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Ovaj rad je ekvivalent završnog rada na specijalističkom studiju Endokrinologija i dijabetologija. Izrađen u Sveučilišnoj Klinici za dijabetes, endokrinologiju i bolesti metabolizma „Vuk Vrhovac“ Kliničke bolnice „Merkur“ te se predaje na ocjenu u akademskoj godini 2023./2024. Rad je objavljen u časopisu Diabetologia Croatica u rujnu 2017. godine.

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Original Research Article

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS DECREASE TOTAL AND LDL-CHOLESTEROL IN OBESE TYPE 2 DIABETIC PATIENTS

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Keywords: type 2 diabetes,
exenatide,
liraglutide,
serum lipid profile,
cardiovascular risk

SUMMARY

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly utilized in the management of type 2 diabetes mellitus (T2DM). GLP-1 RAs have been associated with improvements in serum lipid profiles in clinical trials. Their long-term cardiovascular safety and benefit have also been confirmed in the recently published LEADER trial. In the current study, we assessed the effects of GLP-1 RAs (exenatide and liraglutide) on serum lipid profiles (total, LDL, HDL-cholesterol and triglycerides) of obese patients with T2DM. A total of 85 patients were included in the study (43 on exenatide and 42 on liraglutide) and followed up for 22 and 13 months, respectively. Treatment with exenatide was associated with a significant decrease in total cholesterol from 5.1±1.3 to 4.9±1.2 mmol/L (p=0.02) and LDL-cholesterol from 3.0±1.1 to 2.6±0.8 mmol/L (p=0.01). Treatment with liraglutide was also associated with a significant decrease in total cholesterol from 4.8±1.2 to 4.2±0.8 mmol/L (p=0.001) and LDL-cholesterol from 2.5±0.8 to 2.1±0.5 mmol/L (p=0.006). Treatment with liraglutide and exenatide did not significantly affect HDL-cholesterol and triglyceride levels. The results of our study suggest that treatment with exenatide and liraglutide may significantly reduce total and LDL-cholesterol in obese patients with T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder associated with a significant risk of cardiovascular disease, which is the leading cause of morbidity and mortality in these patients (1). The etiology may be divided into the effects of hyperglycemia and the effects operating through the components of metabolic syndrome such as obesity, hypertension and dyslipidemia. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are distinctive compounds with their blood-glucose lowering capacity by inducing insulin secretion and reducing glucagon

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secretion in a glucose-dependent manner. They also promote weight loss, lower blood pressure, reduce albuminuria and have favorable effects on different components of the serum lipid profile (2). However, after the unexpected association of rosiglitazone with a significant increase in the risk of myocardial infarction and death from cardiovascular causes, the focus has shifted from efficiency of antihyperglycemic agents to the cardiovascular safety of these compounds (3).

Glucagon-like peptide-1 receptor agonists are increasingly utilized in the treatment of T2DM since they address not only hyperglycemia but also numerous cardiovascular risk factors. They have been associated with improvements in serum lipid profiles in numerous clinical trials (4-7). The results of a large meta-analysis have demonstrated that GLP-1 RAs are associated with reductions in total and LDL-cholesterol levels, as well as triglycerides but not improvements in HDL-cholesterol levels (8). The results of the LEADER trial prove that liraglutide is not only effective in achieving optimal glycemic control but also in reducing the risk of death from cardiovascular causes (or any cause) (9).

The aim of our study was to explore the effects of GLP-1 RAs exenatide and liraglutide on serum lipid profiles (total, LDL, HDL-cholesterol and triglycerides) in obese patients with T2DM.

SUBJECTS, MATERIALS AND METHODS

A total of 43 obese T2DM patients on exenatide were included and followed-up for 22 months (age 57±7 years, 22 M/21F, body mass index (BMI) 38±5 kg/m2, weight 114±18 kg, HbA1c 8.6±1,2%, duration of diabetes 11±6 years). Forty-two patients on liraglutide were also included in this study and were followed up for 13 months (age 58±7 years, 18 M/24 F, BMI 38±5 kg/m2, weight 111±21 kg, HbA1c 8.1±0,9%, duration of diabetes 13±6 years). Basic anthropometric measurements were performed on all study subjects, including BMI and waist circumference (WC). Venous blood samples were collected in the morning between 08:00 and 09:30 AM after an overnight fast for determination of glucose, HbA1c and serum lipids. HbA1c was measured using spectrophotometry by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Results of HbA1c (%) are expressed in the DCCT-equivalent. Glucose, cholesterol and triglycerides levels were measured by an enzymatic colorimetric method, after precipitation with polyethylene glycol, using an automatic spectrophotometer (Olympus AU600, Beckman-Coulter, USA). Exenatide was started at 5 μg twice daily and increased to 10 μg twice daily if needed in patients with estimated glomerular filtration rate ≥60 ml/min/1.73m2. Liraglutide was started at 0.6 mg once daily and increased up to 1.8 mg.

The study protocol complied with the Declaration of Helsinki, as well as local institutional guidelines and was approved by local ethics committees. Data are expressed as means±SD for normally distributed values, as medians with range for non-normally distributed values, and percentages. Differences between groups were examined, depending on the nature of the data, by parametric (t-test) or nonparametric (Mann-Whitney) tests. Statistical analysis was performed using statistical package STATA/IC ver.11.1.

RESULTS

At the end of the 22-month follow-up, 43 patients treated with exenatide demonstrated significant reductions of HbA1c from 8.6±1.2 to 8.0±1.3% (p=0.01), BMI from 38±5 to 36±5 kg/m2 (p<0.001), weight from 114±18 to 106±18 kg (p<0.001) and WC from 119±12 to 115±11 cm (p<0.001). Exenatide treatment was also associated with a significant decrease in total cholesterol from 5.1±1.3 to 4.9±1.2 mmol/L (p=0.02) and LDL-cholesterol from 3.0±1.1 to 2.6±0.8 mmol/L (p=0.01), while HDL-cholesterol and triglyceride levels were not significantly affected (Table 1).

Treatment with liraglutide was associated with significant reductions in BMI (38±5 to 36±6 kg/m2; p<0.001), weight (111±21 to 106±23 kg; p<0.001) and WC from 120±14 to 114±15 cm (p<0.001), while HbA1c was not significantly affected (from 8.1±0.9 to 8.0±1.3% (p=0.1). However, the 13-month administration of liraglutide was associated with a significant decrease in total cholesterol (from 4.8±1.2 to 4.2±0.8 mmol/L; p=0.001), and LDL-cholesterol (from 2.5±0.8 to 2.1±0.5 mmol/L; p=0.006), while HDL-cholesterol and triglyceride levels were not significantly affected (Table 2).

Table 1. **Baseline and end-of-study characteristics of patients treated with exenatide**

	Baseline	End of study	p value
Age (years)	57±7		
Gender (male/female)	22/21		
Diabetes duration (years)	11±6		
Waist circumference (cm)	119±12	115±11	<0.001
Body mass index (kg/m2)	38±5	36±5	<0.001
Weight (kg)	114± 18	106±18	<0.001
HbA1c (%)	8.6±1.2	8.0±1.3	0.01
Total cholesterol (mmol/L)	5.1±1.3	4.9±1.2	0.02
LDL-cholesterol (mmol/L)	3.0±1.1	2.6±0.8	0.01
HDL-cholesterol (mmol/L)	1.2±0.2	1.2±0.2	0.4
Triglycerides (mmol/L)	2.7±2.5	2.8±2.5	0.5

Table 2. **Baseline and end-of-study characteristics of patients treated with liraglutide**

	Baseline	End of study	p value
Age (years)	58±7		
Gender (male/female)	18/24		
Diabetes duration (years)	13±6		
Waist circumference (cm)	120±14	114±15	<0.001
Body mass index (kg/m2)	38±5	36±5	<0.001
Weight (kg)	111± 21	106±23	<0.001
HbA1c (%)	8.1±0.9	8.0±1.3	0.1
Total cholesterol (mmol/L)	4.8±1.2	4.2±0.8	0.001
LDL-cholesterol (mmol/L)	2.5±0.8	2.1±0.5	0.006
HDL-cholesterol (mmol/L)	1.2±0.3	1.1±0.2	0.1
Triglycerides (mmol/L)	2.7±2.5	2.3±1.1	0.2

DISCUSSION

The results of our study suggest that treatment with GLP-1 RAs exenatide and liraglutide may favorably affect serum lipid profiles in obese patients with T2DM by reducing total and LDL-cholesterol levels. Furthermore, treatment with GLP-1 RAs led to significant reductions in weight, BMI, WC and HbA1c.

Liraglutide has been consistently linked to beneficial changes in lipid profiles, according to the results of numerous relevant clinical trials (4,5). A meta-analysis of all LEAD-6 trials demonstrated that liraglutide significantly decreased total cholesterol, LDL-cholesterol and triglyceride levels compared to insulin and thiazolidinediones. HDL-cholesterol levels were decreased in all liraglutide treatment arms, except for those with thiazolidinediones (10). According to the results of a systematic review and network meta-analysis analyzing the effects of GLP-1 RAs on lipid profiles, it was shown that liraglutide was associated with a decrease in HDL-cholesterol independently of dose and a statistically significant reduction of LDL-cholesterol, total cholesterol, as well as triglyceride levels, which were dose-dependent. Liraglutide 1,8 mg daily was associated with the best LDL-cholesterol, total cholesterol and triglyceride level reduction compared to other doses and to daily exenatide (but not with exenatide 2 mg weekly formulation for LDL-cholesterol) (8).

The evidence concerning the effects of exenatide on the serum lipid profile is not as consistent. According to a systematic review, there were no significant differences in lipid profiles in the exenatide groups compared to placebo or an active comparator (11). A single study showed a significant reduction in HDL-cholesterol, compared to placebo (12). A study by Simó et al. showed a statistically significant HDL-cholesterol increase, compared to glimepiride (13). However, significant improvements of lipid profiles were observed in the study analyzing the effects of once-weekly exenatide. Moreover, the improvement of total cholesterol was greater using a weekly formulation of exenatide compared to twice daily use (6, 7). Compared to liraglutide 1,8 mg, exenatide twice daily was associated with a significantly lesser reduction of triglyceride levels but with a more significant reduction of VLDL-cholesterol (4). The results of the large network meta-analysis showed no impact on HDL but significant reductions of LDL-cholesterol when compared to placebo and insulin. The once-weekly formulation of exenatide was associated with greater reductions of LDL compared to exenatide twice-daily and even with liraglutide. Exenatide significantly decreased total cholesterol when compared to placebo (twice-daily) or an active comparator (once-weekly formulation). Again, liraglutide was associated with more significant reductions. Triglyceride levels were not significantly improved when compared to placebo or active comparators (8) which is in line with the results of our study.

Glucagon-like peptide-1 receptor agonists have not been found to consistently increase HDL-cholesterol (8). However, it has been proposed that the vascular-protective capacities of HDL may be more relevant in inhibiting atherosclerosis, independent of HDL levels (14). This can be attributed to the redistribution of cholesterol from small, dense LDL particles, decreasing apolipoprotein B concentration and a shift toward smaller size HDL particles which may be of clinical relevance as major mediators of the cardioprotective properties of HDL-cholesterol (15).

Even modest improvements in lipid profiles can be clinically significant for patients with T2DM, albeit only confirmed when using statins (16, 17). The impact of GLP-1 RAs on cardiovascular risk is more comprehensive than the impact on lipid profiles, also including lowering of blood pressure, weight loss and reduction of albuminuria as well as other cardiovascular risk factors. As the results of the LEADER trial clearly show, liraglutide was proven to be not only safe for use in patients with high cardiovascular risk but that there was a clear benefit for these patients (9), which has not been demonstrated using other GLP-1 RAs (18, 19).

In conclusion, the results of our study suggest that treatment with exenatide and liraglutide may significantly reduce total and LDL-cholesterol in obese patients with T2DM. Treatment with liraglutide and exenatide also resulted in weight loss and HbA1c reduction, but without significant changes in HDL-cholesterol and triglyceride levels.

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ŽIVOTOPIS

Rođen sam 17. ožujka 1987. godine u Splitu. Tijekom studija na Medicinskom fakultetu Sveučilišta u Zagrebu bio sam demonstrator pri katedrama za internu medicinu, patologiju te histologiju i embriologiju. Diplomirao sam u srpnju 2011. godine. Pripravnički staž sam odradio pri KB Dubrava te sam u siječnju 2013. godine položio stručni ispit za doktora medicine. Od 2013. god 2016. godine bio sam zaposlen u službi obiteljske medicine Doma zdravlja Zagreb- zapad nakon čega započinjem specijalističko usavršavanje iz endokrinologije i dijabetologije u Sveučilišnoj klinici za dijabetes, endokrinologiju i bolesti metabolizma „Vuk Vrhovac“ Kliničke bolnice „Merkur“. Specijalistički ispit položio sam u srpnju 2021. godine te sam i trenutno zaposlen kao specijalist endokrinologije i dijabetologije pri Sveučilišnoj klinici Vuk Vrhovac. Sudjelovao sam u brojnim istraživanjima i kliničkim studijama te publicirao radove u stručnim časopisima. Član sam europskog endokrinološkog društva (ESE) te Hrvatskog društva za endokrinologiju i dijabetes te aktivno sudjelujem na brojnim međunarodnim kongresima i simpozijima.