The effect of combination therapy of insulin glargine, metformin, and sitagliptin on insulin secretion, insulin resistance, and metabolic parameters in obese subjects with type 2 diabetes

Teodora Beljić-Živković[1,2], Milica Marjanović-Petković[2], Miljanka Vuksanović[2], Ivan Soldatović[3], Dobrila Kanlić[2], Drina Topalov[4]

[1]University of Belgrade, School of Medicine, Belgrade, Serbia;
[2]Zvezdara University Hospital, Department of Endocrinology, Diabetes and Metabolic Disorders, Belgrade, Serbia;
[3]University of Belgrade, School of Medicine, Institute of Medical Statistics, Belgrade, Serbia;
[4]Konzilijum Laboratory, Belgrade, Serbia

SUMMARY

Introduction A combination of drugs is required for treatment of obese subjects with diabetes, due to multiple pathogenic mechanisms implicated in the development of both diabetes and obesity.

Objective Assessment of the effect of sitagliptin added to insulin glargine and metformin, in obese subjects with type 2 diabetes.

Methods A total of 23 obese subjects on metformin and insulin glargine participated in the study. Titration of insulin glargine during a one-month period preceded the addition of 100 mg of sitagliptin daily. Body mass index, waist circumference, fasting, and prandial glucose were measured monthly, lipids and hemoglobin A1c (HbA1c) every three months, insulin, c-peptide and glucagon at the start and after six months of treatment. Homeostatic models for insulin secretion (HOMA B) and insulin resistance (HOMA IR) were calculated.

Results Participants were 58.65 ± 7.62 years of age with a body mass index of 35.06 ± 5.15 kg/m^2, waist circumference of 115.04 ± 15.5 cm, and the duration of diabetes of 4.11 ± 2.57 years. With the titration of insulin glargine, target fasting glucose levels were not achieved. Waist circumference and body mass index decreased during three months of sitagliptin treatment, thereafter remaining stable. HbA1c decreased significantly after three and six months of therapy. C-peptide increased significantly, while glucagon level fell. HOMA indexes were unchanged.

Conclusion Sitagliptin can improve diabetes control and induce modest weight loss in obese subjects poorly controlled on insulin glargine and metformin. Titration of insulin glargine to optimal fasting glucose values is a prerequisite of success of this combination therapy.

Keywords: sitagliptin; glargine; obesity; diabetes

INTRODUCTION

Multiple pathogenic mechanisms are implicated in the development of diabetes mellitus type 2, a progressive condition characterized by hyperglycemia, often dyslipidemia, and hypertension. Decreased insulin secretion and incretin response, increased insulin resistance, peripheral outflow of free fatty acids, and increased reabsorption of glucose from the proximal tubules of the kidney may complicate metabolic control of diabetes [1].

Basal insulin secretion is insufficient to stop hepatic glucose production, due to hepatic insulin resistance, leading to high fasting glucose values. This is usually the first secretory insulin abnormality to develop in type 2 diabetes. However, loss of first phase of insulin prandial secretion may develop early in the course of the disease. The second phase of insulin secretion is slow in onset and is insufficient, leading to prandial hyperglycemia. Prandial secretion of proinsulin is increased. At the same time, hyperglycemia does not stop glucagon production, which further stimulates gluconeogenesis and glycogenolysis in the liver [2]. Incretin effects are controlled by gut hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide, secreted after food consumption [3]. Diminished incretin effects lead to inadequate insulin secretion, glucagon hypersecretion, low satiety, and fast transition of food through the stomach.

Obese people with diabetes present a clinical challenge. Insulin resistance occurs when insulin levels are sufficiently high over a prolonged period of time causing the reduction of body's own sensitivity to insulin. Insulin resistance in type 2 diabetes, brought on by obesity, is closely linked to inflammation [4]. Hepatic insulin resistance precedes peripheral insulin resistance in the muscle and adipose tissue. Glucose utilization in the muscle is diminished, whereas outflow of free fatty acids from the adipose tissue is uninhibited. Free fatty acids have a lipotoxic effect on beta cell.

The National Serbian Guideline for the Treatment of Diabetes Mellitus [5], as well as

Correspondence to:
Teodora BELJIĆ ŽIVKOVIĆ
KBC "Zvezdara"
Department of Endocrinology, Diabetes and Metabolic Disorders
Dimitrija Tucovića 161
11000 Beograd
Srbija
dorabeljic@beotel.net

recent American Diabetes Association and European Association for the Study of Diabetes position statement [6], defines four optional steps in diabetes therapy. A combination of metformin, basal insulin and DPP-4 inhibitors corrects insulin resistance, secretory defects and diminished incretin effects. This three-step optional combination may be useful in treating diabetes in obese subjects. Sitagliptin is an orally active inhibitor of DPP-4, with a fully reversible action [7]. It increases glucose-dependent insulin secretion, while decreasing glucagon secretion and hepatic glucose production. Sitagliptin has been associated with an approximate two-fold increase in postprandial GLP-1 plasma concentrations, compared to placebo, in healthy human study participants and in patients with type 2 diabetes mellitus [8].

OBJECTIVE

The objective of this study was to assess the effect of combination therapy of insulin glargine, metformin and sitagliptin on insulin secretion, insulin resistance, and metabolic parameters in obese subjects with type 2 diabetes.

METHODS

Twenty-three obese subjects with diabetes were included in the study. They were recruited from the outpatient clinic of the Department of Endocrinology, Diabetes and Metabolic Disorders of Zvezdara University Hospital. After obtaining a signed informed consent, subjects were scheduled an appointment in the daily outpatient unit. This study was approved by the Ethics Committee of Zvezdara University Hospital.

Inclusion criteria for the participation in the study were as follows: unfavorable control of diabetes with glycosylated hemoglobin (HbA1c) of 7–12%, on combined insulin glargine and metformin therapy lasting at least 12 months, age between 35 and 75 years, and body mass index (BMI) ≥25 kg/m². At first visit, the subjects were educated to titrate insulin glargine to fasting glucose levels between 3.9 and 5.5 mmol/l, using a simple algorithm [9]. They were instructed to perform fasting glucose measurements every morning. An average of three consecutive fasting glucose measurements was calculated. If it exceeded 5.5 mmol/l, two units of insulin glargine were added to the previous dose. If the measurement was equal to or lower than ≤3.9 mmol/l, two units were subtracted from the previous dose. If the average fasting glucose reading was 3.9–5.5 mmol/l, the dose of insulin glargine remained unchanged. The subjects were instructed to write down the measurements with dose titration changes in the diary and to titrate the dose of insulin glargine every three days.

After one month of insulin glargine titration, 100 mg of sitagliptin was added to metformin and insulin glargine for six months, to improve prandial control. The subjects were invited for monthly visits for blood glucose, blood pressure and body weight measurements. BMI was calculated as body weight in kilograms divided by square of height expressed in meters. At start, after three and six months of triple combination therapy, blood samples were taken for the measurement of HbA1c, lipids, fasting and two hours prandial glucose levels. Low density lipoprotein (LDL) cholesterol was calculated from total cholesterol, high density lipoprotein cholesterol (HDL) and triglycerides using Friedwald's formula: LDL (mmol/l) = total cholesterol - HDL - (triglycerides / 2.17). Insulin, c-peptide and glucagon levels were assessed before and after six months of sitagliptin therapy. The time between the last dose of insulin glargine and blood sampling had to be longer than 24 hours. Insulin and c-peptide were evaluated by the electrochemiluminescence (ECLIA) method, on the Roche analyzer at the Konzilijum Laboratory. The referent range for insulin was 6.0–27.0 μIU/ml, and for c-peptide 0.9–7.1 ng/ml. Glucagon was analyzed using the radioimmunoassay (RIA) method. The referent values for glucagon were 60–177 ng/L. Insulin secretion was evaluated using the HOMA-B model. It was calculated from the formula by Matthews [10]: HOMA B = Insulin (mU/l) × 2 / fasting glucose level (mmol/l) - 3,5. Insulin resistance was evaluated with the HOMA-IR model. It was calculated as HOMA IR = Insulin (mU/l) × fasting glucose (mmol/l) / 22.5.

Data are presented as mean ± standard deviation or n (%) depending on the data type. Paired samples tests (t-test and Wilcoxon signed-rank test) were used to assess significant differences within measurements. All the data were analyzed using SPSS 20.0 (IBM corp., Armonk, NY, USA) statistical software. All p-values less than 0.05 were considered statistically significant.

RESULTS

Twenty-three obese subjects, 13 men and 10 women, with type 2 diabetes inadequately controlled by insulin glargine and metformin participated in the study. Their mean age was 58.65 ± 7.62 years, while mean diabetes duration was 4.11 ± 2.57 years. The mean weight of the studied subjects was105.30 ± 19.29 kg, BMI 35.06 ± 5.15 kg/m², and the mean waist circumference 115.04 ± 15.47 cm.

After three months of treatment with 100 mg of sitagliptin added to insulin glargine and metformin, a significant reduction of weight, waist circumference, and BMI was observed. The difference in baseline weight and weight at six months was also significant. However, there was no significant weight change between three and six months of therapy, indicating that the loss of weight achieved in the first three months was maintained through the whole follow-up period. Similar changes were observed in waist circumference and BMI (Table 1). The triple combination therapy had no effects on lipids and blood pressure.

During one month of insulin glargine titration, its dose was significantly increased from an average of 38.97 ± 15.28 units to 48.64 ± 20.62 units, $p < 0.01$. However, target fasting blood glucose values were not achieved. The average fasting blood glucose value at the end of insulin

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Table 1. The effect of sitagliptin added to insulin glargine and metformin on body weight, waist circumference, body mass index, lipids and blood pressure during six months of therapy (mean value ± SD)

Parameter	Baseline	3 months	6 months	p (baseline vs. 3 months)	p (baseline vs. 6 months)
BW (kg)	105.30 ± 19.29	102.57 ± 17.84	102.61 ± 17.41	<0.001	<0.001
WC (cm)	115.04 ± 15.47	107.65 ± 12.78	107.91 ± 11.84	<0.001	<0.001
BMI (kg/m^2)	35.06 ± 5.15	34.19 ± 4.93	34.16 ± 4.90	<0.001	<0.001
sBP (mmHg)	125.22 ± 9.94	128.04 ± 9.97	125.00 ± 9.29	0.170	0.954
dBP (mmHg)	78.04 ± 6.51	78.70 ± 4.05	75.65 ± 4.60	1.000	0.400
CHOL (mmol/l)	5.44 ± 1.52	5.50 ± 1.30	5.52 ± 1.16	1.000	1.000
TGL (mmol/l)	3.44 ± 2.58	3.11 ± 2.23	3.27 ± 2.33	0.308	1.000
HDL-c (mmol/l)	1.11 ± 0.22	1.07 ± 0.28	1.08 ± 0.23	0.470	1.000
LDL-c (mmol/l)	2.97 ± 1.14	3.16 ± 1.04	3.05 ± 1.09	0.200	1.000

SD – standard deviation; BW – body weight; WC – waist circumference; BMI – body mass index; sBP – systolic blood pressure; dBP – diastolic blood pressure; CHOL – total cholesterol; TGL – triglycerides; HDL-c – high density lipoprotein; LDL-c – low density lipoprotein

Table 2. The effect of sitagliptin added to insulin glargine and metformin on fasting and prandial glucose levels and glycosylated hemoglobin during six months of therapy (mean value ± SD)

Parameter	Baseline	3 months	6 months	p (baseline vs. 3 months)	p (baseline vs. 6 months)
Fasting glucose levels (mmol/l)	9.92 ± 2.58	8.75 ± 3.02	8.62 ± 2.28	0.192	0.032
Prandial glucose levels (mmol/l)	11.32 ± 3.50	10.14 ± 3.09	9.66 ± 2.71	0.184	0.012
HbA1c %	9.06 ± 1.16	7.91 ± 1.10	8.20 ± 1.14	<0.001	<0.001

HbA1c – glycosylated hemoglobin A1c

Table 3. The effect of sitagliptin added to insulin glargine and metformin on circulating insulin, c-peptide and glucagon levels during six months of therapy (mean value ± SD)

Parameter	Baseline	6 months	p (baseline vs. 6 months)
Insulin (μIU/ml)	16.55 ± 10.10	19.56 ± 13.98	0.492
C-peptide (ng/ml)	1.05 ± 0.99	1.50 ± 1.52	0.163
Glucagon (ng/l)	48.43 ± 16.81	43.61 ± 16.41	0.086

Table 4. The effect of sitagliptin added to insulin glargine and metformin on HOMA-B and HOMA-IR indices during six months of therapy

Parameter	Baseline	6 months	p (baseline vs. 6 months)
HOMA-B	18.33 ± 15.59	35.05 ± 22.71	0.076
HOMA-IR	3.79 ± 1.91	4.09 ± 1.54	0.092

glargine titration was 9.92 ± 2.58 mmol/l. Postprandial blood glucose level, before the addition of sitagliptin, was 11.32 ± 3.50 mmol/l.

After three months of treatment with 100 mg of sitagliptin added to insulin glargine and metformin, the average fasting blood glucose levels were reduced to 8.75 ± 3.02 mmol/l, while after six months it was 8.62 ± 2.28 mmol/l. The average postprandial blood glucose value was 10.14 ± 3.09 mmol/l after three months and 9.66 ± 2.71 mmol/l after six months of treatment. Glycosylated hemoglobin A1c (HbA1c) was 9.06 ± 1.16% before initiating sitagliptin add-on therapy. It significantly decreased after three (8.01 ± 1.11%) and six (8.29 ± 1.13%) months of introducing sitagliptin in therapy. It was only after six months of triple combination therapy that the average fasting and postprandial blood glucose values achieved a significant reduction compared to values at start (Table 2).

Insulin, c-peptide and glucagon values were evaluated at start and after six months of therapy. The average plasma insulin value was 16.55 ± 10.10 μIU/ml before, and 19.56 ± 13.98 μIU/ml six months after addition of 100 mg of sitagliptin to insulin glargine and metformin.

At the same time, plasma c-peptide values significantly increased from 1.05 ± 0.99 ng/ml to 1.50 ± 1.52 ng/ml. Glucagon levels decreased from 48.43 ± 16.81 ng/L to 43.61 ± 16.41 ng/L after six months of sitagliptin add-on therapy (Table 3).

Sitagliptin added on to insulin glargine and metformin did not significantly change insulin secretion and insulin resistance, evaluated through HOMA-B and HOMA-IR models. Non-significant increase in basal insulin secretion was the only observed change (Table 4).

DISCUSSION

Our study has shown that there is a place for the addition of sitagliptin to obese subjects with type 2 diabetes inadequately controlled by insulin glargine and metformin. Sitagliptin add-on therapy significantly lowered weight, BMI and waist circumference. It increased basal insulin secretion and lowered glucagon levels. However, target fasting and prandial glucose levels were not achieved, although levels of HbA1c were significantly reduced after three and six months of therapy. This indicated that optimal titration of insulin glargine to target fasting glucose levels had to be performed before the addition of sitagliptin. This was not the case in our group of participants.

The safety and tolerability of sitagliptin, the first dipeptidyl peptidase-4 (DPP-4) inhibitor used in clinical practice, was previously tested in many trials. It has been used as monotherapy, or in combination with metformin, sulfonylurea, pioglitazone, or insulin [11]. It reduces HbA1c for 1%, fasting plasma glucose for 1 mmol/l, and postprandial glucose levels for 2.6 mmol/l, during 24 weeks of treatment, and does not induce hypoglycemia and weight gain [12]. Nausea is tolerable and no other adverse events

have been reported. Sitagliptin therapy in combination with metformin has been shown to increase circulating insulin levels, c-peptide and HOMA B. It had no influence on HOMA IR, when compared to placebo. Sitagliptin has been shown to reduce postprandial lipemia [13]. In subjects with renal impairment, sitagliptin can be safely used in a reduced dose of 50 mg when creatinine clearance is 30–50 ml/min., and in dose of 25 mg when creatinine clearance is less than 30 ml/min. [14]. Urinary albumin levels are reduced on sitagliptin therapy in subjects with diabetes and albuminuria [15]. The results of the recently completed TECOS trial (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin) has shown that sitagliptin does not increase major adverse cardiovascular events, hospitalization for heart failure, or other adverse events in 14.671 high cardiovascular risk subjects with diabetes [16].

Two clinical problems with DPP-4 inhibitors use have not been resolved so far. The question that bothers many physicians is whether it is justified to use sitagliptin in long-term diabetes on insulin therapy. Will this kind of combination therapy lower the dose of insulin, decrease HbA1c, induce hypos and will it be weight neutral? The second dilemma is the use of DPP-4 inhibitors in obese subjects. Glucagon-like peptide-1 analogues are preferable in obese subjects, as they successfully reduce weight. However, they are injectables, and some patients do not like this form of therapy. Hence, our study addressed both questions.

Very few clinical studies have been published on combined use of sitagliptin with insulin analogues. An extension of the EASIE study, randomized controlled study performed on 515 subjects that tested the combination of sitagliptin or insulin glargine with metformin, as initial therapy for type 2 diabetes [17], was similar to ours. In the extension of the EASIE study, sitagliptin was added to therapy of 37 subjects not attaining goal of HbA1c less than 7%, after 24 weeks of treatment of insulin glargine and metformin [18]. Half of the subjects attained HbA1c of less than 7% on 12 weeks of triple therapy of sitagliptin, metformin and insulin glargine.

A study with aims similar to ours assessed the effect of sitagliptin or exenatide added to insulin glargine and metformin, compared to glargine and metformin alone. In enrolled 48 subjects with diabetes duration of 6 ± 1 years and with a BMI of 31.7 ± 3.4 kg/m^2 [19]. During the four weeks of the study, HbA1c was reduced significantly in all groups, with better prandial control on incretin therapy. Subjects on exenatide lost weight, while sitagliptin was weight neutral. Subjects on insulin glargine and metformin gained in weight. As titration of insulin was allowed, the dose of insulin glargine remained the same on incretin therapy, while it increased for five units in the glargine and metformin group. When compared to our study, the subjects in our group were more obese. Sitagliptin did induce significant reduction in fasting and prandial blood glucose levels, HbA1c, weight and waist circumference. It is probable that this could have also happened in the study by Arnolds et al. [19] with its longer duration. The dose of insulin glargine remained stable for SIX months in our study, while it was titrated in the study by Arnolds et al. [19], which represents a difference in study design. Both studies have shown that it is justified to add sitagliptin to insulin glargine and metformin in obese patients with longer duration of diabetes, thus resolving the above mentioned clinicians' dilemmas.

Sitagliptin therapy decreases appetite and glucagon levels, even in subjects with low residual insulin secretion [20]. It improves quality of life [21]. The question of biomarkers that could adequately specify the positive effects of incretin therapy in obese subjects with diabetes remains open [22, 23]. HOMA indices, used in our study, are not standardized. In clinical studies, they have been used with caution, indicating only whether the effect of the drug is in favor of increased insulin secretion or decreased insulin resistance [24]. Although our study was done on a small group of subjects with great variations in HOMA indices, it did show that the main effect of sitagliptin therapy, added to insulin glargine and metformin in obese subjects, is to increase insulin secretion. It did not induce hypoglycemia, nor did it provoke an increase in blood pressure and lipids, proving its safety profile.

CONCLUSION

The results of our study have shown that it is justified to add sitagliptin to the treatment of obese subjects with type 2 diabetes inadequately controlled by insulin glargine and metformin. This kind of add-on therapy significantly decreased fasting and prandial glucose levels and HbA1c. Increase in residual insulin secretion, measured through c-peptide levels and HOMA-B index, and decrease in glucagon levels, may explain its favorable metabolic effects. It seems that the success of this treatment combination depends on the early initiation of insulin therapy, which spares residual insulin secretion. Another prerequisite for successful treatment is previous titration of insulin glargine to target fasting glucose levels.

Sitagliptin is safe in obese subjects with diabetes. It significantly reduced body weight and waist circumference. The subjects did not experience severe hypoglycemia. Blood pressure and lipids remained unchanged. Until GLP-1 analogues and bariatric surgery become a widely available method of treatment for obese subjects with diabetes, a safe and effective combination of sitagliptin, insulin glargine, and metformin may be considered.

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REFERENCES

1. Defronzo R. From the triumvirate to the ominous octate: The new paradigm for the treatment of type 2 diabetes mellitus. Diab Care. 2009; 58:773–95. [DOI: 10.2337/db09-9028] [PMID: 19336687]
2. Ahrén B, Pratley RE, Soubt M, Dunning BE, Foley JE. Clinical measures of islet function: usefulness to characterize defects in diabetes. Curr Diab Rev. 2008; 4:129–45. [DOI: 10.2174/157339908784220714] [PMID: 18473760]
3. Meier JJ, Nauck MA. Is the Diminished Incretin Effect in Type 2 Diabetes Just an Epi-Phenomenon of Impaired β-Cell Function? Diabetes. 2010; 59:1117–25. [DOI: 10.2337/db09-1899] [PMID: 20427697]
4. Eckel RH, Kahn S, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, et al. Obesity and type 2 diabetes: What can be unified and what needs to be individualized? Diab Care. 2011; 34:1424 –30. [DOI: 10.2337/dc11-0477] [PMID: 21602431]
5. Nacionalni vodič dobre kliničke prakse DIABETES MELLITUS. Beograd: Agencija za akreditaciju zdravstvenih ustanova Srbije; 2012.
6. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38:140–9. [DOI: 10.2337/dc14-2441] [PMID: 25538310]
7. Ku Ej, Jung KY, Kim Yj, Kim KM, Moon JH, Choi SH, et al. Four-year durability of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes in clinical practice; COSMIC Study. PLoS One. 2015; 10(6): e0129477. [DOI: 10.1371/journal.pone.0129477] [PMID: 26068661]
8. Ahrén B. Dipeptidyl peptidase-4 inhibitors: clinical data and clinical implications. Diabetes Care. 2007; 30:1344–50. [DOI: 10.2337/dc07-0233] [PMID: 17337494]
9. Yki Jarwinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: The LANMET Study. Diabetologia. 2006; 49:443. [DOI: 10.1007/s00125-005-0132-0] [PMID: 16456680]
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and B cell function from fasting plasma glucose and insulin concentration in man. Diabetologia. 1985; 28(7):412–9. [PMID: 3899825]
11. Katzeff HL, Williams-Herman D, Xu L, Golm GT, Wang H, Dong Q, et al. Long term efficacy of sitagliptin as either monotherapy or add-on therapy to metformin: improvement in glycemic control over 2 years in patients with type 2 diabetes. Curr Med Res Opin. 2015; 31:1071–7. [DOI: 10.1185/03007995.2015.1037259] [PMID: 25850968]
12. Ascher P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006; 29:2632–7. [DOI: 10.2337/dc06-0703] [PMID: 17130196]
13. Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. Diabetes Obes Metab. 2011; 13:366–73. [DOI: 10.1111/j.1463-1326.2011.01362.x] [PMID: 21226820]
14. Ariona Ferreira JC, Mogensen CE, Sloan L, Xu L, Golm GT, Gonzales GL, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013; 61:570–87. [DOI: 10.1053/j.ajkd.2012.11.043] [PMID: 23352379]
15. Mori H, Okada Y, Aroa T, Tanaka Y. Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. J Diabetes Investigation. 2014; 4:313–19. [DOI: 10.1111/jdi.12142] [PMID: 24843780]
16. Green JB, Bettel A, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 373:232–42. [DOI: 10.1056/NEJMoa1501352] [PMID: 26052984]
17. Ascher P, Chan J, Owens DR, Picard S, Wang E, Dain MP, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomized open-label trial. Lancet. 2012; 379:2262–9. [DOI: 10.1016/S0140-6736(12)60439-5] [PMID: 22683131]
18. Chan JC, Aschner P, Owens DR, Picard S, Vincent M, Dain MP, et al. Triple combination of insulin glargine, sitagliptin and metformin in type 2 diabetes: the EASIE post-hoc analysis and extension trial. J Diab Complications. 2015; 29:134–41. [DOI: 10.1016/j.jdiacomp.2014.08.007] [PMID: 25283485]
19. Arnolds S, Dellweg S, Kapritza C. Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin. Diab Care. 2010; 33:1509–15. [DOI: 10.2337/dc09-2191] [PMID: 20357372]
20. Kutoh E. Sitagliptin is effective and safe as add-on to insulin in patients with absolute insulin deficiency: a case series. J Med Case Reports. 2011; 5:117–21. [DOI: 10.1186/1752-1947-5-117] [PMID: 21443773]
21. Sakamoto Y, Oyama JI, Ikeda H, Kuroki S, Gondo S, Iwamoto T, et al. Effects of sitagliptin beyond glycemic control: focus on quality of life. Cardiovasc Diab. 2013; 12:35–9. [DOI: 10.1186/1475-2840-12-35] [PMID: 23432786]
22. Mathieu C, Shankar R, Lorber D, Umpierrez G, Wu F, Xu L, et al. A Randomized Clinical Trial to Evaluate the Efficacy and Safety of Co-Administration of Sitagliptin with Intensively Titrated Insulin Glargine. Diab Ther. 2015; 6:127–42. [DOI: 10.1007/s13300-015-0105-3] [PMID: 25820927]
23. Giampietro O, Giampietro C, Bartola LD, Mason MC, Matteucci E. Sitagliptin as add-on therapy in insulin deficiency: biomarkers of therapeutic efficacy respond differently in type 1 and type 2 diabetes. Drug Des Devel Ther. 2013; 7:99–104. [DOI: 10.2147/DDDT.S38346] [PMID: 23439744]
24. Gayoso-Diz P, Otero-Gonzales A, Rodrigez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross sectional study. BMC Endocrine Disorders. 2013; 13:47. [DOI: 10.1186/1472-6823-13-47] [PMID: 24131857]

Утицај комбинације инсулина гларгин, метформина и ситаглиптина на инсулинску секрецију, инсулинску резистенцију и метаболичке параметре код гојазних особа са дијабетесом мелитусом типа 2

Теодора Бељић–Живковић[1,2], Милица Марјановић-Петковић[2], Миљанка Вуксановић[2], Иван Солдатовић[3], Добрила Канлић[2], Дрина Топалов[4]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Клиничко-болнички центар „Звездара", Клиничко одељење за ендокринологију, дијабетес и болести метаболизма, Београд, Србија;
[3]Универзитет у Београду, Медицински факулет, Институт за медицинску статистику и информатику, Београд, Србија;
[4]Лабораторија „Конзилијум", Београд, Србија

КРАТАК САДРЖАЈ

Увод За лечење гојазних са дијабетесом типа 2 неопходна је комбинација лекова, због многоструких патогенетских механизама умешаних у настанку гојазности и дијабетеса.

Циљ рада Циљ овог рада је био испитивање ефекта додавања ситаглиптина комбинацији метформина и инсулина код гојазних особа са дијабетесом типа 2 .

Методе рада У испитивање су биле укључене 23 гојазне особе са дијабетесом мелитусом типа 2, неадекватно лечене са метформином и инсулином гларгин. Титрација инсулина гларгин током месец дана претходила је увођењу ситаглиптина у дози од 100 *mg*. Индекс телесне масе (ИТМ), обим струка (ОС), гликемије наште и два сата постпрандијално мерени су једном месечно. Липиди и гликозилирани хемоглобин (*HbA1c*) евалуирани су једном у три месеца, а *c*-пептид и глукагон на почетку и након шест месеци терапије. Израчунати су хомеостатски индекси инсулинске секреције (*HOMA B*) и резистенције (*HOMA IR*).

Резултати Испитаници су били просечне старости 58,65 ± 7,62 година, ИТМ 35,06 ± 5,15 *kg/cm²*, ОС 115,04 ± 15,47 *cm* и просечне дужине трајања *T2DM* 4,11 ± 2,57 година. Титрацијом инсулина гларгин, током месец дана, нису постигнуте циљне вредности јутарње гликемије. Укључивање 100 *mg* ситаглиптина довело је до значајног смањења ОС и ИТМ током три месеца, уз одржавање ефекта до шест месеци терапије. Вредности *HbA1c* значајно су смањене након три и шест месеци терапије. *C*-пептид се значајно повећао, док се ниво глукагона смањио. Инсулин и *HOMA* индекси су остали непромењени.

Закључак Ситаглиптин може побољшати контролу дијабетеса и довести до мањег смањења у телесној маси гојазних особа на метформину и инсулину гларгин. Титрација инсулина гларгин до оптималне јутарње гликемије је предуслов успеха ове комбинације.

Кључне речи: ситаглиптин; гларгин; гојазност; дијабетес

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