
LIRAGLUTIDE AS A MEANS OF MODIFYING CARDIOMETABOLIC RISK IN PATIENTS WITH ARTERIAL HYPERTENSION AND CONCOMITANT OBESITY

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ABSTRACT

Background. Arterial Hypertension (AH), in combination with OBesity (OB), significantly increases cardiometabolic risk, leading to the development of cardiovascular events, chronic kidney disease, and metabolic disorders. In such patients, the effectiveness of standard antihypertensive therapy may be insufficient, which requires the use of drugs with pleiotropic action.

Aim. To assess the effectiveness of liraglutide, Glucagon-Like Peptide-1 Receptors Agonist (GLP-1RA), as a component of combination therapy in patients with AH and OB, with the determination of its effect on cardiometabolic status, functional state of the kidneys, heart and neuro-humoral regulation.

Materials and Methods. The study involved 62 patients with AH and OB who received liraglutide at a dose of up to 3.0 mg/day for 12 months. The dynamics of anthropometric, biochemical, hormonal, hemodynamic, and echocardiographic parameters were assessed. Statistical processing was performed using the Statistica 13.0 package (StatSoft Inc., USA).

Results. During the treatment, a significant decrease in systolic and diastolic blood pressure, body mass index, insulin levels, leptin, Cardiotrophin-1 (CTF-1), N-terminal propeptide of brain natriuretic hormone (NT-proBNP), as well as an improvement in the lipid profile were observed. According to echocardiography, regression of myocardial hypertrophy and improved systolic and diastolic function of the left ventricle was recorded. Positive but insignificant dynamics of functional renal parameters were noted.

Conclusions. Liraglutide demonstrates a pronounced multicomponent efficacy in patients with hypertension and obesity, reducing leptin resistance and improving neuroendocrine regulation and metabolic and hemodynamic profile. Our findings suggest that it can be used in complex therapy to modify cardiometabolic risk.

Keywords: *leptin, GLP-1RA, N-terminal propeptide of brain natriuretic hormone, cardiohemodynamics.*

Abbreviations

AH – Arterial Hypertension;
BMI – Body Mass Index;
CTF-1 – Cardiotrophin-1;
Cys C – Cystatin C;
DBP – Diastolic Blood Pressure;
DM2 – Type 2 Diabetes Mellitus;
GFR – Glomerular Filtration Rate;
GLP-1 – Glucagon-Like Peptide-1;

GLP-1RA – Glucagon-Like Peptide-1 receptor agonist;
HDL – High Density Lipoproteins;
HDL-C – High-Density Lipoprotein Cholesterol;
IVST – Interventricular Septum Thickness;
LA – Left Atrium;
LAESD – Left Atrial End-Systolic Dimension;
LDL – Low Density Lipoproteins;
LVEDD – Left Ventricular End-Diastolic Dimension;
LVEF – Left Ventricle Ejection Fraction;
LVESD – Left Ventricular End-Systolic Dimension;
LVMM – Left Ventricle Myocardium Mass;
LVMMI – Left Ventricle Myocardium Mass Index;
LVMMI1 – Left Ventricle Myocardium Mass Index (relative to body area);

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LVMMI2 – Left Ventricular Mass Index`
(adjusted for height to the power of 2.7);
LVPWT – Left Ventricular Posterior Wall
Thickness;
LVRWT – Left Ventricle Relative Wall
Thickness;
NT-proBNP – N-Terminal pro-Brain
Natriuretic Peptide;
OB – Obesity;
RA – Right Atrium;
RAD – Right Atrium Diameter;
RV – Right Ventricle;
RVD – Right Ventricle Diameter;
SBP – Systolic Blood Pressure;
TC – Total Cholesterol;
TG – Triglycerides;
VA – Velocity Atrial, Late Diastolic Filling
Velocity, A-wave);
VE – Velocity, Early, Peak Early Diastolic
Filling Velocity, E-wave;
VE/VA – Early to Late Diastolic Filling ratio
(E/A ratio).
VLDL – Very Low Density Lipoproteins.

Introduction

The combination of AH and OB is one of the most common forms of cardiometabolic comorbidity, which is accompanied by a significant increase in the risk of cardiovascular complications, chronic kidney disease, and premature mortality [1–3]. OB produces a pathogenetic effect on blood pressure by activating the renin-angiotensin-aldosterone and sympathoadrenal systems, increasing insulin resistance, and developing systemic inflammation and endothelial dysfunction [4]. In conditions of excessive body weight, the effectiveness of antihypertensive therapy is often reduced, which necessitates the search for drugs with a multi-component mechanism of action.

One of the promising areas of pharmacotherapy in this category of patients is the use of drugs that affect not only individual symptoms but also key links in the pathogenesis of cardiometabolic disorders [5; 6]. Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) receptor agonist approved for treating DM2 and OB, demonstrating powerful pleiotropic effects. The mechanism of action of liraglutide consists of stimulation of insulin secretion in a glucose-dependent manner, inhibition of glucagon secretion, gastric emptying deceleration, and appetite reduction by affecting the satiety centers in the hypothalamus [7–9].

Clinical studies have shown that liraglutide contributes to a significant reduction in body weight,

blood pressure, and both SBP and DBP, as well as improves the lipid profile and inflammation markers. Its effect on blood pressure is due to a decrease in sympathetic activity, increased sensitivity to sodium, improved endothelial function, and reduced arterial stiffness. It is important that liraglutide does not cause hypotension in patients with normal or moderately elevated blood pressure, which makes it safe for use in patients with comorbid pathology [8].

In addition, liraglutide demonstrated cardioprotective properties in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study, reducing the incidence of cardiovascular events in patients with DM2. These effects are partly associated with weight loss, improved glycemic control, and direct effects on the myocardium and blood vessels [10; 11].

The relevance of studying the effectiveness of liraglutide in patients with a combination of AH and obesity is due to the need for an individualized approach to treatment and the desire to reduce overall cardiometabolic risk. This drug has the potential to be integrated into a comprehensive therapeutic strategy aimed at both lowering blood pressure and modifying the metabolic profile of patients.

The study **aimed** to determine the effectiveness of liraglutide in the complex therapy of patients with arterial hypertension and concomitant obesity by assessing its effect on cardiometabolic status, renal function, neurohumoral regulation, and systemic hemodynamics.

Materials and Methods

The study involved 62 patients (35 men and 27 women) with combined AH and OB who were under outpatient observation at the polyclinic of the State Institution "National Institute of Therapy named after L.T. Mala, NAMS of Ukraine". The mean age of the patients was $[53.52 \pm 9.24]$ years.

Diagnostic criteria for AH verification were based on the recommendations of the European Society of Cardiology (ESC, 2021); OB was defined according to the World Health Organization (WHO, 1997) classification by $BMI \geq 30 \text{ kg/m}^2$.

Exclusion criteria were the presence of acute infectious or inflammatory conditions, systemic autoimmune or oncological diseases, symptomatic AH, pathology of the hypothalamic-pituitary system, severe renal function impairment ($GFR < 35 \text{ ml/min/1.73 m}^2$), established diabetes mellitus, drug or alcohol addiction, COVID-19, acute cardiovascular events (myocardial infarction,

stroke) in the history within the recent 6 months, pregnancy or belonging to vulnerable social groups.

The clinical study was conducted in accordance with the ethical standards of biomedical research involving humans as set out in the Declaration of Helsinki and was approved by the Bioethics Committee of Kharkiv National Medical University. Each study participant provided written informed consent to participate.

The treatment strategy involved the administration of Liraglutide as a component of combination therapy. The drug was administered subcutaneously, starting at a dose of 0.6 mg with subsequent titration to 3.0 mg/day depending on individual tolerability and achievement of target BMI. In addition, the patients received basic antihypertensive therapy (perindopril 2–8 mg once daily) and hypolipidemic therapy (rosuvastatin [10–20] mg/day).

Before starting the study, none of the patients received GLP-1 drugs or medications for OB treatment. The choice of liraglutide was justified by the discrepancy between body weight and expected indicators when using only non-drug agents, as well as the need to modify cardiometabolic risk following the recommendations of the European Society of Cardiology (ESC, 2023) and the American Diabetes Association (ADA, 2023).

The patient examination program before the start and 12 months after therapy included determining the following indicators: glycated hemoglobin (HbA1c), insulin, BMI, TC, HDL and LDL, VLDL, TG, serum creatinine, leptin, insulin, CTF-1, NT-proBNP and Cys C. Commercial test systems were used according to the manufacturer's instructions for biochemical measurements. GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, taking into account creatinine and Cys C, according to the recommendations of Kidney Disease: Improving Global Outcomes (KDIGO, 2021):

$$eGFR_{cr-cys} = 135 \times \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{Scr}{\kappa}, 1\right)^{-0.544} \times \min\left(\frac{Scys}{0.8}, 1\right)^{-0.323} \times \max\left(\frac{Scys}{0.8}, 1\right)^{-0.778} \times 0.9961^{Age} \times 0.963 \text{ (for women)} \quad (1),$$

where

Scr – standardized creatinine level (mg/dl),

κ – coefficient (0.7 – for women;

0.9 – for men),

α – exponent (–0.219 – for women;

–0.144 – for men),

Scys – cystatin C concentration (mg/l),

Age – patient age.

In addition, all patients had their blood pressure measured, SBP and DBP, under standard conditions.

An echocardiographic examination was performed according to the protocols of the European Association of Cardiovascular Imaging (EACVI, 2016). The parameters assessed included LVMMI, LA and RA dimensions, LA end-systolic dimensions, LVEDD and LVESD, RV dimensions, IVST and LVPWT, LVMM, LVMMI2, LVRTW, LVEF, early diastolic filling velocity (VE), late diastolic filling velocity (VA) as well as their ratio (VE/VA).

Statistical data processing was performed using Statistica 13.0 (StatSoft Inc., USA). Quantitative indicators were presented as mean $\pm$ standard deviation ($M \pm SD$). Distribution normality was tested using the Shapiro-Wilk test. To assess changes before and after treatment, paired Student's t-test or Wilcoxon test (in case of deviation from normal distribution) was used. Correlations were assessed by Spearman's coefficient. Changes were considered statistically significant at $p < 0.05$.

Results

The study assessed the changes in the main clinical, laboratory, and instrumental parameters in patients with AH and concomitant OB. The analysis included a comparison of data before the start of treatment and after 12 months of therapy. The findings obtained allow for characterizing the effectiveness of the selected therapeutic approach in terms of metabolic profile, cardiovascular adaptation, and functional state of the kidneys (*Table 1*).

Table 1 shows that 12-month therapy with liraglutide in patients with combined AH and OB resulted in significant positive changes in most of the evaluated parameters. First of all, a significant decrease in both SBP from $[144.74 \pm 10.08]$ mm Hg to $[132.58 \pm 8.92]$ mm Hg ($p < 0.001$) and DBP from $[89.76 \pm 9.32]$ mm Hg to $[83.12 \pm 8.14]$ mm Hg ($p < 0.001$) was noted, which indicates an antihypertensive effect of the drug, probably due to its effect on the sympathoadrenal system, natriuretic mechanism and improvement of endothelial function.

Table 1. Effect of a 12-month course of liraglutide treatment on cardiometabolic and renal parameters in patients with arterial hypertension and obesity (n=62)

Indices	Before treatment	After treatment	p
SBP, mm Hg	144.74±10.08	132.58±8.92	<0.001
DBP, mm Hg	89.76±9.32	83.12±8.14	<0.001
BMI, kg/m ²	34.25±2.85	29.75±2.41	<0.001
TC, mmol/l	5.43±1.6	4.62±1.22	<0.01
HDL-C, mmol/l	1.28±0.35	1.45±0.32	<0.05
TG, mmol/l	1.87±0.7	1.37±0.54	<0.01
VLDL, mmol/l	0.81±0.3	0.68±0.28	>0.05
LDL, mmol/l	3.2±1.46	2.41±1.27	<0.01
Leptin, ng/ml	27.68±14.46	19.42±12.34	<0.001
CTF-1, ng/ml	1021.76±130.83	887.42±121.46	<0.01
Insulin, mIU/ml	17.77±9.63	13.03±8.18	<0.01
HbA1c, %	5.95±0.92	5.49±0.74	<0.05
Creatinine, μmol/l	92.45±16.26	86.21±14.38	>0.05
GFR, ml/min/1.73m ²	68.91±11.02	74.35±10.11	>0.05
NT-proBNP, ng/ml	456.88±152.59	388.26±137.64	<0.05
Cys C, ng/ml	145.31±40.83	129.74±36.27	>0.05

An important clinical achievement is a significant decrease in body mass index from [34.25±2.85] kg/m² to [29.75±2.41] kg/m² (p<0.001), indicating the effectiveness of liraglutide as a means of correcting body weight in obese patients, even in the absence of diabetes. The positive dynamics of body weight was accompanied by an improvement in lipid metabolism indicators: a decrease in TC from [5.43±1.6] mmol/l to [4.62±1.22] mmol/l (p<0.01); a decrease in LDL-C from [3.2±1.46] mmol/l to [2.41±1.27] mmol/l (p<0.01); a decrease in TG – from [1.87±0.7] mmol/l to [1.37±0.54] mmol/l (p<0.01); and an increase in HDL-C – from [1.28±0.35] mmol/l to [1.45±0.32] mmol/l (p<0.05). The decrease in VLDL-C concentration did not reach a significant level (p>0.05), which may be due to the variability of the indicator in the patients.

Hormonal changes reflecting a decrease in leptin resistance and an improvement in insulin sensitivity are indicative: leptin concentration decreased from [27.68±14.46] ng/ml to [19.42±12.34] ng/ml (p<0.001), and insulin level decreased from [17.77±9.63] mIU/ml to [13.03±8.18] mIU/ml (p<0.01). The decrease in HbA1c from [5.95±0.92] % to [5.49±0.74] % (p<0.05) also confirms the effect of the drug on carbohydrate metabolism, even in individuals without a diagnosis of DM2. Another important aspect is the effect of the therapy on neurohumoral and cardiometabolic markers. The decrease in CTF-1 le-

vels from [1.021.76±130.83] ng/ml to [887.42±121.46] ng/ml (p<0.01) and NT-proBNP from [456.88±152.59] ng/ml to [388.26±137.64] ng/ml (p<0.05) indicates a decrease in myocardial load and improved neurohumoral adaptation, which is important in patients with hypertension and overweight.

Against the background of therapy, a positive, albeit statistically insignificant, dynamics of renal function markers was observed: creatinine level decreased from [92.45±16.26] μmol/l to [86.21±14.38] μmol/l (p>0.05) and the GFR according to the CKD-EPI formula increased from [68.91±11.02] ml/min/1.73 m² to [74.35±10.11] ml/min/1.73 m² (p>0.05). Similarly, the decrease in Cys C concentration from [145.31±40.83] ng/ml to [129.74±36.27] ng/ml (p>0.05) indicates a trend of improving renal filtration capacity, which requires further studies with a larger sample size.

Thus, the results obtained confirm the multifactorial positive effect of liraglutide on the clinical and metabolic status of patients with AH and concomitant OB. The detected changes include not only correction of BP, body weight, lipid and carbohydrate metabolism but also a decrease in the levels of hormonal and neurohumoral markers associated with high cardiometabolic risk. At the same time, an important aspect of the comprehensive assessment of the effectiveness of therapy is the study of the structural and functional state of the heart. For this purpose, changes in cardiohe-

mododynamic parameters were analyzed according to the echocardiography results presented in *Table 2*.

Our findings suggest that 12-month therapy with liraglutide in patients with AH and OB resulted in significant positive changes in cardiohemodynamic parameters, indicating remodeling of heart structures and improving its functional state.

In particular, a significant decrease in the size of the left atrium was recorded from $[4.04 \pm 0.46]$ cm to $[3.86 \pm 0.41]$ cm ($p < 0.05$), and the right atrium from $[4.00 \pm 0.47]$ cm to $[3.81 \pm 0.43]$ cm ($p < 0.05$), which is probably due to a decrease in the volume and pressure load on the atrium as a result of blood pressure normalization and improvement in the vasodilation capacity of the vessels.

The dynamics of the left ventricle dimensions were less pronounced: LVEDD decreased from $[5.05 \pm 0.56]$ cm to $[4.88 \pm 0.49]$ cm, but this change did not reach statistical significance ($p > 0.05$), while the decrease in the LVESD from $[3.46 \pm 0.35]$ cm to $[3.32 \pm 0.32]$ cm was significant ($p < 0.05$), which may indicate an improvement in ventricular systolic function.

There was also a decrease in the IVST and the LVPWT, with the latter being statistically significant from $[1.32 \pm 0.18]$ cm to $[1.27 \pm 0.16]$ cm ($p < 0.05$). These indicators reflect a decrease in the degree of concentric cardiac remodeling against the background of long-term therapy.

A significant result is the decrease in LVMMI from $[250.19 \pm 40.28]$ g to $[232.5 \pm 35.2]$ g ($p < 0.05$), as well as LVMMI1 and LVMMI2, which

indicates the regression of hypertrophy, characteristic of patients with hypertension and metabolic disorders. The decrease in LVRWT from $[0.52 \pm 0.05]$ to $[0.48 \pm 0.04]$ ($p < 0.05$) additionally indicates positive changes in ventricular geometry.

Systolic function indicators also underwent positive changes: LVEF increased from $[51.63 \pm 3.57]\%$ to $[54.1 \pm 3.44]\%$ ($p < 0.05$), which may indicate an improvement in the pumping function of the heart.

Left ventricular diastolic function also improved: VE increased from $[63.99 \pm 7.94]$ to $[67.12 \pm 7.15]$ cm/s, while VA velocity decreased from $[67.47 \pm 6.6]$ to $[64.39 \pm 5.91]$ cm/s, which resulted in an increase in VE/VA from $[0.95 \pm 0.12]$ to $[1.04 \pm 0.1]$, ($p < 0.05$). This indicates a normalization of the diastolic phase ratio and an improvement in myocardial relaxation capacity.

Thus, the data presented confirm that the use of liraglutide in patients with hypertension and obesity not only contributes to weight loss and correction of metabolic disorders but also has a beneficial effect on the morphofunctional state of the heart. The results obtained justify the feasibility of including this drug in the complex therapy of patients with increased cardiometabolic risk and can also serve as a basis for forming a favorable phenotype in this cohort of patients.

Thus, the results obtained in our study showed that long-term use of liraglutide in patients with a combination of AH and OB was accompanied by a significant decrease in leptin levels, which was

Table 2. Effect of a 12-month course of liraglutide treatment on cardiohemodynamic parameters in patients with arterial hypertension and obesity (n=62)

Indices	Before treatment	After treatment	p
LAESD, cm	4.04 ± 0.46	3.86 ± 0.41	< 0.05
RAD, cm	4 ± 0.47	3.81 ± 0.43	< 0.05
LVEDD, cm	5.05 ± 0.56	4.88 ± 0.49	> 0.05
LVESD, cm	3.46 ± 0.35	3.32 ± 0.32	< 0.05
LV, cm	1.96 ± 0.22	1.92 ± 0.2	> 0.05
IVST, cm	1.24 ± 0.07	1.2 ± 0.06	> 0.05
LVPWT, cm	1.32 ± 0.18	1.27 ± 0.16	< 0.05
LVMM, g	250.19 ± 40.28	232.5 ± 35.2	< 0.05
LVMMI1, g/m ²	118.16 ± 18.51	109.78 ± 16.32	< 0.05
LVMMI2, g/m ²	59.49 ± 9.61	55.64 ± 8.74	< 0.05
LVRTW	0.52 ± 0.05	0.48 ± 0.04	< 0.05
LVEF, %	51.63 ± 3.57	54.1 ± 3.44	< 0.05
VE, cm/s	63.99 ± 7.94	67.12 ± 7.15	< 0.05
VA, cm/s	67.47 ± 6.6	64.39 ± 5.91	< 0.05
VE/VA	0.95 ± 0.12	1.04 ± 0.1	< 0.05

accompanied by an improvement in the mass-insulin profile, glycemic control, and a decrease in neurohumoral activation. Such leptin dynamics is considered not only a secondary consequence of a decrease in fat mass but also a marker of overcoming leptin resistance, which plays a key role in the formation of high cardiometabolic risk in patients with OB.

It is important to note that our data are entirely consistent with the results of numerous randomized clinical trials that investigated the effect of liraglutide on the hormonal activity of adipose tissue, particularly on leptin secretion. Thus, in the large-scale SCALE Obesity and Prediabetes study (n=3731), it was demonstrated that therapy with liraglutide at a dose of 3.0 mg was accompanied by a significant decrease in leptin levels compared to placebo. At the same time, leptin dynamics correlated with clinical improvement in the glycemic profile, body mass index, and restoration of central regulation of appetite [12].

The weight-reducing effect of liraglutide on weight loss was confirmed by the results of a randomized, double-blind study lasting 52 weeks, which demonstrated that the reduction in leptin occurs not only due to weight loss but also through direct modulation of leptin sensitivity, which was accompanied by a decrease in left ventricular hypertrophy and improvement in diastolic function [13]. In a crossover randomized trial conducted among women with OB, it was found that liraglutide therapy was accompanied by a significant decrease in leptin and the leptin/adiponectin index after 16 weeks of treatment. The authors of the study emphasize that these changes are not necessarily dependent on body weight and may indicate a neuroendocrine restructuring of hunger and satiety signals [14; 15]. It was also confirmed that liraglutide not only improves energy balance but also suppresses pro-inflammatory signaling pathways involved in the formation of leptin resistance, including the JAK-STAT (Janus Kinase-Signal Transducer and Activator of Transcription), SOCS3 (Suppressor of Cytokine Signaling 3) and TNF- α (Tumor Necrosis Factor- α) pathways. This creates favorable conditions for the restoration of leptin receptor communication with the hypothalamus, which confirms the concept of a multifactorial effect of the drug [14; 16].

Thus, both our results and data from randomized multicenter trials indicate that liraglutide is an effective means of modifying cardiometabolic risk, in particular by reducing leptin, improving hormonal activity of adipocytes and reducing leptin-dependent sympathoadrenal activation. This emphasizes the importance of considering leptin not only as a biomarker but also as a target for therapeutic influence in treatment strategies for comorbid conditions, in particular, AH combined with OB.

Conclusions

1. Liraglutide is an effective means of complex therapy in patients with arterial hypertension and obesity, contributing to a significant reduction in body weight, blood pressure, improvement of lipid and hormonal profiles without developing hypoglycemia.

2. Liraglutide therapy normalizes leptin levels and reduces leptin resistance, which indicates a positive effect of the drug on the metabolic activity of adipose tissue, appetite control, and systemic neuroendocrine regulation.

3. The inclusion of liraglutide in the treatment regimen helps reduce overall cardiometabolic risk, reduce hormonal and inflammatory burden, and improve hemodynamic parameters and the functional state of the cardiovascular system, which is confirmed by both our data and the results of multicenter randomized studies.

DECLARATIONS:

Disclosure Statement

The author have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The author has no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the author.

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