



ADROPIN – POTENTIAL LINK IN CARDIOVASCULAR PROTECTION FOR OBESE MALE TYPE 2 DIABETES MELLITUS PATIENTS TREATED WITH LIRAGLUTIDE

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SUMMARY – The aim of this study was to determine plasma adropin concentration and parameters of insulin resistance in obese male type 2 diabetes mellitus (T2DM) patients before and after 3-month liraglutide treatment. In this interventional study, we enrolled 15 obese male T2DM patients with body mass index (BMI) >35 kg/m², uncontrolled disease and HbA_{1c} >7.5%, having previously taken two oral antidiabetic drugs. We modified their therapy to metformin and liraglutide for the next three months. After three months of liraglutide treatment, we observed significant decrease in body weight (from 111.5±18.7 kg to 109.2±17.5 kg, p=0.016) and BMI (from 40.9±7.3 to 40.1±7.0 kg/m², p=0.021). Plasma adropin concentration increased significantly (p=0.003) compared with baseline. Fasting plasma insulin level decreased from 17.79±6.53 to 13.38±3.51 mU/L (p=0.002), fasting plasma glucose level decreased from 8.66±3.07 to 7.41±2.21 mmol/L (p=0.004) and HbA_{1c} decreased from 7.98±0.70% to 7.26±0.36% (p=0.003). Insulin resistance presented as HOMA-IR decreased significantly from 7.30±5.19 to 4.52±2.61 (p=0.002). Systolic blood pressure, lipid status, liver and kidney function improved, but not reaching statistical significance. Treating obese male T2DM patients with liraglutide resulted in a significantly higher plasma adropin concentration, significant weight loss and improved parameters of insulin resistance, i.e. decreased fasting plasma insulin, plasma glucose levels and HOMA-IR.

Key words: *Diabetes mellitus type 2; Insulin resistance; Obesity; Adropin; Liraglutide; Endothelial cell dysfunction*

Introduction

Nowadays, type 2 diabetes mellitus (T2DM) seems to be one of the most important public health challenges. Current estimates of its incidence are imprecise, only providing a rough picture, and probably underestimating the disease burden¹. Dealing with T2DM implies coping with the complex chronic disease that demands lifelong medical and self care in order to prevent acute and delay chronic complications².

Body mass index (BMI) has a strong relationship to insulin resistance and T2DM development. In obese individuals, the amount of substances involved in the development of insulin resistance is increased. The pathogenesis of T2DM development is based on the fact that pancreatic β -cells are impaired, causing a lack of blood glucose control. The development of T2DM becomes inevitable if the pancreatic β -cell failure is accompanied by insulin resistance³. T2DM increases overall mortality primarily due to cardiovascular disease, which is the major cause of morbidity and mortality among these patients. Further on, patients with poor glycemic control are at risk of developing micro- and macrovascular complications, unlike those who maintain tight glycemic control^{4,5}.

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Ten years ago, Kumar *et al.* identified a new protein named adropin, which is believed to play an important role in metabolic homeostasis, insulin resistance prevention, dyslipidemia and impaired glucose tolerance⁶⁻⁸. It is encoded by the ENHO gene (Energy Homeostasis Associated Gene) and its expression in the liver, heart, brain and coronary arteries is diet dependent⁶. Results of the studies conducted so far show that the diseases resulting from metabolic syndrome, such as obesity, T2DM, non-alcoholic fatty liver disease, polycystic ovary syndrome, or cardiovascular disease are accompanied by significant changes in the concentration of this peptide⁸. Plasma adropin concentration is decreased in T2DM patients, especially those overweight or obese^{9,10}. Moreover, adropin is a potent regulator of cardiovascular function and plays a protective role in the pathogenesis and development of cardiovascular disease¹¹. It regulates endothelial cell function and its plasma concentration has been found to be lower in individuals with endothelial dysfunction, which seems to be an autonomous indicator of cardiovascular incidents in individuals with T2DM. Furthermore, adropin concentration and HbA_{1c} are shown to be independent risk factors for endothelial dysfunction in these patients¹²⁻¹⁴.

Diabetes mellitus type 2 is characterized by a reduced incretin effect and inappropriate glucagon levels, so the incretin-based therapy could provide beneficial effects, not only because of the antidiabetic effect but also for the favorable effect on body weight^{15,16}. In 2010, the National Institute for Health and Care Excellence (NICE) issued guidance on the use of one of the incretins called liraglutide in T2DM¹⁷. Liraglutide is an analog of human glucagon-like peptide-1 (GLP-1) and acts as GLP-1 receptor agonist (GLP-1 RA). Its efficacy in glycemic control has already been established. It increases insulin and reduces glucagon secretion, slows down gastric emptying, postpones carbohydrate absorption, and augments satiety^{18,19}. The majority of T2DM patients on liraglutide treatment report more significant weight loss than those treated with other GLP-1 RA²⁰. To assess the long-term effects of liraglutide on cardiovascular outcomes and clinically important events, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was initiated in 2010²¹. Trial results showed a lower rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal

stroke among T2DM patients treated with liraglutide as compared to those on placebo²².

Considering the fact that T2DM patients are characterized with lower plasma adropin concentration⁹ and that liraglutide has a positive effect on both glycemic control and cardiovascular outcomes²⁰⁻²², we decided to explore plasma adropin concentration in obese T2DM patients after three months of liraglutide treatment. As far as we know, this is the first report on adropin concentration in obese T2DM patients undergoing liraglutide treatment.

The aim of this study was to determine plasma adropin concentration and parameters of insulin resistance in male obese T2DM patients before and after 3-month liraglutide treatment.

Materials and Methods

This was a non-randomized, controlled, interventional study. The primary objective was to determine plasma adropin concentration and parameters of insulin resistance in male obese T2DM patients before and after three months of liraglutide treatment. Patients treated at Department of Endocrinology and Diabetes, Split University Hospital Centre from April 2017 to June 2017 were invited to participate in the study. Investigators had meetings with patients and explained the study nature, aim, potential hazards, and expected outcomes. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice, with a written informed consent obtained from each participant. It was approved by Ethics Committee of the Split University Hospital Centre. Sampling was performed in 15 male obese T2DM patients with BMI >35 kg/m², uncontrolled diabetes mellitus and HbA_{1c} >7.5%. All the participants had previously received two oral antidiabetic drugs. In all cases, first-line agent was metformin, while second-line agent was sulfonylurea in 12 and dipeptidyl peptidase-4 (DPP-4) inhibitor in three participants. In our study, we modified their therapy, which now consisted of metformin (1000 mg b.i.d.) and liraglutide (Victoza®, Novo Nordisk A/S, Bagsvaerd, Denmark) for the next three months. To improve gastrointestinal tolerability, the starting dose was 0.6 mg liraglutide daily. After two weeks, the dose was increased to overall 1.2 mg daily until the end of the study.

In each participant, we observed anthropometric data, blood pressure, parameters of glucose metabolism, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index and plasma adropin concentration at the beginning and after three months of the study. Anthropometric measurements included body height, weight, BMI, body circumferences (waist and hip), and waist to hip ratio (WHR). Body height was measured using a stadiometer with the investigator standing behind the participant. Subjects stood with their scapula, buttocks and heels resting against the stadiometer, the neck was held in a natural non-stretched position, the heels were touching each other, the toe tips formed a 45° angle and the head was held straight with the inferior orbital border in the same horizontal plane as the external auditory canal (Frankfort's plane). The horizontal arm of the stadiometer was lowered until it touched the scalp (anthropometric point vertex). Body weight was measured on a medical decimal scale with sliding weight, with a ±250 g error margin. Patients were barefoot, only wearing their underwear. The weight was rounded up to the nearest 0.5 kg. BMI was estimated by dividing weight (kg) by height² (m²)²³⁻²⁵. Waist and hip circumferences were measured using a flexible non-elastic measuring tape. Individuals stood with their feet together and arms resting by their sides. Hip circumference was measured from the maximum perimeter of the buttocks. Waist circumference was taken as the plane between the umbilical scar and the inferior rib border. Each measurement was performed twice and the mean result was calculated^{26,27}. Waist circumference was used to identify individuals with possible health risks based upon threshold values of ≥88 cm for women and ≥102 cm for men. WHR measurement is used to estimate visceral or android obesity. WHR was estimated by dividing waist circumference by hip circumference. The threshold WHR was ≥0.85 for women and ≥1.00 for men and was used as a criterion for android obesity. Abdominal circumference and WHR are good indicators of body fat distribution and cardio-metabolic risk^{27,28}. Blood pressure was measured using a mercury sphygmomanometer with the corresponding cuff size (Riester desk model), following the WHO MONICA Protocol (MONItoring of trends and determinants in Cardiovascular disease and Protocol)²⁹. Patients were seated and relaxed for 5 minutes before the measurements were taken. Measurements

were performed on the right forearm, at the position of the brachial artery by trained measurers. Values were noted with ±2 mm Hg accuracy. Two measurements were done, 5 minutes apart, and the mean value of the two measurements was used for analysis³⁰.

According to the regular protocol, the same experienced biochemist took and analyzed blood samples obtained from the antecubital vein after 12-hour overnight fasting. Fasting blood samples were analyzed in the same laboratory, using the same method for each substance. The biochemist had no knowledge of the patient medical condition. Insulin blood levels were measured using the electrochemiluminescence immunoassays (Roche® Diagnostics GmbH, Mannheim, Germany). Enzymatic hexokinase photometric assay (Abbott®, Chicago, IL, USA) was used to measure fasting plasma glucose and turbidimetric inhibition immunoassay (Roche® Diagnostics GmbH, Mannheim, Germany) to measure HbA_{1c} plasma levels. Plasma adropin levels were measured using an enzyme-linked immunosorbent assay kit (Phoenix Pharmaceuticals, Belmont, CA, USA) according to the manufacturer's instructions. Other laboratory analyses were performed according to the standard laboratory protocols. Insulin resistance score (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mmol/L) x fasting serum insulin (μU/mL) divided by 22.5.

Statistical analyses were performed using MedCalc for Windows, version 11.5.1.0 (MedCalc Software, Mariakerke, Belgium) statistical software. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as whole numbers and percentages. Differences between baseline and after three-month treatment values were determined using Wilcoxon matched paired test. The level of statistical significance was set at $p < 0.05$.

Results

Fifteen male obese T2DM patients receiving therapy that consisted of metformin (1000 mg b.i.d.) and liraglutide (Victoza®, Novo Nordisk A/S, Bagsvaerd, Denmark) were followed up for three months. Median age of the patients included in our study was 60 years, body weight (mean ± standard deviation [SD]) was 111.5±18.7 kg, BMI (mean ± SD) was 40.9±7.3 kg/m² and HbA_{1c} (mean ± SD) was 7.98±0.70%. Baseline waist to hip ratio (mean ± SD) was 0.96±0.08.

Table 1. Anthropometric data

Variable	Baseline*	After 3 months of treatment*	p***
Age (years)**	60 (55-68)	60 (55-68)	1.000
Body height (cm)	165.5±8.6	165.5±8.9	1.000
Body weight (kg)	111.5±18.7	109.2±17.5	0.016
Body mass index (kg/m ²)	40.9±7.3	40.1±7.0	0.021
Waist circumference (cm)	121.6±8.8	120.9±8.5	0.168
Hip circumference (cm)	126.7±11.7	125.5±11.2	0.086
Waist to hip ratio	0.96±0.08	0.97±0.08	0.721
Systolic blood pressure (mm Hg)	140±11	139.5±9.9	0.767
Diastolic blood pressure (mm Hg)	85.9±4.4	87.3±3.4	0.224

*Data presented as mean ± standard deviation (SD); **data presented as median; ***Wilcoxon matched paired test

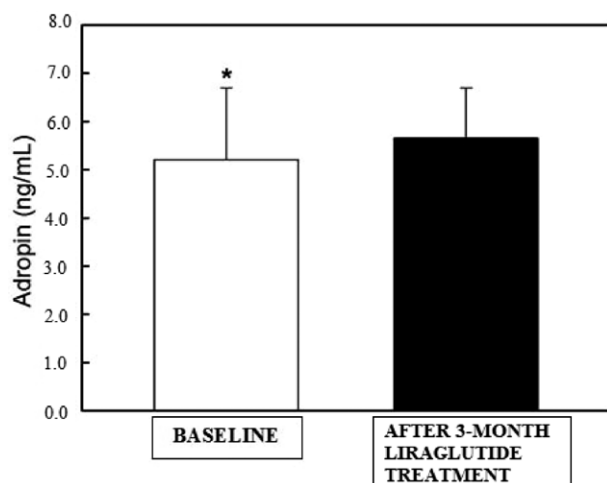


Fig. 1. Plasma adropin concentration – baseline and after 3-month liraglutide treatment.

After three months of liraglutide treatment, we observed changes in anthropometric parameters (Table 1). Analysis confirmed a significant decrease in both body weight and BMI; body weight was reduced from 111.5±18.7 kg to 109.2±17.5 kg (p=0.016) and BMI from 40.9±7.3 to 40.1±7.0 kg/m² (p=0.021). Over these three months, systolic blood pressure decreased but not significantly. After 3-month liraglutide treat-

Table 2. Glucose metabolism parameters

Variable	Baseline	After 3 months of treatment	p*
Fasting insulin (mU/L)	17.79±6.53	13.38±3.51	0.002
Fasting blood glucose (mmol/L)	8.66±3.07	7.41±2.21	0.004
HbA _{1c} (%)	7.98±0.70	7.26±0.36	0.003
HOMA-IR	7.30±5.19	4.52±2.61	0.002

Data presented as mean ± standard deviation (SD); *Wilcoxon matched paired test; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance

Table 3. Biochemical parameters

Variable	Baseline	After 3 months of treatment	p*
Triglycerides (mmol/L)	1.88±1.34	1.78±1.14	0.449
Cholesterol (mmol/L)	5.49±0.92	5.45±0.83	0.343
HDL cholesterol (mmol/L)	1.18±0.28	1.27±0.27	0.063
LDL cholesterol (mmol/L)	3.39±0.71	3.26±0.72	0.082
AST (U/L)	20.4±7.71	21.2±8.12	0.173
ALT (U/L)	30.6±22.32	31.9±18.65	0.102
GGT (U/L)	30.70±18.95	29.1±15.75	0.332
Creatinine (µmol/L)	79.09±23.29	81.36±23.91	0.230
Urea (mmol/L)	6.02±1.12	6.05±1.12	0.476
Urate (µmol/L)	398.09±71.98	391.0±67.57	0.104

Data presented as mean ± standard deviation (SD); *Wilcoxon matched paired test; HDL = high-density lipoprotein; LDL = low-density lipoprotein; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyltransferase

ment, plasma adropin concentration increased significantly (p=0.003) as compared with the baseline (Fig. 1). Besides obesity reduction, disease control was remarkably improved. All the parameters of glucose metabolism improved significantly. Fasting plasma insulin level decreased from 17.79±6.53 to 13.38±3.51

mU/L ($p=0.002$), fasting blood glucose level from 8.66 ± 3.07 to 7.41 ± 2.21 mmol/L ($p=0.004$) and HbA_{1c} from 7.98 ± 0.70 to $7.26\pm 0.36\%$ ($p=0.003$). Insulin resistance presented as HOMA-IR improved significantly and its value decreased from 7.30 ± 5.19 to 4.52 ± 2.61 ($p=0.002$) (Table 2).

Our study showed improvement in lipid profile (cholesterol, triglycerides, low-density lipoproteins), but these results did not show significant change. Additionally, we noticed improvement in liver function through a decrease of aspartate transaminase (AST), alanine transaminase (ALT) and gamma-glutamyl-transferase (GGT) levels but these results were not statistically significant. Kidney function was slightly improved, although creatinine, urea and urate levels did not show significant change (Table 3).

Discussion

Considering the fact that obesity and insulin resistance play key roles in the development of T2DM, therapeutic options leading to the resolution of these issues may be of utmost importance^{3,5,31,32}. Identifying adropin as a marker of endothelial cell dysfunction that is found to be lower in T2DM patients^{9,10} and that liraglutide may afford protection against endothelial cell dysfunction, which is an early abnormality in diabetic vascular disease³³, led us to explore adropin levels in T2DM patients treated with liraglutide. Therefore, this study is of great importance because it is the first one to compare the effects of liraglutide treatment on plasma adropin concentration and parameters of insulin resistance in T2DM patients.

Kumar *et al.* hypothesize that adropin is involved in regulation of metabolic homeostasis and that its deficiency has a negative effect on glucose homeostasis and carries an increased risk of developing insulin resistance and T2DM progression⁶⁻⁸. Our study provided data on the effect of 3-month liraglutide treatment applied once daily in combination with metformin in male obese patients with T2DM. We showed that liraglutide treatment led to a significantly higher plasma adropin concentration ($p=0.003$), one of the regulators of endothelial cell dysfunction in T2DM¹²⁻¹⁴. Hence, elevated plasma adropin concentration could partially explain cardiovascular benefits and protection provided by liraglutide. Furthermore, the application of liraglutide and higher adropin concentration were associ-

ated with decreased insulin resistance parameters. Consequently, the levels of fasting plasma glucose ($p=0.004$), fasting plasma insulin ($p=0.002$) and HOMA-IR ($p=0.002$) decreased significantly after three months of liraglutide treatment.

Recent studies demonstrated that patients with T2DM treated with GLP-1 RA improved their glycaemic control and had modest weight loss³⁴. Other studies showed that liraglutide treatment significantly decreased weight and improved insulin resistance³². Our results also confirmed that this treatment led to significant weight loss ($p=0.016$), decreased BMI ($p=0.021$) and improved insulin resistance parameters ($p=0.002$). Decreased adiposity could be the outcome of early satiety and slower gastric emptying caused by liraglutide²⁰. Following the previous information, not only BMI was significantly reduced, but also HbA_{1c} ($p=0.003$), which was shown in previous studies^{32,34,35}.

Furthermore, we observed a small decrease in systolic blood pressure, but it was not statistically significant, unlike several other studies that investigated liraglutide effect^{36,37}. Considering the fact that our study was shorter (12 weeks) than the mentioned studies (24 weeks), we think that our results would probably be of the same relevance with longer study duration. In addition to a significantly decreased level of systolic blood pressure, liraglutide appears to improve the levels of cholesterol, low-density lipoprotein cholesterol and triglycerides²⁰. Our study showed improvement in lipid profile (cholesterol, triglycerides, low-density lipoproteins) and systolic blood pressure, but did not demonstrate statistical significance compared to other studies. This may be due to the lower baseline BMI (33.49 ± 5.15 kg/m²)³⁵ when compared to our patient BMI (40.9 ± 7.3 kg/m²).

Another interesting finding was a slight reduction in ALT, AST and GGT concentrations. This GGT result found in our study was similar to the previously reported results, but ALT and AST results in our study were not in concordance with other studies. These differences may have been due to the lower baseline BMI level (30.1 kg/m²) and lower body weight in the above-mentioned study.

Conclusions

In conclusion, treating male obese T2DM patients with liraglutide results in a significantly higher plasma

adropin concentration, significant weight loss and improved parameters of insulin resistance, i.e. decreased fasting plasma insulin and glucose levels and decreased HOMA-IR. Liraglutide treatment also ameliorates systolic blood pressure, lipid profile and kidney function, but these results were not statistically significant. Additional studies of longer duration and larger number of participants are needed so we could have more precise and reliable results.

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Sažetak

ADROPIN – POTENCIJALNI ČIMBENIK KARDIOVASKULARNE SIGURNOSTI U MUŠKARACA OBOLJELIH OD ŠEĆERNE BOLESTI TIP 2 LIJEČENIH LIRAGLUTIDOM

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Cilj je bio usporediti plazmatske vrijednosti adropina i parametre inzulinske rezistencije kod pretilih muškaraca koji boluju od šećerne bolesti tip 2 (ŠBT2) prije i nakon 3 mjeseca primjene liraglutida. U ovoj intervencijskoj studiji sudjelovalo je 15 pretilih muškaraca koji boluju od ŠBT2 s indeksom tjelesne mase (ITM) >35 kg/m², loše reguliranom bolešću i HbA_{1c} >7,5%. Ispitanici su prethodno u terapiji imali dva peroralna antidijabetična lijeka. Nakon uključanja u studiju terapija im je modificirana na metformin i liraglutid tijekom tri mjeseca. Nakon primjene liraglutida kod ispitanika je zamijećeno smanjenje tjelesne mase (sa 111,5±18,7 na 109,2±17,5 kg, p=0,016) i ITM (s 40,9±7,3 na 40,1±7,0 kg/m², p=0,021), dok su plazmatske vrijednosti adropina bile značajno povišene (p=0,003). Zamijećeno je sniženje vrijednosti inzulina natašte (sa 17,79±6,53 na 13,38±3,51 mU/L, p=0,002), glukoze natašte (s 8,66±3,07 na 7,41±2,21 mmol/L, p=0,004) te HbA_{1c} (sa 7,98±0,70% na 7,26±0,36%, p=0,003). HOMA-IR se značajno smanjio (sa 7,30±5,19 na 4,52±2,61, p=0,002). Također su zabilježene niže vrijednosti sistoličkog arterijskog tlaka, bolji lipidni profil te poboljšanje jetrene i bubrežne funkcije, iako ne statistički značajno. Primjena liraglutida u pretilih muškaraca koji boluju od ŠBT2 rezultira statistički značajno višim razinama plazmatskog adropina, značajnim smanjenjem tjelesne težine i poboljšanjem svih parametara inzulinske rezistencije, tj. sniženjem plazmatskog inzulina i glukoze natašte te nižim HOMA-IR.

Ključne riječi: Šećerna bolest tip 2; Inzulinska rezistencija; Pretilost; Adropin; Liraglutid; Endotelna disfunkcija