sciendo
ПРИЛОЗИ. Одд. за мед. науки, XLIV 1, 2023 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLIV 1, 2023 MASA

10.2478/prilozi-2023-0008 ISSN 1857-9345

EFFICACY AND SAFETY OF EMPAGLIFLOZINE AND SEMAGLUTIDE (ONCE WEEKLY) IN T2DM PATIENTS IN SHTIP

Valentina Velkoska Nakova[1, 2], Zoran Nakov[2], Stojka Dokuzova[1], Tatjana Prosheva[3], Brankica Krstevska[4]

[1] Clinical Hospital, Shtip, RN Macedonia

[2] Faculty of medical science, University Goce Delchev, Shtip, RN Macedonia

[3] University Clinic of Endocrinology, Diabetes and Metabolic Disease, Skopje, RN Macedonia

[4] Internal Medicine Centre "Srce", Skopje, RN Macedonia

Corresponding author: Valentina Velkoska Nakova, Clinical Hospital, Shtip, RN Macedonia, email: valentina.velkovska@ugd.edu.mk

ABSTRACT

Objective: The efficacy and safety of the following new treatment agents were analyzed: once weekly semaglutide (OWSem) and the empagliflozine (Empa). This was done with patients with type 2 diabetes mellitus (T2DM) at the Clinical Hospital in Shtip, R.N. Macedonia.

Material and methods: One-hundred-twenty-one diabetic patients were treated for the first time with OWSema or Empa and were retrospectively analyzed. Glycemic control, serum creatinine, decrease in weight, co-morbidities, and hospitalization during treatment were recorded.

Results: Among the 61 patients treated with OWSema and 60 patients treated with Empa, there were not any statistically significant differences in age, sex, BMI, duration of diabetes, and a number of patients treated with insulin. Both agents (OWSema and Empa) achieved statistically significant HbA1c reduction after 6, 12, and 18 months (9.2; vs. 7.6; 6.7; 6.6, and 9.3; vs. 7.5; 7.2, 7.5%, respectively) treatment. There were not any differences in the value of creatinine between the visits in both groups. During the period of 2 years, 3 patients (5%) from the Empa group died, all with multiple comorbidities. One patient from Empa group was hospitalized because of acute pulmonary edema and two from the OWSema group because of TIA and acute coronary syndrome. The median decrease in weight was more pronounced in the OWSema group (6.0 vs. 4.0kg). Five patients stopped the treatment with Empa because of a simple urinary infection, and one stopped the OWSema because of GIT intolerance. Eight patients did not tolerate the dose of 1mg, and they therefore continued with 0.5mg of OWSema.

Conclusion: Once weekly treatment with semaglutide and empagliflozine achieves a great reduction in HbA1c, and as such are safe for treatment of T2DM.

Keywords: once weekly semaglutide, empagliflozin, glycosylated hemoglobin, hospitalization

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT-2i) are new therapies for type 2 diabetes mellitus (T2DM) [1]. According to guidelines for the treatment of T2DM, both are considered second-line therapies, or first-line in patients with high or very high cardiovascular risk [1-3].

The action mechanism of GLP-1 RAs includes: glucose-mediated stimulation of insulin secretion, reduced glucagon release, reduced hepatic glucose output, delayed gastric emptying,

increased satiety, and improved cardiovascular risk factors [4-7]. Thus, GLP-1RAs provide effective glycemic control, with a low risk of hypoglycemia, reducing body weight, blood pressure, and cardiovascular events [4]. Semaglutide is a human GLP-1 RA available as a once-weekly subcutaneous injection and oral semaglutide.

The mechanisms of action of SGLT-2i are as follows: reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release. Empagliflozin as SGLT-2i improves glycemic control, blood pressure, and body weight [8-12] and is associated with a reduced risk of cardiovascular and all-cause mortality in patients at high cardiovascular risk [13].

The aim of the study was to evaluate the efficacy and safety of once weekly semaglutide (OWSema) and empagliflozin (Empa) in our patients with T2DM.

MATERIAL AND METHODS

This was a retrospective study conducted at the Diabetic Centre in the Clinical Hospital in Shtip, R. of North Macedonia. We enrolled patients with T2DM who had been treated with OWSema and Empa. Both medications were used for better glycemic control or were indicated according to the current guidelines (high cardiovascular risk, heart failure or chronic kidney failure) [2, 3]. OWSema was started at with 0.25mg, and after 1 month the dose was increased to 0.5mg. If the dose was well tolerated after 1 month, it was increased to 1mg. Empa was given in a dose of 10mg during the whole study period. In all patients who initiated these medications medical records were collected retrospectively as well as baseline demographic data (age, sex, BMI, duration of diabetes, concomitant medications, co-morbidities), results from blood parameters (fasting blood glucose (FPG), HbA1c, creatinine, estimated GFR), side effects from the drugs, cardiovascular events, and eventual hospitalization. The data were obtained from the beginning of the treatment with these drugs until 1 August, 2022. All patients were scheduled for a doctor's visit every 3 months. Not one of the patients received both medications. Patients were not included in the study who had acute metabolic disorders, such as diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome and were taking steroids, had acute infectious disease, or had any newly diagnosed cancer, or who required hospitalization.

STATISTICAL ANALYSES

We expressed continuous variable data as means (± standard deviations) and categorical variable data as numbers and percentages. Statistical analyses were performed by SPSS 20.0. The t-test and ANOVA were used for the analysis of quantitative variables. $\chi 2$-test with Yates correction was used for the analysis of qualitative variables.

To explore the effects of various clinical factors on the good therapy response we performed a logistic regression analysis. We divided the patients into younger and elderly groups (below and above 65 years of age), non-obese and obese groups (BMI below and above 30 kg/m2), with and without chronic kidney disease (CKD) (eGFR\below and above 60 mL/min/1.73 m2), duration of diabetes (below or above 14 years), and it was considered a good response for therapy if HbA1c decreased more than 1%. We accepted all P values less than 0.05 as statistically significant.

Table 1. *The demographic characteristics of both analyzed groups*

	Empa (n=60)	OWSema (n=61)	P value
Age (years)	61.3±7.9	56.8±9.5	NS
Sex (w:m)	19:41	18:43	NS
BMI (kg/m2)	32.8±5.4	33.8±5.5	NS
Mean duration of diabetes (years)	9.2±6.6	9.7±6.9	NS
Insulin treatment	22 (36.7%)	15 (24.6%)	NS (p=0.14)
Ischemic coronary disease	24 (40%)	26 (42.6%)	NS
Ischemic CVI	7 (11.7%)	14 (22.9%)	NS
CMP dilatata	10 (16.7%)	5 (8.3%)	NS
Hypertension	47 (78.3%)	45 (73.8%)	NS
Diabetic nephropathy	10 (16.7%)	9 (14.7%)	NS

RESULTS

The baseline characteristics of the 121 patients, 60 treated with Empa and 61 treated with OWSema, are shown in Table 1. Between the two groups, there were no statistically significant differences in age, sex, BMI, duration of diabetes, co-morbidities, concomitant medications, and the number of patients treated with insulin (Table 1).

Statistically significant reductions in the mean values of FPG and HBA1c were found in patients treated with OWSema and Empa. The mean values of creatinine were not increased during the whole follow-up period (Tables 2 and 3).

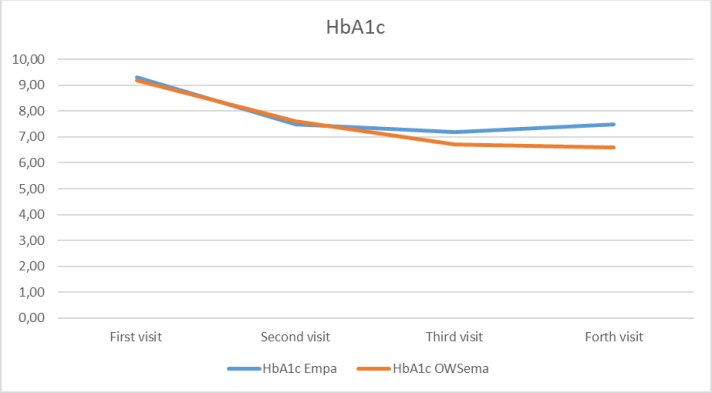
The changes in HbA1c in the two groups were significantly improved from their baseline HbA1c values (Fig.1). In a mean period of 18 months, we found a 2.6% reduction in HbA1c in the OWSema group, and 1.8% reduction in HbA1c in the Empa group. The percentage of patients who achieved a HbA1c lower than 7% significantly changed with Empa and OWSema treatment, from 8.33% and 13.11% at baseline to 35.1% and 52.46% respectively. (Fig. 2).

Table 2. *Glycaemic control and serum creatinine in patients treated with OWSema*

	First visit	Second visit (4.5±2.5 months)	Third visit (9.7±2.7 months)	Forth visit (15.5±3.3 months)	P value
FPG (mmol/l)	10.5±3.3	8.4±3.3	7.5±2.5	7.0±1.2	<0.01
HbA1c (%)	9.2±1.8	7.6±1.8	6.7±0.9	6.6±0.9	<0.01
Creatinine (µmol/l)	89.9±25.7	89.7±26.9	89.4±22.8	97.2±24.1	NS

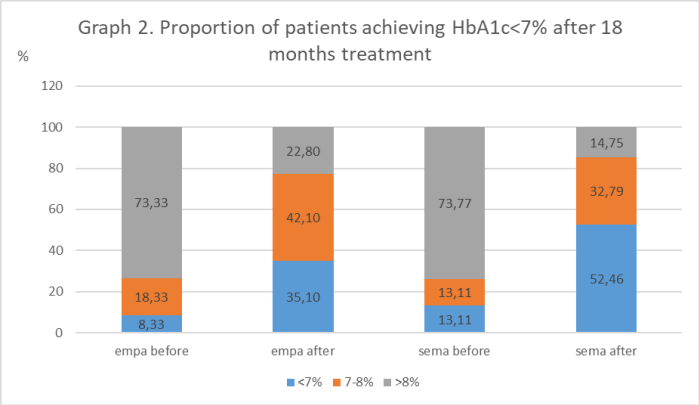
Table 3. *Glycaemic control and serum creatinine in patients treated with Empa*

	First visit	Second visit (5.9±1.5 months)	Third visit (12.6±4.7 months)	Forth visit (16.5±4.7 months)	P value
FPG (mmol/l)	11.0±3.6	8.4±2.3	8.5±2.1	8.1±1.6	<0.01
HbA1c (%)	9.3±1.9	7.5±1.2	7.2±1.7	7.5±1.2	<0.01
Creatinine (µmol/l)	81.5±14.8	82.8±13.6	85.4±13.5	83.7±19.2	NS



Graph 1. *Changes in HbA1c during the visits in both groups*

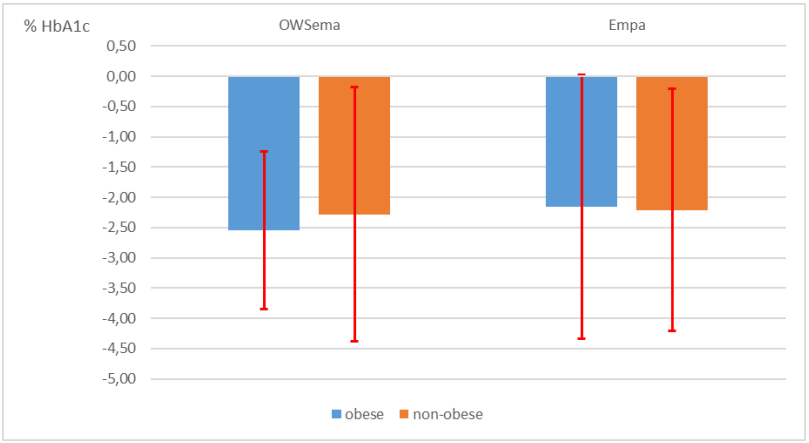
The patients were divided according to their BMI, above and below 30kg/m2, and the degree of lowering of HbA1c was analyzed in both groups. Reduction of HbA1c was higher in obese patients treated with OWSema (2.54±1.3 vs. 2.28±2.1), but without statistical significance. There was no difference in the reduction of HbA1c, considering the weight in the group treated with Empa (2.15±2.18 vs. 2.21±2.0) (Graph 3). Also, there were no significant differences among the subgroups divided by age, gender, and duration of diabetes. The degree of improvement in HbA1c was greater in the patients with a higher baseline HbA1c. (Table 4)



Graph 2. *Proportion of patients achieving HbA1c<7%*

Table 4. *The effect of various clinical factors on the good therapy response (decreased HbA1c more than 1%)*

		Score	df	Sig.
Variables	BMI	0.805	1	0.37
	gender	0.369	1	0.543
	age	0.031	1	0.86
	Duration of T2DM	0.147	1	0.701
	Baseline Hba1c	3.94	1	0.047
	CKD	0.706	1	0.401
Overall Statistics		5.524	6	0.479



Graph 3. *Reduction of HbA1c in obese and non-obese patients in both group*

Adverse events during the follow-up

Cardiovascular events were statistically not significant in both groups: 4 (6.7%) patients from the Empa group, and 2 (3.3%) patients from the OWSema group. During the period of 2 years, 3 patients deaths (5%) were registered, all from the Empa group. All 3 patients had multiple co-morbidities such as aorto-coronary bypass (ACBP), heart failure, and CKD. Two of them died after acute pulmonary edema, one died in hospital, and the other refused hospitalization. For the third dead patient the reason for death was not known. Another patient was hospitalized because of acute pulmonary edema, and surprisingly he survived. In the OWSema group there no one died, but 2 had hospitalizations because of ACBP and transitory ischemic insult (TIA).

Effect on weight

In the Empa group, weight data were available for 36 patients, of which 15 (41.7%) patients decreased their initial weight by an average of 4 kg, 1 patient increased, and 20 patients had no changes in their weight during the follow-up.

In the OWSema group, weight data were available for only 32 patients. Twenty-two (68.7%) patients decreased their initial weight by an average of 6 kg, 1 patient increased, and 9 patients had no changes in weight during the follow-up.

All patients who followed a healthy diet and physical activity lost weight.

Safety profile

In the Empa group, 5 patients stopped the treatment because of the uncomplicated urinary infection, and they did not want to start again. Another patient with a previous urinary infection with proteus mirabilis was taking the empagliflozin 1.5 years without a new urinary infection.

In the OWSema group, 1 patient stopped the treatment because of GIT intolerance, and 8 patients were returned to 0.5mg semaglutide, after GIT intolerance of 1mg dose.

DISCUSSION

We showed that the addition of OWSema or 10mg Empa was highly effective in our patients with T2DM, reducing the HbA1c for 2.6% and 1.8%, respectively.

Lingvay et al. show that 1mg of OWSema was superior to empagliflozin at 25 mg in reducing HbA1c and lowering body weight from baseline to end-of-treatment at around 1 year [14]. We cannot compare the effectiveness of both agents, because most of the patients were receiving other hypoglycemic therapies, including insulin. Our goal was to see the grade of reducing the Hba1c and safety profile, especially the effect on serum creatinine. The degree of reducing HbA1c in our study was higher than the same results published previously. A prospective, observational study conducted in Switzerland showed a 0.8% reduction in HbA1c (baseline HbA1c 7.8%) with the introduction of OW semaglutide (mean dose 0.78 mg) at approximately 30 weeks [15]. In our study, patients with higher HbA1c were included and were followed for a longer time.

There were no significant differences in reducing the HbA1c among the subgroups divided by age, gender, and BMI. The highest improvement was observed in patients with baseline higher HbA1c. Similar results were found in one Japanese study [15].

Glucose control in the Empa group after 1 year was waning, the mean HbA1c value started slightly to increase, but in the OWSema group the glucose control was still maintained. Ferrannini et al. demonstrated that long-term empagliflozin treatment provided sustained glycemic control and body weight loss in patients with T2DM for up to 90 weeks. Furthermore, long-term treatment with empagliflozin was well tolerated [16]. After 78 weeks of treatment in that study, the HbA1c curve was slightly increased, as in our study. This can be related to changes in lifestyle or the natural course of T2DM.

We did not evaluate the cost-benefit effect in our study, but OWSema at 0.5 mg and 1 mg were projected to be cost-effective compared to empagliflozin at 10 mg and 25 mg for the treatment of patients with T2DM with inadequate glycemic control on oral anti-hyperglycemic medications in the Spanish setting, irrespective of patients' BMI at baseline [17].

Other studies reported higher weight reduction with OWSema [14, 15] as in our study, but all patients without reduction in their weight admitted that they did not follow a healthy lifestyle. The patients in our study were not motivated to reduce weight, and they received no education regarding the subject. Otherwise, the reduction in weight would have been higher.

In our study, we did not have any serious complicated conditions related to the agents. But 6 patients, 5 from the Empa group, and 1 from the OWSema group did not want to continue the treatment after experiencing mild to moderate adverse effects, such as simple urogenital infection or nausea and vomiting. No new adverse effect concerns were identified, therefore, the new agents were tolerable for the majority of our study population. The mortality was higher in the Empa group, but the number of patients with heart failure was doubled in this group.

This study had several limitations. It was a single-center retrospective study without a control group; therefore, there may have been confounding factors that were not eliminated. The analyzed patients received different antihyperglycemic treatments besides OWSema and Empa. Patients with insulin treatment may change the insulin doses, which has a substantial effect on the HbA1c. Hypoglycemic episodes were not evaluated. On the other hand, however, there are no similar studies published in our country on our population. There are not enough studies which evaluate long-term safety and efficacy, yet this is very important for antihyperglycemic agents, as they are used for chronic treatment. Large double-blind controlled studies with a control group should be done to confirm the results.

CONCLUSION

The study results show that the introduction of OWSema or Empa in patients with T2DM who had not achieved the target reduction in HbA1c level with existing therapy was useful for better glucose regulation in the majority of patients. Greater reduction in HbA1c was obtained in patients with higher baseline values of HbA1c. Additionally, OWSema and Empa are safe for the treatment of T2DM.

REFERENCES

1. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018; 41(12): 2669-2701.
2. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes–2019. Diabetes Care. 2019; 42(Suppl 1): S90-S102.
3. Cosentino F, Grant PJ, Aboyans V, et al. ESC Scientific Document Group 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020; 41(2): 255-323.
4. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012; 8: 728–42.
5. Nauck MA, Meier JJ. Management of endocrine disease: are all GLP-1 agonists equal in the treatment of type 2 diabetes? Eur J Endocrinol. 2019; 181: R211–34.
6. DeFronzo RA, Triplitt CL, Abdul-Ghani M, Cersosimo E. Novel agents for the treatment of type 2 diabetes. Diabetes Spectr. 2014; 27: 100–12.
7. Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, Gomez-Peralta F, Reviriego J. A review of practical issues on the use of glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes. Diabetes Ther. 2019; 10: 5–19.
8. Roden M, Weng J, Eilbracht J, et al. EMPA-REG MONO trial investigators. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013; 1: 208–219.
9. Häring HU, Merker L, Seewaldt-Becker E, et al. EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013; 36: 3396–3404.
10. Häring HU, Merker L Seewaldt-Becker E, et al. EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014; 37: 1650–1659.
11. Kovacs CS, Seshiah V, Swallow R, et al. EMPA-REG PIO™ trial investigators Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab 2014; 16: 147–158.
12. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. EMPA-REG H2H-SU trial investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014; 2: 691–700.
13. Zinman B, Wanner C, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–2128.
14. Lingvay I, Capehorn MS, Catarig AM, Johansen J, Sandberg P, Shaw R, Paine A. Efficacy of Once-Weekly Semaglutide vs Empagliflozin Added to Metformin in Type 2 Diabetes: Patient-Level Meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2020; 105(12): e4593–e4604.
15. Yamada H, Yoshida M, Suzuki D, Funazaki Sh, Nagashima Sh, Masahiko K, Kiyoshi O, Hara K. Effectiveness and Safety of Once-Weekly Semaglutide in Japanese Patients with Type 2 Diabetes in Treatment Intensification: A Retrospective Observational Single-Center Study. Diabetes Ther. 2022. doi: 10.1007/s13300-022-01313-0.
16. Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, Broedl UC. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013; 36(12): 4015-21.
17. Gorgojo-Martínez JJ, Malkin SJP, Martín V, Hallén N, Hunt B. Assessing the cost-effectiveness of a once-weekly GLP-1 analogue versus an SGLT-2 inhibitor in the Spanish setting: Once-weekly semaglutide versus empagliflozin. J Med Econ. 2020;23(2):193-203.

Резиме

ЕФИКАСНОСТ И БЕЗБЕДНОСТ НА ЕМПАГЛИФЛОЗИН И СУБКУТАН СЕМАГЛУТИД ЕДНАШ НЕДЕЛНО КАЈ ПАЦИЕНТИ СО ДИЈАБЕТЕС ТИП 2 ВО ШТИП

Валентина Велкоска Накова[1, 2], Зоран Наков[2], Стојка Докузова[1], Татјана Прошева[3], Бранкица Крстевска[4]

[1] Клиничка болница, Интерно одделение, Штип, РС Македонија

[2] Факултет за медицински науки, Универзитет „Гоце Делчев“, Штип, РС Македонија

[3] Универзитетска клиника за ендокринологија, дијабетес и болести на метаболизмот, Скопје, РС Македонија

[4] Центар за внатрешни болести „Срце“, Скопје, РС Македонија,

Цел: Ефикасноста и безбедноста на новите лекови [субкутан семаглутид (OWSem) еднаш неделно и емпаглифлозин (Empa)] беа анализирани кај пациенти со дијабетес тип 2 (T2DM) во Клиничката болница во Штип, РС Македонија.

Материјал и методи: Сто дваесет и еден пациент лекувани за првпат со OWSema или Empa беа ретроспективно анализирани. Се следеше гликемиската контрола, серумскиот креатинин, намалувањето во телесната тежина, присутните коморбидитети и евентуалната хоспитализација за време на третманот.

Резултати: Меѓу 61 пациент третиран со OWSema и 60 пациенти третирани со Empa немаше статистички значајни разлики во возраста, полот, индексот на телесна маса, времетраењето на дијабетот и бројот на пациенти третирани со инсулин. Двата лека (OWSema и Empa) постигнаа статистички значајно намалување на HbA1c по 6, 12 и 18 месеци (9,2; наспроти 7,6; 6,7; 6,6 и 9,3; наспроти 7,5; 7,2, 7,5 %, соодветно) третман. Немаше разлики во вредноста на серумскиот креатинин меѓу посетите во двете групи. Во периодот од 2 години починале троца пациенти (5 %) со повеќе коморбидитети од групата Empa. Еден пациент од групата Empa беше хоспитализиран поради акутен пулмонален едем и двајца од групата OWSema поради транзиторен исхемичен инсулт и акутен коронарен синдром. Просечното намалување на тежината беше поизразено во групата OWSema (6 наспроти 4 kg). Пет пациенти го прекинаа третманот со Empa на почетокот поради некомплицирана уринарна инфекција, а еден го прекина OWSema поради гастроинтестинална нетолеранција. Осум пациенти не ја толерираа дозата од 1 mg и продолжија со 0,5 mg OWSema.

Заклучок: Субкутаниот семаглутид и емпаглифлозин постигнаа голема редукација во Хба1ц и се безбедни за третман на Т2ДМ.

Клучни зборови: субкутан семаглутид еднаш неделно, емпаглифлозин, гликолизиран хемоглобин, хоспитализација