significant and P<0.001 considered highly significant.

Definitions

Patients were considered to have type 2 diabetes if they fulfilled the ADA criterion for diagnosis of diabetes mellitus (FBG >/=126, 2hours postprandial glucose >/= 200 mg/dl, or HbA1c >/=6.5%), or if the patient was already on OHA other than metformin or on insulin. Patients on metformin alone are not considered diabetic unless they fulfilled the ADA criteria. Hypertension was defined as a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or being on antihypertensive medications.

Results

We screened 463 patients; 365 agreed to sign an informed consent. 29% of the studied population was males (n=106) compared to 71% females (n=259). The mean age was 50.4 10. At the base line, 56.3% of patients were on an insulin-based regimen either basal-plus, basal bolus, or premixed. 90.1% of patients were on metformin, 43.5% were on Sulphonyureas, 10.7% were on DPP4 inhibitors, 0.8% on Acarbose, and 85.2% were on statins.
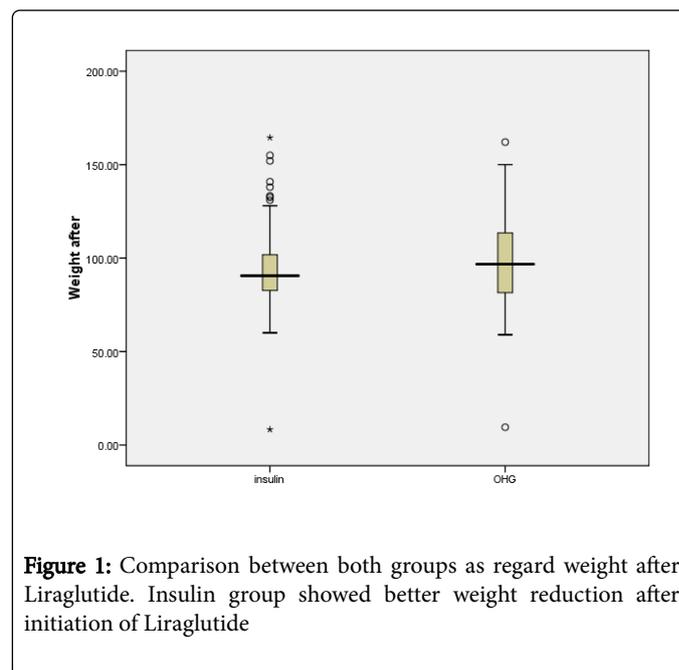
Figure 1: Comparison between both groups as regard weight after Liraglutide. Insulin group showed better weight reduction after initiation of Liraglutide

Base line mean weight was 96.01 ± 19.2 Kilograms (KG). While baseline HbA1c was 8.3 ± 1.7, both parameters improved at the end of the study. Surprisingly, upon further analysis of the weight reduction between those who used to be on insulin or not, the weight loss was higher in the insulin treated group at the start and end of the study 96+3 to 93+5 VS 93 +5 to 98+3.5, P value at the end of the study was 0.02 (Table 1, and Figure 1). Interestingly, upon further analysis of HbA1c results, the group who had weight reduction did not have lower HbA1c than the weight constant group (Table 2).

P	t	Treatment		Variables
		Non-insulin group	**Insulin group**	
0.87NS	0.95	98+4.6	96+3	Weight before (Kilograms)
0.02S	3	98+3.5	93+5	Weigh after (Kilograms)
0.45NS	1.2	97+2.5	93.4+4.3	Weigh after follow up (Kilograms)
0.89NS	0.3	163+24	166+23	Total cholesterol before
0.45NS	1.5	151+10	155+11	Total cholesterol after
0.34NS	1.8	143+22	137+20	TG before (mg/dl)
0.49NS	1.6	124+20	135+20	TG after (mg/dl)
0.33NS	1.1	0.78+0.11	0.77+0.2	CR before (mg/dl)
0.70NS	0.6	0.77+0.3	0.76+0.2	CR after (mg/dl)
0.55NS	0.9	23.7+6	25.3+2	AST before
0.90NS	0.13	21+4	22.8+5	AST after
0.67NS	0.60	29.2+3	28.1+4	ALT before
0.78NS	0.23	26.1+4	25.6+3	ALT after
0.40NS	0.80	132+15	131+17	SBP before (mmHg)
0.33NS	1.30	129+11	132+16	SBP after (mmHg)
0.05S	2.2	76+4	73+4	DBP before (mmHg)
0.02S	2.6	73+4.6	71+5	DBP after (mmHg)

This table shows that insulin treated group had more weight reduction and lower DBP after Liraglutide compared to non-insulin with statistically significant difference by using unpaired t-test.

TG=Triglycerides, CR=Creatinine, ALT: Alanine aminotransferase, AST: Aspartate transaminase, SBP=Systolic blood pressure, DSP=Diastolic blood pressure

Table 1: Comparison between insulin and non-insulin group as regard different parameters before and after Liraglutide

There was a highly significant improvement in total cholesterol and triglycerides at 6 months after initiation of Liraglutide. Nonetheless, the reduction of the lipid profile took place equally in both the statin and non- statin contained regimens (Table 3). Similarly, being on insulin or not did not affect the lipids panel change through the study (Table 1).
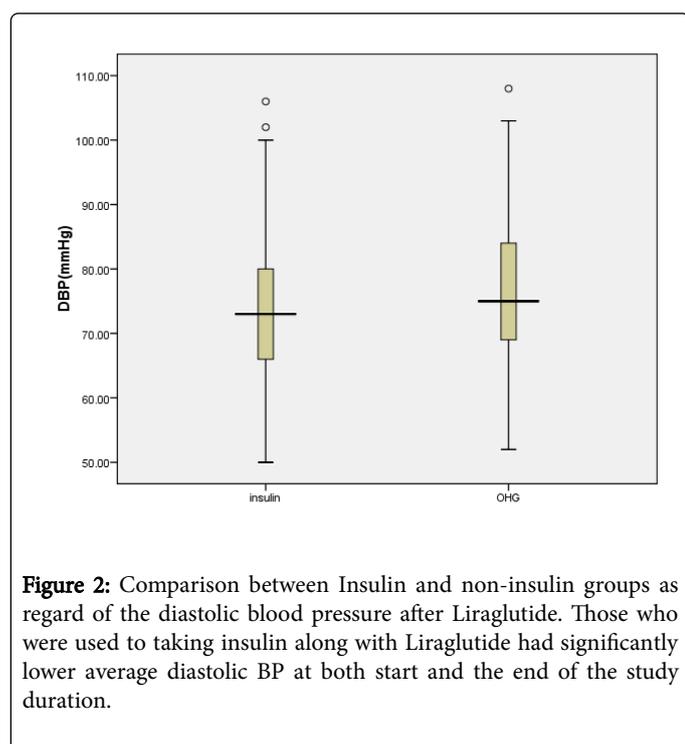
There was no significant change in systolic blood pressure, but it is worth mentioning that the average diastolic blood pressure improved remarkably (74.4 ± 10 to 72 ± 9 mmHg at 6 months P<0.001). Interestingly, those who were used to taking insulin along with Liraglutide had significantly lower average diastolic BP at both start and the end of the study duration; 73+4 VS 76+4 P=0.05, and (71+ 5 VS 73+4.6) p=0.02, respectively (Table 1 and Figure 2).

P	t	Statin supplements		Variables
		Yes	**No**	
0.78NS	0.7	168+45	164+40	TC before (mg/dl)
0.46NS	1.02	133+52	143+33	TG before (mg/dl)
0.40NS	1	160+45	152+50	TC after (mg/dl)
0.33NS	1.5	122+40	133+34	TG after (mg/dl)
0.88NS	0.8	6+3	5+2.2	TC % of reduction

0.83NS	0.6	5.5+2.5	4.3+2	TG % of reduction
This table shows no statistically significant difference between both groups as regard lipid profile before and after Liraglutide by using unpaired t-test. TC=Total cholesterol, TG=Triglycerides				

Table 2: Relation between lipid profile versus statin before Liraglutide.

Figure 2: Comparison between Insulin and non-insulin groups as regard of the diastolic blood pressure after Liraglutide. Those who were used to taking insulin along with Liraglutide had significantly lower average diastolic BP at both start and the end of the study duration.

and end of study 29+18 to 25.7+ 13 and 25.1+ 20 to 22.2+ 16 for ALT and AST, respectively. Both of them showed highly significant P value (0.0000) (Table 4). Being on insulin did not change the liver enzymes ranges.

We have excluded all patients with impaired kidney function, but even out of the mean normal creatinine levels, the average serum creatinine reports showed trend of numerical improvement after 6 months of Liraglutide 0.77+0.19 to 0.76+0.2 p=0.1.

Discussion

Liraglutide showed remarkably positive outcomes in different randomized controlled studies. In a prospective study conducted over 8 weeks, the Liraglutide reduced the HbA1c significantly versus placebo (-0.8% versus 0.09%), as well as the B-cell function using HOMA-S, but the difference was not statistically significant with regard of the weight and the reduction of the insulin resistance [1,4]. Another study evaluated different dosages of the Liraglutide (0.65, 1.25, or 1.90 mg), the HbA1c reduction was attained in the last two dosages, but not with the 0.65 mg, and the average HbA1c reduction was 1.74% out of the average baseline of 8.5% upon starting the study. All the three dosages did reduce the weight; with a maximum reduction attained was 2.99 kg in the 1.9 mg dose [5]. The weight reduction privilege of Liraglutide has been reproduced in many studies [7,8]. Surprisingly, the weight reduction was had no correlation with HbA1c reduction in our cohort (Table 3).

Mean AST and ALT was within normal range at baseline and despite that there was a highly significant reduction between baseline

P	t	% Of change	At 6 months Mean+SD	Baseline Mean+SD	Variables
0.0000 HS	4#	13 ± 7	25.7 ± 13	29 ± 18	ALT (mg/dl)
0.000 HS	4.7#	12 ± 8	22.2 ± 16	25.120	AST (mg/dl)
0.10 NS	1.6	2 ± 1.4	0.76 ± 0.2	0.77 ± 0.19	Cr (mg/dl)
This This table shows that ALT and AST were decreased after 6 months of the treatment with significant difference by using Wilcoxon test. ALT: Alanine Aminotransferase, AST: Aspartate Transaminase, CR=Creatinine					

Table 3: Changes in liver enzymes and creatinine after Liraglutide

In our study, weight reduction was more pronounced in the group taking insulin at the baseline, 96+3 to 93+5 VS 93 +5 to 98+3.5, P value at the end of the study was 0.02. This is a mirror image of DeVries's study when they added insulin Detemir to Metformin plus liraglutide. The HbA1c continued to improve after adding Detemir. The weight loss continued to take place, but at lower rate in Detemir group (-3.5 kg during run-in time, then by 0.16 kg with insulin Detemir or 0.95 kg without insulin Detemir). Kielgast and his team studied Liraglutide in type 1 diabetes patients, it showed improvement in HbA1c, weight, and total insulin dose [6]. Interestingly, in our study the duration of diabetes did not have any negative impact on the effectiveness of Liraglutide.

| P | HBA1C | | Variables |
	Improved	Not improved	
0.25 NS	41(52.6%)	133(57.8%)	Weight improved
	37(47.4%)	97(42.2%)	Not improved
This table shows no statistically significant association between weight improvements as regard HBA1C improvement by using Fisher exact test			

Table 4: Relation between HBA1c reduction versus weight reduction among the studied cases.

Alongside weight reduction, our patients experienced highly significant improvement in total cholesterol and triglycerides at 6 months after initiation of Liraglutide. Nonetheless, the reduction of the lipid profile took place equally in both the statin and non-statin contained regimens. This, perhaps, directs this privilege to the addition of Liraglutide, with or without the weight reduction status. This observation was exactly reproduced upon cross-tabulation of the weight reduction and HbA1c improvement. The weight constant group had similar glycemic improvement after 6 months of Liraglutide. This would strengthen the non-weight mediated effect of GLP-1 privileges —namely in our study, glycemic and lipids control.

In our cohort, the diastolic blood pressure showed constant lower readings after Liraglutide in comparison to the baseline; this is somehow consistent with systolic blood pressure reduction in former studies [4,7-9]. Although the systolic blood pressure modulation was more evident in the former studies, in our ethnic group (Arabs), Liraglutide proved to have higher efficacy in reducing the diastolic component of the blood pressure. This was even more augmented in those who used to take insulin along with Liraglutide had significantly lower average diastolic BP at both start and the end of the study duration; 73+4 vs. 76+4 P=0.05, and (71+5 vs. 73+4.6) p=0.02, respectively. To our best search, we could not find similar results in the preceding published data.

Serum creatinine was not affected by the Liraglutide administration over 6 months. This augments the previous data that showed no safety concerns in patients with mild renal impairment [10].

Despite having normal mean AST and ALT at baseline, and none of them reported having liver problems in the past, both ALT and AST mean showed decrement at 3 and 6 months period after initiation of Liraglutide. Being on insulin or not, did not change the Liver enzymes stability. This is again consistent with previous similar trials [11] in which the investigators studied liraglutide in subject with mild to moderate Liver impairment. Liraglutide did not show any deterioration in liver enzymes. Nonetheless, Liraglutide did not increase the hypoglycemic episodes in those with deranged liver function [11]. Using a much bigger cohort, a met-analysis of phase III Liraglutide studies of 4442 patients, 2241 with abnormal Liver enzymes, Liraglutide proved to be safe, and even had a trend of reducing the mean liver enzymes, a difference thought to be mediated by weight loss (and the related fatty liver) and glycemic control [11].

Kidney function, one of the major concerns in diabetes treatment cascade, has been shown in many trials to be protected by early diabetes control. Moreover, Zhao and his team showed protective mechanism of Liraglutide at the cellular level in the renal tubules [12]. Nevertheless, a recent pilot trial showed even a protective, non-glycemic mechanism by which Liraglutide improves the kidney function in patients with diabetes [13]. We have not studied these

parameters, but at least the serum creatinine level was maintained within normal ranges all through the study. With a trend of numerical improvement after 6 month of Liraglutide initiation; 0.77+0.19 to 0.76+0.2 p=0.1.

Conclusion

Our study of Liraglutide showed remarkable improvement in weight, HbA1c, liver enzymes, and diastolic blood pressure when added to multiple oral hypoglycemic agents, with or without insulin, in patients with type 2 diabetes. Patients who used insulin at base line had better results in weight and lipids reduction.

The results of this study were not very surprising, but rather confirm the findings of older studies with few differences that might be attributed to the ethnic variation. But we believe those differences are not substantial to have different recommendations or doses as in the Japanese population.

Limitations

We believe that our study is a real-life trial; Liraglutide was added to patients across the whole spectrum of type 2 diabetes mellitus, even those who require insulin for control. Extension of the trial to 52 weeks could likely have helped in consolidation of the results.

Authors Contribution

Elamin: Protocol writing, Data collection, Manuscript writing. Alaaeldin: Protocol writing, Data collection, Manuscript writing and revision. Ahmed El-tinay: Data collection. Fatheya Al Alwadi: Manuscript revision, Azza Abdulaziz: Manuscript revision. Mohamed Abdelatif: Manuscript revision. Fauzia Rashid: Manuscript revision.

Trial Registration

The trial is approved and registered with institutional ethical committee board (Dubai Health Authority Medical research committee) with registration Number (MRC-08/2013_03) approves the trial.

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Conflicts of interest

All Authors disclose no conflict of interest.

References

1. Harder H, Nielsen L, Tu DT, Astrup A (2004) The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care 27: 1915-1921.

2. Nauck MA, Holst JJ, Willms B, Schmiegel W (1997) Glucagon-like peptide 1 (GLP-1) as a new therapeutic approach for type 2-diabetes. Exp Clin Endocrinol Diabetes 105: 187-195.

3. Drucker DJ (1998) Glucagon-like peptides. Diabetes 47: 159-169.

4. Montanya E, Sesti G (2009) A review of efficacy and safety data regarding the use of liraglutide, a once-daily human glucagon-like peptide 1

analogue, in the treatment of type 2 diabetes mellitus. Clin Ther 31: 2472-2488.

5. Tina Vilsbøll (2007) liraglutide, a long-acting human glucagon-like peptide-1 nalog, given as monotherapy significantly improves glycemic control and owers body weight without risk of hypoglycemia in patients with type 2 diabetes. Diabetes Care

6. Kielgast U, Krarup T, Holst JJ, Madsbad S (2011) Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function. Diabetes Care 34: 1463-1468.

7. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, et al. (2009) Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia 52: 2046-2055.

8. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, et al. (2009) Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 32: 1224-1230.

9. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M (2009) Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. Br J Clin Pharmacol 68: 898-905.

10. Flint A, Nazzal K, Jagielski P, Hindsberger C, Zdravkovic M (2010) Influence of hepatic impairment on pharmacokinetics of the human GLP-1 analogue, liraglutide. Br J Clin Pharmacol 70: 807-814.

11. Armstrong MJ, Houlihan DD, Rowe IA, Clausen WH, Elbrønd B, et al. (2013) Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther 37: 234-242.

12. Zhao X, Liu G, Shen H, Gao B, Li X, et al. (2015) Liraglutide inhibits autophagy and apoptosis induced by high glucose through GLP-1R in renal tubular epithelial cells. Int J Mol Med 35: 684-692.

13. Zavattaro M, Caputo M, Samà MT, Mele C, Chasseur L, et al. (2015) One-year treatment with liraglutide improved renal function in patients with type 2 diabetes: a pilot prospective study. Endocrine.