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Effect of Liraglutide on Patients with Type 2 Diabetes in Real Practice: Experience from A Regional Hospital

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Abstract

Liraglutide is a new injectable anti-diabetic medicine. It can lower blood glucose and also result in a neutral or lowered body weight. However, the interaction of changes in blood glucose and body weight is not clear. This study is a retrospective chart review study. Patients with type 2 diabetes who initiated liraglutide therapy from 1, Sep. 2016 to 30 Nov. 2016 were enrolled. We assessed the change in blood glucose and body weight after liraglutide treatment. Results: The study found that most patients had lower A1C and body weight simultaneously but no relationship between body weight and blood glucose change was found. In multivariable linear regression models, variables such as male, diabetes duration, and baseline A1C are all positively correlated and numbers of anti-diabetic drugs is negatively correlated to the change of A1C. Age is positively correlated and the number of anti-diabetic drugs is negatively correlated to body weight change. We found that liraglutide could decrease body weight and blood glucose. However, there is no relationship between the glucose reduction and body weight lowering effects. In respect of glucose reduction, male patients with longer diabetes durations, using less oral anti-diabetic drugs or higher baseline A1C are good candidates for liraglutide treatment. In respect of body weight reduction, younger patients with more anti-diabetic drugs are less likely to lose their body weight. (J Intern Med Taiwan 2020; 31: 202-209)

Key Words: Liraglutide, Type 2 diabetes, Body weight change

Introduction

Type 2 diabetes is not only a growing epidemic in all ages but also all around the globe[1]. It can cause tremendous economic loss from both medical expenditures and reduced productivity. The largest components of medical expenditures are hospital inpatient care[2]. Fortunately, the economic loss can be minimized since diabetes complications can be reduced if it is controlled well[3,4]. However, the effect of anti- diabetic agents cannot last long because the progressive loss of beta cell function of type 2 diabetes[5]. Accordingly, many kinds of anti- diabetic agents were developed in the last two decades[6].

Traditionally, insulin resistance was thought to be the main characteristic of type 2 diabetes. But

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then more and more defections of type 2 diabetes were found[7]. Reduced incretin effect in type 2 diabetes is one of the defections[8]. Dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RA) both target incretin effects. However, these new drugs are expensive. Therefore, choosing the appropriate one will be an important issue in both treating diabetes efficiently and reducing medical cost.

In this retrospective study, we tried to find the characteristics of type 2 diabetes patients who have better responses to liraglutide.

Materials and Methods

Study participants

The present study was done at the diabetes outpatient clinic of Cardinal Tien hospital. Ethical approval was given by the Cardinal Tien hospital. The electronic medical records were reviewed from 1 Sep. 2016 to 30 Nov. 2016 and all patients with type 2 diabetes who used liraglutide *de novo* were enrolled. Patients who had no regular follow up or didn't use liraglutide for 1 year were excluded.

Data management

The demographics and laboratory data of all patients were collected and analyzed. The changes of body weight and A1C were represented by percentages of reduction from the baseline. Percentage of reduction was calculated as below: Percentage of body weight reduction (%)= (the lowest body weight after liraglutide- body weight at baseline)/ body weight at baseline) x 100 x (-1). Percentage of A1C reduction (%)= (the lowest A1C after liraglutide- A1C at baseline)/A1C at baseline) x 100) x (-1)

The therapeutic agents were classified into 6 classes of OAD and insulin. The regimen was recorded according to medical charts before and after liraglutide add-on.

Statistical analysis

Continuous variables that were distributed normally are presented as means (SD). Due to the small sample size, continuous variables were analyzed with a nonparametric test or were analyzed after logarithmic transformations. The distribution of continuous variables was examined by the Shapiro-Wilk test. Categorical variables are reported as the percentage of patients in the subgroup. The Wilcoxon rank-sum (Mann-Whitney) test and chi-square test were used to identify the differences in clinical characteristics by gender. Pearson's correlation coefficients were used to determine the relationship between the change of body weight and the change to A1C and clinical characteristics. A multivariate linear regression model was used for adjusting percentage reduction with other variables. The relationship between A1C and body weight change were illustrated in scatter plots and analyzed by linear regression. Figures and graphs were performed using GraphPad Prism 6 for Windows (GraphPad Software Inc., San Diego, CA, USA). A 2-tailed p-value below 0.05 was considered significant. Stata/SE 14.0 for Windows (StataCorp LP, College Station, TX) was used for statistical analyses.

Results

A total of 65 patients were screened and 45 patients were included in the analysis. Baseline characteristics were shown in table 1. Of those 45 patients, those who are female are slightly more than those who are male. The body weight index and other factors such as biochemistry and blood pressure are similar. In table 2, the medication used before liraglutide were summarized. Most than 90% of patients were on metformin. Besides, more than three-quarters of patients were using more than 2 kinds of oral anti- diabetic drugs because of the reimbursement policy of the national health insurance.

In terms of the glucose lowering effect of lira-

glutide, A1C decreased progressively and reached the nadir (-1.22%) at 12 months (Figure 1a). In terms of the body weight losing effect, body weight lost from 85.0 ± 13.4 kg at baseline to 81.3 ± 13.8 kg at 6 months (-3.7 kg) and 83.1 ± 15.8 kg at 12 months (-1.9 kg).

For men, A1C decreased from 8.49 ± 1.67% to 7.11 ± 0.47% at 12 months and body weight lost from 92.9 ± 10.9 kg to 89.3kg ± 12.4 kg at 6 months and 90.7kg ± 15.3kg at 12 months. For women, A1C

Table 1. Patient demographics and baseline characteristics. Data are expressed as mean ± standard deviation. HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, GPT glutamic-pyruvic transaminase

N	45
Age	57.6 ± 10.8
Diabetes duration (year)	10.2 ± 4.8
Body height (cm)	163.2 ± 8.9
Body weight (Kg)	85.0 ± 13.4
Body mass index	30.9 ± 8.9
Systolic blood pressure (mmHg)	132.4 ± 14.7
Diastolic blood pressure (mmHg)	76.1 ± 9.3
HbA1c (%)	8.24 ± 1.3
Fasting plasma glucose (mg/dL)	161.2 ± 57.6
Postprandial plasma glucose (mg/dL)	216.9 ± 72.3
Total cholesterol (mg/dL)	162.9 ±30.1
Triglyceride (mg/dL)	167.3 ± 66.6
HDL-C (mg/dL)	43.7 ± 11.1
LDL-C (mg/dL)	93.8 ± 29.6
GPT	39.3 ± 22.4
creatinine	0.88 ± 0.24
eGFR	87.9 ± 25.2
urine albumin-creatinine ratio	83.8 ± 209.1
Complication	
Diabetic neuropathy	15.5%
Diabetic nephropathy	28.8%
Diabetic retinopathy	22.2 %
Comorbidities	
Coronary artery disease	6.6%
Stroke	0%

Table 2. Baseline therapeutic regimens. Most patients (86.67%) use 2 or 3 kinds of OADs at baseline. OAD oral anti-diabetic drugs, SU sulfonylureas, DPP4 Dipeptidyl peptidase, TZD thiazolidinedione, AGI alpha glucosidase inhibitor

Medication	N (%)
Metformin	43 (95.56%)
SU	31 (68.89%)
Glinides	3 (6.67%)
DPP4 inhibitor	6 (13.33%)
TZD	23 (51.11%)
AGI	8 (17.78%)
Basal insulin	6 (13.33%)
Statin	41 (91.11%)
One OAD + insulin	3 (6.67%)
Two OADs + insulin	12 (26.67%)
Three OADs + insulin	27 (60%)
Four OADs + insulin	3 (6.67%)

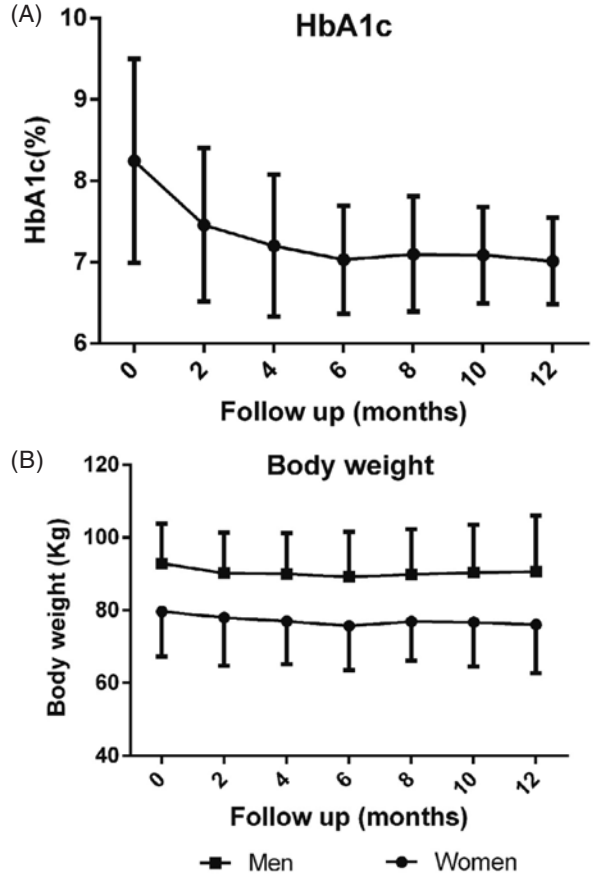

Figure 1. (a) A1C change during 12 months liraglutide treatment period. (b) Body weight change during 12 months liraglutide treatment period.

decreased from 8.08 ± 0.87% to 6.92 ± 0.60% at 12 months and body weight lost from 79.7 ± 12.4 kg to 75.8kg ± 12.1 kg at 6 months and 76.1kg ± 13.3kg at 12 months. No significant difference was noted between men and women (-2.2 kg vs -3.6 kg at 12 months) (Figure 1b). Then we analyzed the relationship between body weight and glucose lowering effect. Most patients had both lowered A1C and body weight simultaneously, but some were gaining weight with better glucose control and some were losing weight with worse glucose control (Figure 2a). Then we analyzed the relationship between glucose reduction and body weight lowering effect. There is no relationship between them (Figure 2b).

Univariate correlations of A1C and body weight change were done. Baseline A1C was negatively correlated to the change of A1C. Age, gender, duration of diabetes, numbers of oral anti- diabetic drugs, baseline body weight and BMI are not correlated to change of A1C. In terms of the change of body weight, younger patients lost more body weight. The number of anti- diabetic drugs showed a trend of being correlated to body weight change (Table 3). In multivariable linear regression models, we found that being male, diabetes duration, and baseline A1C are all positively correlated and the number of anti- diabetic drugs is negatively correlated to change of A1C. Age is positively correlated and the number of anti -diabetic drugs is negatively correlated to body weight change (Table 4).

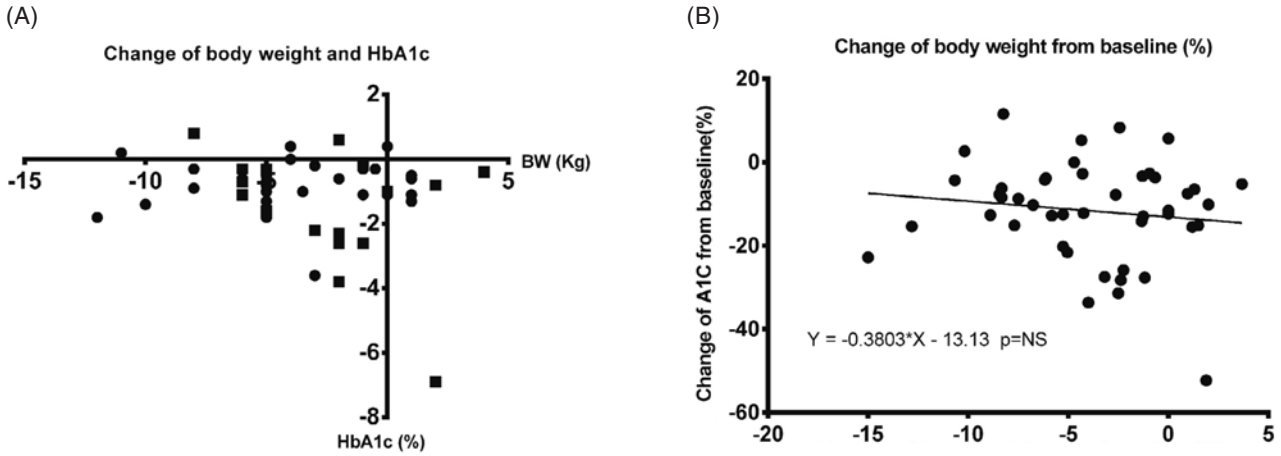

Figure 2. (a) Relationship of A1C and body weight change. (b) Linear regression of A1C and body weight change.

Table 3. Univariate correlations of the percentage reduction of A1C the body weight change between various factors. BMI body mass index

	Percentage of A1C reduction		Percentage of body weight reduction	
	r[a]	*p*	r	*p*
Age	-0.0942	0.5382	0.4382	0.0026
Male	0.2264	0.1347	-0.2559	0.0898
DM duration	0.0037	0.9809	0.2109	0.1643
Numbers of other glucose lowering drugs	-0.0968	0.527	-0.2845	0.0582
Baseline A1C [b]	0.7798	<0.001	-0.2191	0.1481
Baseline body weight	0.089	0.5611	-0.2417	0.1097
Baseline BMI	-0.1508	0.3595	0.0423	0.7983

[a] Pearson correlation coefficient.
[b] Log-transformed for normality.

Discussion

In our study, we found that both A1C and body weight decreased after liraglutide use. In addition to glucose reduction, body weight reduction is also important in treating diabetes. Obesity or body weight gain is associated with insulin resistance and development of type 2 diabetes[9]. Non-esterified fatty acids, proinflammatory cytokines and other hormones or factors are released from adipose tissue of obese individuals. Insulin resistance develops and abnormal glucose intolerance, even diabetes appears thereafter[10]. When obese patients become diabetes patients and receives some kinds of anti-diabetes drugs, like sulfonylurea, thiazolidinedione, blood glucose improves along with the cost of body weight gain[6]. Therefore, some anti-diabetic drugs, like GLP-1 RAs or sodium-glucose co-transporter 2 (SGLT2) inhibitors, are promising when they become clinically available since they can both decrease body weight and blood glucose at the same time[11].

In liraglutide effect and action in diabetes (LEAD) studies, A1C decreases from -0.6% to -1.5% under 1.2 mg liraglutide and body weight changes from +0.3kg to -2.6 kg [12-17]. Body weight gain only appears when liraglutide is not combined with metformin in LEAD-1 SU study[12]. In LEAD studies, the duration is usually 26 weeks except in LEAD-3 study, which is 52 weeks. No correlation analysis between body weight change and A1C reduction were made in LEAD studies. In the Diabetes Therapy Utilization: Research Changes in A1C, Weight and Other factors Through Intervention with Exenatide Once Weekly (DURATION) studies, the long-acting release (LAR) formation of exenatide decreases body weight from -2.0 to -4.4 kg and A1C from -1.28 to -1.6% in around 6 months treatment[18-23]. In DURATION 3, the association of baseline body weight and A1C change or body weight change was analyzed. The baseline body weight was not associated with either body weight change or A1C change[20]. In Assessment of Weekly Administration of dulaglutide in Diabetes (AWARD) studies, dulaglutide weekly injection decreases A1C from -0.62 to -1.48%. Body weight changes from 0.9 kg to -2.9 kg. Body weight gains in the end of AWARD 1 where dulaglutide is combined with pioglitazone and AWARD4 where rapid-acting insulin is used with dulaglutide[24-29]. The association between body weight change and A1C reduction was not calculated. In our study, most patients do lose their body weight and decrease their blood glucose in the same time. However, there is no correlation between body weight loss and blood glucose lowering. Patients who have more blood glucose reduction do not have more body weight reduction, and vice versa.

In AWARD studies, the study duration ranges from 52 weeks to 104 weeks. In AWARD studies,

Table 4. Multivariable linear regression models for the A1C and body weight reduction

	Percentage of A1C reduction	Percentage of body weight reduction
	Partial correlation coefficient (p value)	
Age	0.016 (0.897)	0.166 (0.007)
Male	4.991 (0.042)	-1.195 (0.393)
DM duration	0.657 (0.017)	0.085 (0.553)
Numbers of other glucose lowering drugs	-5.108 (0.005)	-2.107 (0.018)
Baseline A1C	7.732 (<0.001)	–
Baseline body weight	–	0.004 (0.943)
Change of body weight from baseline (%)	-0.140 (0.653)	–
Change of A1C from baseline (%)	–	0.034 (0.485)

A1C decreased and reached their nadir at 13 to 26 weeks and became progressively higher in the study period. In DURATION studies, A1C reached their nadir at around 12-16 weeks and became stable or slightly higher afterwards. In LEAD studies, A1C also reached the nadir at around 12-16 weeks and became stable or slightly higher, too. In our study, the A1C reached the nadir at 24 weeks and also kept stable or slightly higher till 52 weeks. Therefore, physicians should be aware of the timeline of A1C change and intensify their therapy if A1C is not at the goal after 24 weeks treatment of liraglutide.

Choosing the right medicine for patients is always critical. Precision medicine for diabetes is well established in monogenic diabetes[30]. Pharmacogenetics in type 2 diabetes is still underdeveloped[31]. Therefore clinical characteristics are still important clues we can currently use for choosing the right patient with the right medicine. For prediction of glucose lowering effect of liraglutide, we found patients who are male, with shorter diabetes duration and higher baseline A1c benefit more after liraglutide therapy and patients who are using more kinds of anti-diabetic drugs benefit less. In terms of body weight lost, patients who are younger and using less oral anti-diabetic drugs will lose more body weight after liraglutide injection.

There are some limitations in our study. First, the study population is small and the males and females were not equal in numbers. Secondly, the observation period is only 12 months. Thirdly, our study is retrospective.

In conclusion, in our one-year retrospective study, we find liraglutide could decrease body weight and blood glucose. However, there is no relationship between glucose reduction and body weight lowering effect. In terms of glucose reduction, patients who are male, with longer diabetes duration or higher baseline A1C are good candidates for liraglutide treatment and patients who use more kinds of anti-diabetic drugs are not. In respect of body weight reduction, patients who are younger or use more kinds of anti-diabetic drugs are less likely to lose their body weight.

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Disclosure

The authors declare that there are no conflicts of interest. C.C Su has received lecture/advisor fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, NovoNordisk and Sanofi.

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第二型糖尿病病人使用胰妥善成效評估

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摘 要

胰妥善為一種較新型的注射型降血糖藥物。它除了降血糖以外甚至有 降體重的效果。目前對於類升糖素胜肽 -1 受體的促效劑使用上作用於血糖和體重變化之間的交互作用目前還不是很清楚。本研究是病歷回顧研究，回顧從 2016 年 9 月 1 日至 2016 年 11 月 30 日期間，有使用胰妥善 (一種類升糖素胜肽 -1 受體的促效劑) 的第二型糖尿病病人列入評估。回顧其使用胰妥善後的血糖及體重變化。其中大部份的病人糖化血色素和體重同時下降，但體重及糖化血色素下降幅度之間並無相關。在多元線性回歸模型分析變數發現，第二型糖尿病病人使用胰妥善治療後糖化血色素的下降幅度和某些變數，例如男性、糖尿病罹病時間長短及初始糖化血色素值，呈現正相關；但和降血糖藥物數目多寡呈現負相關。至於治療後體重變化，則與使用年齡呈正相關，但降血糖藥物數目呈負相關。我們發現胰妥善 (liraglutide) 可以使血糖及體重下降，然而血糖下降幅度及體重下降幅度之間並無呈現出相關性。關於血糖下降此研究發現、男性病患、糖尿病發病時間較長、相對少使用降血糖藥物或初期糖化血色素高的病患是適合使用胰妥善的候選人。在體重下降方面，則是年輕人合併使用降血糖藥物數目多者，其體重下降機會較低。