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PRACA ORYGINALNA

Evaluation of the effect of liraglutide therapy on body weight and insulin resistance

Ocena wpływu terapii liraglutydem na masę ciała i insulinooporność

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Abstract

Introduction and Objective. Insulin resistance is a state of reduced tissue sensitivity to insulin action despite normal or elevated serum insulin levels. Liraglutide (a GLP-1 receptor agonist) stimulates insulin secretion from the pancreas while decreasing excessive glucagon release. GLP-1 analogues have a unique beneficial effect on weight loss by stimulating insulin secretion without increasing blood sugar levels excessively. The aim of the study was to investigate the effects of liraglutide on body mass index and insulin resistance in overweight and obese non-diabetic individuals.

Materials and Method. The study involved 31 overweight and obese women (BMI of ≥25 kg/m2) who received liraglutide treatment between 2021–2022. Liraglutide 3.0 mg was used as an adjunct to behavioural therapy, which included a low-calorie diet and exercise programme. The study collected BMI, glucose and insulin levels, and HOMA index before and during liraglutide treatment. Body weight and blood tests were examined at baseline (BMI1, HOMA1), as well as at 3 (BMI2, HOMA2), and 6 months (BMI3, HOMA3) of treatment to observe any changes.

Results. Average age of participants – 38.32±7.41 years. Changes in BMI from baseline (32.36±4.56 kg/m^2) to 6 months (27.46±4.45kg/m^2) were associated with a significant reduction in weight ($p < 0.001$). Changes in HOMA index from baseline (4.73±1.48) to 3 (3.59±1.26) and 6 months (2.47±0.91) were statistically significant ($p < 0.03$, $p < 0.001$).

Conclusions. Liraglutide represents a promising option for reducing body weight and obesity in non-diabetic patients as an adjunct to behavioural therapy. Agonists GLP-1 receptor, representing a new class of antidiabetic drug, undoubtedly offer unique benefits for overweight or obesity patients. Liraglutide in 3.0 mg use was associated with a significant weight reduction and lowering of insulin resistance.

Key words

obesity, overweigh, liraglutide, weight loss

Streszczenie

Wprowadzenie i cel pracy. Insulinooporność to stan zmniejszonej wrażliwości tkanek na działanie insuliny pomimo prawidłowego lub podwyższonego poziomu tego hormonu w surowicy. Liraglutyd (agonista receptora GLP-1) stymuluje wydzielanie insuliny z trzustki, jednocześnie zmniejszając nadmierne uwalnianie glukagonu. Analogi GLP-1 mają wyjątkowo korzystny wpływ na odchudzanie poprzez stymulację wydzielania insuliny bez nadmiernego wzrostu poziomu cukru we krwi. Zbadaliśmy wpływ liraglutydu na wskaźnik masy ciała i insulinooporność u osób z nadwagą i otyłością, które nie chorują na cukrzycę.

Materiał i metody. W badaniu wzięło udział 31 kobiet z nadwagą i otyłością (BMI ≥ 25), które były leczone liraglutydem w latach 2021–2022. Liraglutyd w dawce 3,0 mg stosowano jako dodatek do terapii behawioralnej, która obejmowała dietę niskokaloryczną i program ćwiczeń. W badaniu wykorzystano następujące informacje o uczestniczkach: wartość BMI, poziomy glukozy i insuliny oraz wskaźnik HOMA przed i podczas leczenia liraglutydem. Masę ciała określono i badania krwi przeprowadzono na początku leczenia (BMI1, HOMA1), a także po 3 (BMI2, HOMA2) i 6 miesiącach (BMI3, HOMA3) leczenia w celu zaobserwowania zmian.

Wyniki. Średni wiek uczestniczek badania wynosił 38,32 ± 7,41 lat. Zmiany BMI od wartości wyjściowej (32,36 ± 4,56) do niższej (27,46 ± 4,45), co nastąpiło w okresie 6 miesięcy, wiązały się ze znaczną redukcją masy ciała ($p < 0,001$). Zmiany wskaźnika HOMA od wartości wyjściowej (4,73 ± 1,48) do tej uzyskanej w ciągu 3 (3,59 ± 1,26) i 6 miesięcy (2,47 ± 0,91) były istotne statystycznie ($p < 0,03$; $p < 0,001$).

Wnioski. Liraglutyd stanowi obiecującą redukcję masy ciała i otyłości u pacjentów bez cukrzycy jako uzupełnienie terapii behawioralnej. Agonisty receptora GLP-1, reprezentujący nową klasę leków przeciwcukrzycowych, niewątpliwie oferują wyjątkowe korzyści pacjentom z nadwagą lub otyłością. Stosowanie liraglutydu w dawce 3,0 mg wiązało się ze znaczną redukcją masy ciała i obniżeniem insulinooporności.

Słowa kluczowe

otyłość, nadwaga, liraglutyd, utrata masy ciała

Abbreviations

BMI – Body Mass Index; **HOMA** – Homeostasis Model Assessment – Insulin Resistance; **GLP-1** – Glucagon-Like Peptide-1

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INTRODUCTION AND OBJECTIVE

Insulin resistance is a state of reduced tissue sensitivity to insulin action despite normal or elevated serum levels of insulin. Insulin resistance may be primary, genetically determined, or secondary, accompanied by various disorders such as impaired glucose tolerance, type 2 diabetes, polycystic ovary syndrome, hypercholesterolemia, hypertriglyceridaemia, obesity, hypertension, or hyperuricaemia [1]. Insulin acts through specific receptors that start the process at the moment of binding to the receptor localized on the cell's membrane of target cells. Insulin receptors are located on the surface of most cells in the body, with the highest number found on the surface of adipocytes, liver cells, and striated muscles [2].

Obesity is a known cardiovascular risk factor for developing type 2 diabetes. Furthermore, weight gain is common in patients treated with insulin or drugs that increase insulin secretion, such as sulfonylureas. Weight loss of over 5% was shown to lower the risk of morbidity and mortality and improve the quality of life [3]. One of the most well-known methods of weight loss is a lifestyle change through a low-calorie diet and increasing regular physical activity. Pharmacological therapy can act as an adjunct to behavioural changes [4].

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonist) which is meant to increase insulin release from the cells of the pancreas, and decrease excessive glucagon release [5]. Common side-effects include nausea, dizziness, and abdominal pain, which tend to be strongest at the beginning of treatment and decrease over time [6]. The unique feature of GLP-1 agonists is their beneficial effect on weight loss despite stimulating insulin secretion. This is primarily due to slower emptying of the stomach, which prolongs the feeling of satiety and reduces appetite. At the same time, stimulation of insulin secretion by GLP-1 agonists depends on the glucose concentration; therefore, hunger pangs caused by hypoglycaemia are avoided.

The aim of the study was to investigate the impact of liraglutide on body mass index (BMI) and insulin resistance in overweight and obese non-diabetic individuals.

MATERIALS AND METHOD

In this retrospective study, 31 overweight and obese women who were treated with liraglutide 3.0 mg as an adjunct to behavioural therapy (low calorie diet and exercises) between March 2021 – March 2022 were analyzed in a single clinic in Warsaw. All patients adhered to a structured diet and exercise programme throughout the trial.

Baseline measurements of BMI, glucose and insulin levels, as well as HOMA index (homeostatic model assessment), were taken before and during liraglutide treatment. HOMA is a method used to quantify insulin resistance and beta-cell function. Changes in body weight and blood tests were examined at baseline (BMI1, HOMA1) and at the 3rd (BMI2, HOMA2) and 6th (BMI3, HOMA3) months of treatment. To be eligible for inclusion in the study, the women had to be aged ≥18 years with a BMI of ≥25 kg/m2, stable body weight, and not receiving treatment with metformin. Those with type 1 diabetes, type 2 diabetes, using dipeptidyl peptidase 4 inhibitors, GLP-1 receptor agonists, or medications known to induce significant weight change in the previous 90 days, were excluded. Other exclusion criteria included recent history of a cardiovascular event, history of hypothyroidism, history of pancreatitis, pregnancy, breastfeeding, or intention to become pregnant.

To compare clinical data and laboratory test results between different stages of treatment, the Chi-squared test was used. A p-value of <0.05 was considered statistically significant. Mean values and standard deviation (SD) were calculated for parametric data.

RESULTS

The average age of participants was 38.32 ± 7.41 years. Changes in BMI from baseline (32.36 ± 4.56 kg/m^2) to 6 months (27.46 ± 4.45kg/m^2) were associated with a significant weight reduction (p <0.0001). Changes in HOMA index from baseline (4.73 ± 1.48) – to 3 (3.59 ± 1.26) and 6 months (2.47 ± 0.91) were statistically significant (p <0.03; p < 0.001, respectively). Figure 1 shows changes in BMI during different stages of treatment. Figure 2 shows changes in HOMA index during different stages of treatment.

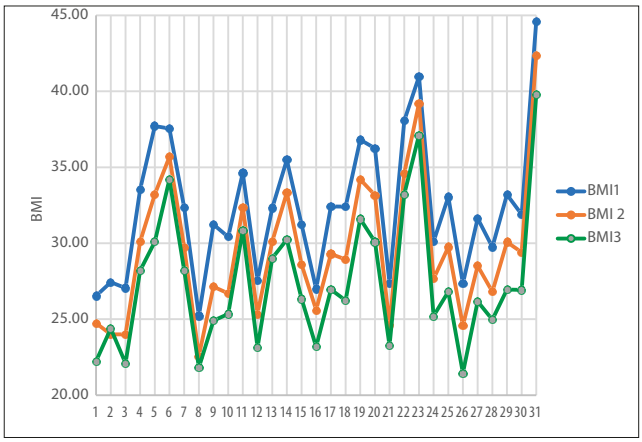

Figure 1. Changes in BMI during different stages of treatment

Table 1. Changes in BMI during liraglutide treatment

BMI	Mean ± SD
BMI1 (kg/m^2)	32.36 ± 4.56
BMI2 (kg/m^2)	29.57 ± 4.60
BMI3 (kg/m^2)	27.46 ± 4.45

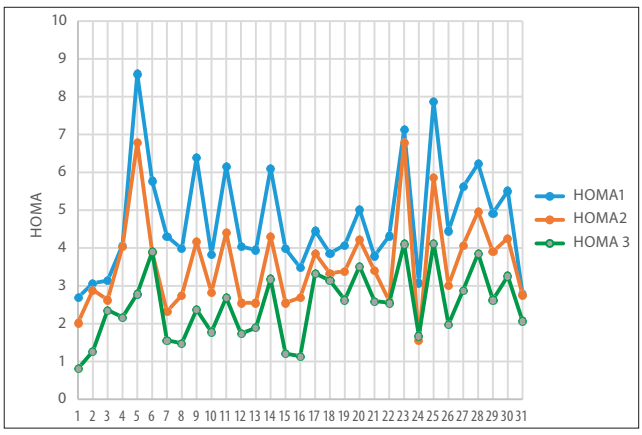

Figure 2. Changes in HOMA index during different stages of treatment

Table 2. Changes in HOMA index during liraglutide treatment

INDEX	Mean ± SD
HOMA1	4.73 ± 1.48
HOMA2	3.59 ± 1.26
HOMA3	2.47 ± 0.91

DISCUSSION

Obesity is a well-known cardiovascular risk factor, and most individuals with type 2 diabetes are overweight or obese. The unique feature of GLP-1 analogues is their beneficial effect on weight loss despite stimulating insulin secretion. It is possible that the occurrence of nausea as a side-effect of the use of GLP-1 analogues contributes to the reduction of appetite. In this study, the treatment with liraglutide at a dose of 3 mg resulted in a statistically significant decrease in the HOMA index after 3 and 6 months of therapy. There was also a significant decrease in BMI after 6 months of therapy. Liraglutide at a dose of 3.0 mg is associated with weight reduction and improvement in insulin resistance.

Studies in the LEAD programme have confirmed the beneficial effect of liraglutide on weight loss in patients with type 2 diabetes receiving GLP-1 analogue treatment.. The one-year observational LEAD-3 study of diabetic type-2 patients showed a decrease of 2.05 kg and 2.45 kg in body weight after receiving a liraglutide monotherapy at doses of 1.2 mg and 1.8 mg, respectively. Meanwhile, glimepiride recipients experienced a weight gain of 1.12 kg [7].

Some favourable outcomes were also obtained in the treatment of obesity in patients without type 2 diabetes. In a randomized double-blind placebo-controlled trial involving 564 subjects with a BMI of 30–40 kg/m^2 and comparing liraglutide to orlistat, patients using the GLP-1 agonist showed significantly higher weight loss (4.8–7.2 kg for various doses of liraglutide vs. 4.1 kg for orlistat with $p < 0.0001$ for the highest dose of liraglutide) [8].

Sharma et al. demonstrated the effectiveness of liraglutide as a weight loss agent in heart failure patients with reduced ejection fraction [9]. As much as 45% of patients with heart failure are obese. The results of this study suggest that liraglutide is effective in restoring normal body weight and reducing triglyceride levels. In another randomized study, individuals were assigned to either a liraglutide 3.0 mg (n = 198) or placebo (n = 198) and received intensive behavioural therapy. After 56 weeks of treatment, the 3.0mg liraglutide dose resulted in a mean weight change of -5.8% compared to -1.5% for placebo (estimated treatment difference -4.3% [95% CI -5.5; -3.2]; p< 0.0001). Furthermore, 51.8% of individuals in the liraglutide 3.0 mg group achieved ≥5% weight loss, compared to 24.0% in the placebo group (OR=3.41 [95% CI 2.19; 5.31]; p< 0.0001). Additionally, liraglutide 3.0 mg was associated with significantly greater reductions in mean HbA_{1c} levels compared to placebo [10].

GLP-1 analogues have been shown to lower blood pressure by exerting a direct impact on blood vessels and promoting sodium excretion. In the LEAD-3 study, liraglutide was found to significantly reduce blood pressure ($p < 0.05$), with systolic blood pressure decreasing by 3.6 ± 14.1 mmHg for a dose of 1.8 mg, compared to a decrease of 0.7 ± 13.7 mmHg for glimepiride [7].

Liraglutide (1.9 mg) has also been shown to reduce the concentration of triglycerides in the blood serum of patients with type 2 diabetes by 22% compared to placebo, along with reductions in HbA1c and body weight [11]. A meta-analysis of studies involving liraglutide treatment in patients showed a significant decrease in total cholesterol levels by 0.13 mmol/l ($p < 0.01$), fractional cholesterol LDL ($p < 0.0001$), triglycerides by 0.2 mmol/L ($p < 0.01$), and free fatty acids by 0.09 mmol/L ($p < 0.0001$) [12]. The mechanism behind the lipid-lowering effect of GLP-1 analogues has not yet been fully clarified, but it is possible that their effect on weight loss plays an important role.

In summary, it is important to emphasize that GLP-1 receptor agonists as a novel class of antidiabetic drugs, offer unique benefits for overweight or obese patients. However, our understanding of the full therapeutic potential of the incretin axis remains incomplete, and requires further research.

CONCLUSIONS

Liraglutide is a promising option for reducing overweight and obesity in non-diabetic patients as an adjunct to behavioural therapy (low calorie diet and exercises). The use of liraglutide at a dosage of 3.0 mg was associated with significant weight reduction and improvement in insulin resistance. Analysis shows the need to offer patients drug therapy with monitoring of physical activity.

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