

Comparison of the effect of liraglutide and metformin therapy on the disease regulation and weight loss in obese patients with Type 2 diabetes mellitus

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Abstract. – **OBJECTIVE:** Obesity and Type 2 diabetes mellitus are growing health problems all over the world. The aim of this study is the comparison of 3 mg liraglutide and metformin combination, metformin monotherapy on the blood glucose regulation, weight loss and lipid panel in the patients with Type 2 diabetes mellitus whose BMI is ≥ 30 kg/m².

PATIENTS AND METHODS: 276 patients included in the study were divided into two groups (1:1); liraglutide (3 mg) + metformin combination (L+M) and metformin monotherapy (M) (2x1,000 mg) (exercise and diet were regulated in both groups). Patients' body composition measurements were performed and fasting blood glucose, postprandial blood glucose, HbA1c, triglyceride, total cholesterol, LDL, HDL levels were measured by TANITA device prior to the therapy and in the week 12 of the therapy.

RESULTS: The average age of 276 patients included in the study was 49.70 ± 7.93 years. A statistically significant decrease was noted in weight, BMI, fasting blood glucose, postprandial blood glucose, HbA1c values of both groups at the end of the third month. 11.3 kg of weight was lost on average in L+M group (-12.3%); 4.5 kg of weight was lost in the monotherapy group (-4.9%). A decrease of 14.3% was seen in the body fat mass, 2.1% in the muscle mass in L+M group and a decrease of 4.4% in the body fat mass and 6.1% in the muscle mass in the monotherapy group. The decrease in the body fat was higher at a statistically significant level in L+M group and the decrease in the muscle mass was higher in the monotherapy group. HbA1c decreased by 17.9% in L+M group (-1.49 ± 0.46 , Cohen's $d=2.68$), 5.3% in the monotherapy group (-0.37 ± 0.26 , Cohen's $d=0.90$). The decrease in TG, total cholesterol, LDL was higher at a statistically significant level in L+M group. The increase in HDL level was higher in the monotherapy group (L+M=22.7%, M=35.4%). A weight loss that was over 10% occurred in 4.3% of the

patients in the monotherapy group and 68.1% of the combined therapy group at the end of 12 weeks (95% C.I. OR=19.49-121.65).

CONCLUSIONS: The effect of the combination of liraglutide 3 mg and metformin on blood glucose regulation, weight loss (fat loss, muscle conservation) was found to be superior to the metformin monotherapy in the obese patients with Type 2 diabetes mellitus according to the early period results.

Key Words:

Diabetes, Obesity, Metformin, Liraglutide.

Introduction

Obesity continues to pose a great risk for the public health all over the world¹. Overweight and obesity are defined as abnormal or excessive fat deposit making up a risk in terms of health. A body mass index (BMI) above 25 kg/m² is defined as overweight and a BMI above 30 kg/m² is defined as obese. According to 2017 global study of disease burden, over 4 million people die in a year because of overweight or obesity. The rates of diabetes have increased four times because of the obesity all over the world since 1980². Diabetes is a chronic, metabolic diseases that is characterized by high blood glucose levels which cause serious damages in heart, blood vessels, eyes, kidneys and nerves over time. Therefore, it is extremely important to control it. It is critically important for people with diabetes to have access to the affordable therapy, including insulin for their survival. There is a set of targets that are globally recognized in order to cease the increase in diabetes and obesity by 2025³.

The obesity therapy guidelines suggest starting pharmacological therapy in the adults whose BMI is 30 kg/m² or higher, or in patients whose BMI is 27 kg/m² or higher and who have at least one comorbid condition that is associated with weight (for instance, hypertension, dyslipidemia, insulin resistance, Type 2 diabetes mellitus)¹. Liraglutide is a glucagon-like peptide-1 receptor agonist which has been used in the treatment of the Type 2 diabetes in recent years⁴⁻⁶. While liraglutide increases the insulin secretion stimulated by the glucose in the pancreas, it decreases the levels of glucagon that has raised improperly. Also, it delays the gastric emptying with the central effects on hypothalamus and increases the feeling of fullness. Since glucagon like peptid-1 (GLP-1) receptor agonists stimulate the insulin secretion and blocks the glucagon secretion in a manner that depends on the glucose, the risk of hypoglycemia is low. This condition is an important point for a new sign in the obesity's treatment, because it is not likely for the patients without diabetes to face with the risk of low blood glucose level if they take drugs in this class^{7,8}. Only when the glucose levels of patients are physiologically high, liraglutide decreases the glucose. As the additional utility of the drug, leading to weight loss and low hypoglycemia risk, has referred the producers to evaluate and develop a formulation with higher dose, particularly to treat the obesity^{1,9}. The aim of this study was to compare the effect of the therapy of high-dose liraglutide and metformin on blood glucose regulation, weight loss and lipide panel in the patients with Type 2 diabetes mellitus and whose BMI was ≥ 30 kg/m².

Patients and Methods

This study was conducted on the records of the obese patients with Type 2 diabetes mellitus who applied to the adult endocrinology polyclinic of Malatya Training Research Hospital, Turgut Özal University in August-December 2021. The study is a retrospective type of research. A permission was obtained from the ethical committee of Malatya Training Research Hospital, Turgut Ozal University, for conducting the study. The minimum sampling size required to reach in the sampling's analysis size performed by taking 95% power range, 99.9% confidence range as reference was found as 274 (reference values; group 1 = 51.8%, group 2=24%). The group ratio was accepted as 1:1 and totally 276 people were accepted, with 138 people into each group⁹.

Inclusion Criteria

Patients who were 18 years old and above, whose BMI was > 30 kg/m², with Type 2 diabetes mellitus, whose HbA1c was between 6-10% were included into the study.

Exclusion Criteria

Type 1 diabetes mellitus patients, those who had had recurrent severe hypoglycemia attacks within the past year, those who used to take dipeptidyl peptidase 4 inhibitors, GLP-1 receptor agonists, bolus insulin or drugs which lead to significant weight changes within the preceding 90 days, those who had had a recent cardiovascular case history, medullary thyroid carcinoma or multiple endocrine neoplasm, pregnancy, breastfeeding, pancreatitis, gallbladder disease history were excluded from the study.

Groups

Patients included in the study were divided into two groups. The first was the group to which liraglutide (3.0 mg) and metformin were administered, and the second group was the group to which only metformin was administered. The energy to be given to the individuals was calculated by subtracting 500 calories from their daily average energy consumptions by asking their food consumption states. A nutritional order was prepared in such manner that the rate of the energy determined coming from carbohydrate was 55-60%, the rate coming from protein was 12-15% and the rate coming from the fat was 25-30%, in compliance with the principles of adequate and balanced nutrition. The diet program was regulated in 3 main meals and 3 refreshments daily.

Liraglutide + Metformin (L+M)

Liraglutide was added to the therapy in patients who had been previously diagnosed with diabetes mellitus but had only taken metformin and whose BMI was > 30 kg/m², while hemoglobin A1c (HbA1C) was $> 6.5\%$. Liraglutide was subcutaneously applied in the middle of the trunk, anterior of femur or upper arm in the following doses. The treatment was continued by increasing it in multiples of 0.6 mg/day weekly. At the fifth week, the maximum dose was reached, and it was continued until the third month.

Metformin Administration (M)

Metformin was started as a daily dose of 2,000 mg/day totally, 1,000 mg tablet in the morning and night. This dose was continued for three months.

Measurements

Blood measurements

The fasting blood glucose, postprandial blood glucose, HbA1c, total cholesterol, triglyceride, low-density lipoproteins (LDL), high-density lipoproteins (HDL) values of the patients were measured at the application moment and in the third month of the treatment. The blood results were studied in the Central laboratory of Malatya Training Research Hospital.

Anthropometrical measurements

The fasting weight, BMI, muscle mass, fat ratio values of the patients were measured by TANITA BC-420 MA (TANITA BIA Technology, Amsterdam, The Netherlands) at the application moment and in the third month of the treatment.

Statistical Analysis

Statistical Package for the Social Sciences 22 (SPSS, IBM Corp., Armonk, NY, USA) program was used in the analysis of data. Data were presented as mean, standard deviation, median, minimum, maximum, percentage. Kolmogorov-Smirnov test was used as a normal distribution test. Wilcoxon test, paired *t*-test, Mann-Whitney U test, Student's *t*-test, binary logistic regression were used in the analysis of data. $p < 0.05$ value was accepted as statistically significant. Effect Size Calculator was used in the calculation of effect size. In the effect's interpretation size (Cohen's *d*), 0.20-0.50 was accepted as small, 0.50-0.80 as medium, 0.80-1 as big and >1 as very big.

Results

The average age of 276 patients included in the study was 49.70 ± 7.93 years (min=29 - max=69). 138 patients (94 females, 44 males, 47.60 ± 7.88 years) were taking liraglutide and metformin (L-M) and 138 patients (91 females, 47 males, 51.80 ± 7.43 years) were taking only metformin (M). The blood glucose, hemoglobin, blood lipides and anthropometrical measurement results of the patients taken prior to the therapies and in the third month after starting the therapy are shown in Table I. A statistically significant decrease was seen in the values of weight, BMI, fasting blood glucose (FBS), postprandial blood glucose (PBS), HbA1c of the patients in both treatment groups at the end of the third month. Once the effect size of the liraglutide and metformin therapy on these parameters was examined, it was found

that the effect on the weight and blood glucose regulation was highly profound. It has been seen that the biggest effect was on HbA1C. Along with weight loss, blood lipid levels are; it was determined that total cholesterol, triglyceride, LDL decreased significantly. It was found that the increase in HDL level (22.7%) was significant, and the effect was highly profound. It was found that the effect of the therapy in the patients who took metformin therapy on the weight and BMI decrease was medium, the effect on decrease in HbA1C was big, while the effect on the lipide parameters was medium-big. The change in other parameters, excluding HDL, was higher in the group to which liraglutide was added compared to the group taking only metformin. It was found that the increase in HDL was higher in the group taking only metformin among the parameters examined (Table I). It was noted that the effect of the combination of metformin and liraglutide was bigger in the blood glucose regulation, weight and decrease in BMI, while the effect on the lipide panel was found to be similar for both groups.

Once the differences between the beginning and third month of the therapy were compared, statistically significant differences between the therapy groups were detected. The decrease in weight, BMI, fat mass, FBS, PBS, HbA1C, total cholesterol, triglyceride and LDL parameters in the group taking liraglutide was significantly higher than the group taking only metformin. In the group taking only metformin, the decrease in the muscle mass and the increase in HDL were found to be significantly higher (Table II).

Distribution of the HbA1C values of the patients at the beginning of the therapy and at week 12 is given in Figure 1.

Once the change in the blood lipide profile of the therapy groups was compared to the use of anti-lipide drugs (difference between week 12 and beginning), LDL was found to be significantly lower, and no significant difference was detected among the changes in the total cholesterol, triglyceride and HDL values in individuals taking anti-lipide drug in both groups (Table III).

There was a weight loss over 10% in 4.3% of the patients in the metformin group and 68.1% in the metformin and liraglutide group at the end of 12 weeks ($p < 0.001$). It was found that the logistic regression analysis established for estimating the state of weight loss over 10% was important (Omnibus test - $p < 0.001$). 54.3% of the 10% weight loss change at the end of the 12-week period was determined by drug groups. The probability of 10% weight loss of the patients in L+M group was 48.6 times higher (Table IV).

Table I. Anthropometrical and biochemistry results of patients at the beginning of therapy and in the third month of the therapy.

	Onset		3 rd month		Change %	p	Cohen's d
	X±S.D.	Median (min-max)	X±S.D.	Median (min-max)			
Metformin+liraglutide							
Weight (kg)	92.08±8.61	90.5 (69-121)	80.71±8.25	81.0 (52-103)	-12.34	<0.001	1.34
BMI (kg/m ²)	37.76±3.29	37.7 (31.2-45.9)	31.35±2.85	31.2 (24.6-40.0)	-16.97	<0.001	2.08
Fat mass (kg)	40.98±6.17	40.6 (25.6-75.8)	35.10±6.83	35.15 (22.3-74.1)	-14.3	<0.001	0.90
Muscle mass (kg)	45.84±5.26	44.90 (33.2-59.3)	44.87±5.15	43.9 (35.0-63.6)	-2.1	<0.001	0.18
FBS (mg/dL)	148.34±25.19	139.0 (108-213)	94.30±16.13	92.5(69-161)	-36.42	<0.001	2.55
PBS (mg/dL)	246.40±40.60	256.0 (159-342)	154.67±27.11	156.0 (13-217)	-37.22	<0.001	2.65
HbA1C (%)	8.32±0.65	8.3 (6.7-9.7)	6.83±0.44	6.8 (6.1-8.1)	-17.90	<0.001	2.68
Total cholesterol (mg/dL)	254.31±21.93	252.5 (184-345)	220.18±19.19	220.0 (129-271)	-13.42	<0.001	1.65
Triglyceride (mg/dL)	226.72±46.76	235.5 (89-389)	190.11±40.30	196.0 (79-265)	-16.14	<0.001	0.83
LDL (mg/dL)	143.42±15.21	141.5 (112-200)	114.25±20.92	112.0 (68-185)	-20.33	<0.001	1.59
HDL (mg/dL)	48.07±6.71	48.0 (33-64)	60.99±9.88	59.0 (37-92)	+22.73	<0.001	1.52
Metformin							
Weight (kg)	92.74±8.93	92.0 (69-123)	88.14±8.43	88.0 (65-119)	-4.9	<0.001	0.52
BMI (kg/m ²)	37.76±3.14	38 (30-45.8)	35.66±3.26	35.85 (30-43.2)	-5.5	<0.001	0.65
Fat mass (kg)	46.68±4.46	46.3 (29.6-59.10)	44.58±4.95	44.85 (17.3-56.3)	-4.4	<0.001	0.44
Muscle mass (kg)	33.55±3.85	33.95 (22.1-42.2)	31.50±3.69	32 (20.1-38.2)	-6.1	<0.001	0.54
FBS (mg/dL)	152.04±21.72	150 (112-198)	130.32±19.68	129 (89-185)	-14.2	<0.001	1.04
PBS (mg/dL)	174.41±21.97	167.5 (132-231)	152.57±19.77	152.5 (99-198)	-12.5	<0.001	1.04
HbA1C (%)	6.96±0.43	7.05 (6-8.1)	6.59±0.39	6.5 (5.6-7.5)	-5.3	<0.001	0.90
Total cholesterol (mg/dL)	227.51±31.00	230 (135-298)	204.20±27.06	202 (121-265)	-10.2	<0.001	0.80
Triglyceride (mg/dL)	212.35±33.29	213 (135-280)	188.62±29.78	195.5 (109-265)	-7.9	<0.001	0.75
LDL (mg/dL)	145.25±19.75	144 (99-195)	121.97±17.69	120.5 (88-162)	-16.0	<0.001	1.24

Table II. Comparison of the differences between the values of beginning and third month by therapy groups.

Measurement	Liraglutide+metformin		Metformin		p
	X±S.D.	Median	X±S.D.	Median	
Weight (kg)	-11.38±4.64	-10.00	-4.59±3.29	-4.00	<0.001
BMI (kg/m ²)	-6.41±2.45	-6.35	-2.11±1.48	-1.90	<0.001
Fat mass (kg)	-5.88±4.40	-5.65	-2.09±2.76	-1.85	<0.001
Muscle mass (kg)	-0.97±1.59	-1.10	-2.05±2.04	-1.80	<0.001
FBS (mg/dL)	-54.04±24.37	-49.50	-21.72±15.99	-20.00	<0.001
PBS (mg/dL)	-91.73±37.93	-94.00	-21.84±18.71	-20.00	<0.001
HbA1C (%)	-1.49±0.46	-1.50	-0.37±0.26	-0.30	<0.001
Total cholesterol (mg/dL)	-34.12±23.63	-29.00	-23.31±22.18	-16.00	<0.001
Triglyceride (mg/dL)	-36.61±42.13	-27.00	-23.73±23.92	-20.00	0.010
LDL (mg/dL)	-29.17±21.83	-30.00	-23.28±17.22	-22.00	0.001
HDL (mg/dL)	12.92±10.40	11.00	17.20±11.71	15.50	0.004

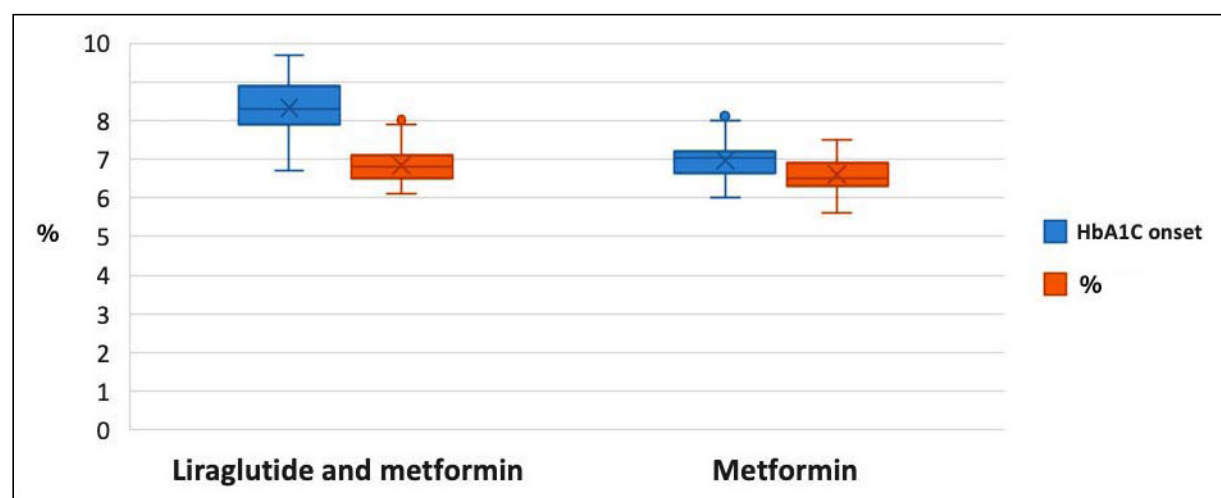


Figure 1. HbA1C beginning and third month values by therapy groups (Box-Plot graphic).

Table III. Comparison of the differences between the values of beginning and third month by therapy groups.

Group	Anti-lipid medication	Difference between baseline and 3 rd month measurements				
			Total cholesterol	Triglyceride	LDL	HDL
L+M	No (n:50)	X± S.D.	-33.24±22.36	-43.36±45.16	-21.94±20.63	12.00±10.73
		Median	-28.0	-25.5	-23.5	11.0
	Yes (n:88)	X± S.D.	-34.63±24.43	-32.77±40.07	-33.28±21.53	13.44±10.23
		Median	-30.0	-27.5	-36.5	12.0
		p	0.672	0.569	0.002	0.486
M	No (n:75)	X± S.D.	-25.96±23.85	-20.75±25.68	-18.00±14.07	17.93±10.65
		Median	-18.0	-19.0	-19.0	16.0
	Yes (n:63)	X± S.D.	-20.16±19.74	-27.29±21.30	-29.56±18.57	16.32±12.89
		Median	-15.0	-20.0	-26.0	13.0
		p	0.127	0.156	<0.001	0.212

Table IV. Logistic regression analysis of the estimate of 10% weight loss.

Variables	B	p	O.R.	95% C.I. for O.R.	
				Lower	Upper
Group	3.886	<0.001	48.697	19.492	121.659
Age	0.006	0.822	1.006	0.954	1.060
Diabetes age	0.012	0.894	1.012	0.846	1.212

Discussion

Liraglutide effectively reduces the body weight and body fat through the mechanisms containing loss of appetite and reduction in energy intake, being independent from the glucose-decreasing effects. In this study, the effects of only metformin and the combination of metformin and liraglutide (3 mg) on the body weight, BMI, blood glucose and blood lipides were compared in the obese patients with Type 2 diabetes mellitus. It was found that, once the measurements of the patients taken at the end of the 12 weeks were compared, the changes observed in the group to which liraglutide was added were evident. While the patients to whom liraglutide was given lost 12.3% of their body weight, 16.9% of their BMI at the end of the week 12, patients to whom only metformin was given lost 4.9% and 5.5%, respectively. The body fat mass decreased by 14.3%, the muscle mass decreased by 2.1% in L+M group; the fat mass decreased by 4.4% and the muscle mass decreased by 6.1% in the monotherapy group. The decrease in the fat mass was higher at a statistically significant level in L+M group, while the decrease in the muscle mass was higher in the monotherapy group. The conservation of the muscle mass in the group to which liraglutide was added was found to be higher.

In a study in which liraglutide doses were investigated by Astrup et al¹⁰, placebo and oral orlistat (120 mg for three times in a day) and different doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg) were compared in 564 patients without Type 2 diabetes mellitus and whose BMI was in a range of 30-40 in the period of 20 weeks. It was found that the effect of liraglutide depended on the dose (average weight losses in 4 doses; 4.8 kg, 5.5 kg, 6.3 kg and 7.2 kg) and liraglutide caused significantly more weight loss than placebo (2.8 kg) at all doses. Also, it was found that liraglutide lowered the blood pressure in all doses and the prediabetes prevalence was also reduced with daily 1.8, 3.0 mg of liraglutide. Our study show that HbA1C

was reduced by 17.9% in the patients taking 3 mg of liraglutide, the fasting and postprandial blood glucoses decreased by 36.4% and 37.2%, respectively¹⁰. Another study conducted by Astrup et al¹¹ was completed on 268 participants in 2 years, by extending the period 84 weeks further. Those who continued to take 2.4/3.0 mg of liraglutide for 2 years lost 7.8 kg compared with their beginning levels and lost more weight compared with orlistat (3.0 kg)¹¹. In our study, the patients to whom 3 mg liraglutide was started lost 11.3 kg on average, lost BMI in 6.41 units, while the group to whom liraglutide was not administered lost 4.5 kg, 2.11 units in BMI at the end of week 12.

In the study performed by Pi-Sunyer et al¹², 3,731 non-diabetic obese patients were administered 3 mg of liraglutide and followed for 56 weeks. The liraglutide group lost 8.4 kg on average and placebo group lost 2.8 kg. Also, a significantly higher decrease was found in total cholesterol, LDL cholesterol, triglycerides, fasting glucose, fasting insulin and HbA1c with liraglutide compared with a placebo and there was a significant increase in the pulse rate with liraglutide compared with placebo¹². In our study, while total cholesterol, triglyceride, LDL and HbA1C decreased by 13.42%, 16.14%, 20.33%, 17.90% respectively at the end of the week 12 in the liraglutide group, while a decrease was found in the monotherapy group at 10.2%, 7.9%, 16.0%, 5.3%, respectively. Once it was examined with the use of anti-lipide, it was found that the change occurred in the decreases in measurements, excluding LDL was not statistically significant.

In the SCALE study¹³, 846 Type 2 diabetes mellitus patients taking 0-3 oral hypoglycemic agents, with HbA1c in a range between 7-10%, a stable body weight, BMI \geq 27 kg/m² were followed by dividing them into 3 groups (diet and daily 3.0 mg of subcutaneous liraglutide, 1.8 mg of liraglutide besides the exercise, placebo) for 56 weeks. The weight loss was found to be higher both in liraglutide 3.0 mg (estimated difference -4.00%) and liraglutide 1.8 mg (estimated differ-

ence -2.71%) compared with the placebo group. It was found that the decrease in HbA1c increased depending on the dose (liraglutide 3.0 mg-1.3, liraglutide 1.8 mg-1.1, placebo- 0.3), and there was a higher decrease in both groups compared to placebo¹³. In our study, it has been noted that more weight was lost with 3 mg liraglutide in a shorter time and the effect size on the BMI was highly profound. It has been seen that the combination of metformin and liraglutide increased the efficiency compared with monotherapy and that the effect of metformin on the weight at the end of 12 weeks was found to be medium. Once it was used together with liraglutide, its effect was registered to be highly profound. It was found to have the same effect on the blood glucose and HbA1c, liraglutide increased the effect. The probability for patients to lose weight over 10% was 48 times higher in the combined therapy group. In the meta-analysis to which 5 studies lasting over 16 weeks were included, it was found that the combination of 1.2 mg and 1.8 mg liraglutide and metformin was more effective than the combination of sitagliptin and metformin for controlling HbA1c levels. Also, once the metformin therapy was compared with sitagliptin combination, it was found that metformin and 1.8 mg liraglutide significantly controlled the weight gain¹⁴.

In the study conducted by Nauck et al¹⁵ in which the efficiency of liraglutide and metformin combination was investigated in Type 2 diabetes mellitus patients, the patients were followed for 2 years. At the end of the follow-up, it was found that HbA1c significantly decreased in the liraglutide and metformin combination (0.4% with 0.6 mg, 0.6% with 1.2 and 1.8 mg), while increased by 0.3% with metformin monotherapy ($p<0.001$). There were significant weight losses in the liraglutide groups (2.1, 3.0 and 2.9 kg with 0.6, 1.2 and 1.8 mg). The weight loss in 1.2 and 1.8 mg liraglutide groups was found to be significantly higher than the metformin monotherapy (1.8 kg for 1.2 and 1.8 mg, respectively)¹⁵. We also found that the liraglutide therapy provided strong weight loss, a higher decrease in the body fat mass and a lower loss in the muscle mass compared with monotherapy.

Limitations

Our study has some limitations, such as the fact that it is a monocenter study. Moreover, patients were followed for 12 weeks only (early period), drug was delivered only in patients who could materially afford it and these patients were the only ones included in the study.

Conclusions

It was found that the efficiency of the combination of 3 mg of liraglutide and metformin on fasting blood glucose, postprandial blood glucose, reduction in HbA1C and weight loss regulation, weight loss (fat loss, muscle conservation) was superior to the metformin monotherapy in the obese patients with Type 2 diabetes mellitus in a period of 12 weeks according to the early period results compared with metformin monotherapy. The combined therapy was more effective in the reduction of fat mass and conservation of muscle mass than the monotherapy. According to literature, such combinations of 0.6, 1.2 and 1.8 mg liraglutide were used and the efficiency in the weight loss and blood glucose was lower compared with our study. The combination of 3 mg of liraglutide and metformin has been found to increase the probability of weight loss over 10% and 48 times more in the early period compared with monotherapy. Administering 3 mg of liraglutide and metformin combination in the convenient patients who can tolerate it may provide better clinical results, such as reduction in associated comorbidity and complications.

Ethics Approval

The Ethics Committee of Malatya Turgut Özal University of Training and Research Hospital gave its approval for the study.

Informed Consent

Not applicable.

Consent for Publication

The publishing rights have been given to your journal by the authors.

Availability of Data and Materials

The data used for publication can be accessed through the corresponding author.

Conflict of Interests

The authors report no conflicts of interest in this work.

Funding

No funding or financial support was received for the study.

Authors' Contributions

Lezzan Keskin: conceptualization, methodology, software, data curation, writing- original draft preparation. Bülent Yaprak: visualization, investigation. supervision, software, validation. Lezzan Keskin, Bülent Yaprak: writing- reviewing and editing.

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