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Possibilities of Early Combination Therapy with Sitagliptin and Metformin in the Correction of Metabolic Disorders in Patients with Type 2 Diabetes and Obesity

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Abstract: Diabetes mellitus is one of the most common diseases of the endocrine system that is encountered in the practice of any doctor in any specialty. Some features of type 2 diabetes are: a slow progressive development and a mild clinical picture in the early stages of the development of the disease. The main goal of diabetes treatment is to prevent the development of late complications that reduce the quality of life of patients, leading to their early disability and death. Despite the increase in the number of antihyperglycemic drugs in the pharmaceutical industry, we are still not successful enough to achieve good glycemic control. In addition, achieving good glycemic control does not always prevent macrovascular complications in patients with diabetes mellitus. The article presents the results of two studies. The first study examined the diurnal fluctuations in blood glucose levels during therapy with type 4 dipeptidyl peptidase inhibitor Sitagliptin, as well as its effect on oxidative stress markers in comparison with MV gliclazide. The second study examined the role of sitagliptin in the correction of disorders of fat metabolism.

Keywords: Diabetes, Obesity, Sitagliptin, Fat Metabolism, Glucose Monitoring

1. Introduction

Type 2 diabetes is a severe and progressive disease associated with the development of micro and macrovascular complications, characterized by the presence of two fundamental pathophysiological defects: insulin resistance and dysfunction of β-cells. The close relationship between the epidemics of type 2 diabetes mellitus and of obesity requires the study of adipose tissue as an endocrine organ that plays an important role in the development of metabolic health problems in patients with obesity. Excessive accumulation of visceral adipose tissue leads to an imbalance of adipokines and lipid metabolism that contributes to the development and progression of insulin resistance diabetes. The main task of diabetes treatment is to prevent the development of late complications, which decrease the quality of patients' life, lead to early disability, as well as death. In this regard, the question arises as to why we are not as successful in achieving good glycemic control, despite the increase in the number of antidiabetic drugs on the pharmaceutical industry. The attitude to the standard indicators of carbohydrate metabolism (glycated hemoglobin (HbA1c), fasting blood glucose level (FBGL), postprandial glucose level (PPGL) was reviewed with the advent of modern systems of daily continuous glucose monitoring (CGMS). Attention is paid to the severity of blood sugar levels oscillations during the day, especially after meals, as a factor leading to the progression of diabetes complications. [1] A number of studies have shown no correlation between the HbA1c level and the PPGL span after eating, while HbA1c was less than 7%, but PPGL could rise to 9 mmol / l [2]. It has been established that the progression of diabetes

complications is affected not only by hyperglycemia, but also by activation of oxidative stress (OS), which is more dependent on the variability of blood sugar level [3].

There are favorable conditions that initiate the OS in diabetes: increases the concentration of glucose and lipids (the main oxidation substrates) decreases the endogenous antioxidants activity (superoxide dismutase - SOD, glutathione, etc.). These processes trigger the mechanism of damage and death of the pancreatic β-cells. Most of free radicals are reactive oxygen compounds. During the oxidation of glucose reactive oxygen forms (ROS) are formed: superoxide, hydroperoxide, as well as nitric oxide, peroxynitrite, and nitrogen. At the same time, the antioxidant capacity is reduced. The formation of ROS occurs in each tissue; however, there are also antioxidant enzymes that neutralize the action of the ROS. The main antioxidants are glutathione, SOD, glutathione peroxidase (GP) and catalase. Hyperglycemia triggers glycosylation and inactivation of antioxidants. Decreased SOD and glutathione levels are markers of chronic OS [4].

It has been proven that antioxidant level in β-cells are significantly lower than in other tissues in clinical studies. In the islets of Langerhans, the expression level of antioxidant genes is reduced, and GP is practically absent. In conditions of hyperglycemia and OS, the pancreas becomes less protected than other tissues [5].

The development of diabetes complications is accompanied by a trend towards increased ROS production and activation of lipid peroxidation [6].

According to modern concepts, in the pathogenesis of DM 2, in addition to IR and impaired insulin secretion, an important role is played by abnormalities related to the "incretin effect", which led to the creation of the class of dipeptidyl peptidase-4 inhibitors (iDPP-4). The advantage of this class is the restoration of the physiological concentration of glucagon-like peptide-1 (GLP-1). Due to the physiological mechanism of action, the use of drugs of this class is associated with a low risk of hypoglycemia. It should be noted that therapy with DPP-4 inhibitors, along with glycemic ones, also has favorable non-glycemic effects, such as: a positive effect on body weight (BW), lipid profile, blood pressure (BP) [7-10].

Our article presents 2 studies that investigates the glycemic and non-glycemic effects of sitagliptin, an inhibitor of DPP-4. The first study is devoted to the study of glycemia variability and oxidative stress on the background of combination therapy in patients with type 2 diabetes.

The aim of our study was to evaluate the effect of the intensification of glucose-lowering therapy on carbohydrate metabolism, as well as the variability of blood sugar level in patients with type 2 diabetes receiving a monotherapy of metformin at the beginning, and 3 months after intensification of therapy.

Research protocols were approved by the expert commission of therapeutic faculty of the State-Funded Educational Institution "Russian Medical Academy of Postgraduate Education" of the Ministry of Health of Russia on issues of medical ethics 29.10.2014 and 14.11.2013).

2. Materials and Methods

The study included 51 patients with diabetes type 2, aged from 35 to 75 years (58.06±8.33 years), the average disease duration was 5.56±4.06 years. All patients received glucose-lowering therapy with metformin at maximum doses (1000 mg 2 times a day), but the target parameters of the glycemic control were not reached (the average HbA1c level in the enrolled patients was 7.92±0.47%).

Patients who met the inclusion criteria (age 35–75 years, confirmed diagnosis of diabetes type 2, stable dose of metformin 2000 mg / day for at least 3 months prior to the screening visit, HbA1c level 7.5–10%), were randomized into 2 groups: 1st group — 25 patients who received 4-type dipeptidyl peptidase inhibitor -sitagliptin 100 mg / day as intensification therapy; 2nd group — 26 patients whose therapy was intensified by the gliclazide MB 60 mg / day.

2.1. Carbohydrate Metabolism

Indicators of carbohydrate metabolism were examined at the beginning and after 3 months of treatment, CGMS was done, as well as the study of the antioxidant status (AOS) by determining the total antioxidant ability of blood plasma.

The blood glucose level was monitored using the iPro2 device (Medtronic, USA) using the original Enlite sensor for 72 hours. The calculation of the blood glucose level variability was performed using the EasyGV calculator. The average amplitude of blood glucose level oscillations (mean amplitude of glycemic excursion - MAGE), standard deviation (SD), lability index - LI, LBGI - the index of the risk of hypoglycemia, HBGI - the index of the risk of hyperglycemia and J-index - determined quality control of blood glucose level.

2.2. Oxidative Stress

The AOS was assessed according to the total antioxidant ability of blood plasma indicator using Randox (Great Britain) reagents on a Konelab 20 biochemical analyzer (Thermo Fisher Scientific, Finland). The normal level of total antioxidants in plasma is 1.5-2.8 mmol / l.

The Mann – Whitney test was used to compare the quantitative indicators of the two groups. The obtained data were processed in the program Statistica 10.

3. Results

The results of the study at the beginning and 12 weeks after the intensification of therapy are presented in the table 1. A significant decrease of FBGL was recorded in the 1st group compared to that at the beginning of treatment. In the 2nd group, FBGL decreased by 13% compared with that at the beginning of treatment, but the difference did not reach statistical significance. There was a significant decrease in PPGL in both groups at the end of the study compared with at the beginning of treatment, but in the 1st group it was closer to physiological values. HbA1c levels decreased significantly in both groups.

MAGE in the 1st group significantly decreased after adding sitagliptin (p<0.001). In the 2nd group, this indicator tended to decrease by 0.28 mmol / l (p = 0.07). The intergroup difference was significant, indicating a positive effect of the addition of sitagliptin on changes in the variability of glycaemia. In both groups, a significant decrease in SD was recorded by 26% in the 1st group and by 38% in the 2nd group.

Indexes of risks for the development of hyper- and hypoglycemia were calculated, which showed a number of tendencies: LI significantly increased in the 2nd group, J-index reliably decreased in the intensification group of the sitagliptin, reaching the indicator of ideal glycemic control - 18.10 (mmol / l), significantly increased LBGI in both groups. HBGI significantly decreased in the 1st group, while in the 2nd group a significant increase in this indicator was shown.

According to the results of the analysis of the glucose variability, the levels of HBGI, LBGI, and MAG varied within the limits of values in persons without type 2 diabetes [11].

At the beginning of the study, the level of total antioxidant ability of blood plasma was comparable in both groups. 12 weeks after the correction of therapy, a significant increase in this indicator was observed in both groups (p<0.05).

Table 1. *Research results.*

Parameter	1st group (n=25)		2nd group (n=26)		*P* 1st vs. 2nd group
	M±SD	*P vs. start*	*M±SD*	*P vs. start*	
Glycemic control					
FGP, mmol\l					
start	7,78±2,36		7,80±1,93		
week 12	6,03±0,88	<0,001	6,76±0,85	0,16	0,003
PPG, mmol\l					
start	9,84±2,39		10,03±1,99		
week 12	7,21±1,00	<0,001	8,03±1,32	<0,001	0,05
HbA1c, %					
start	7,91±0,44		7,93±0,50		
week 12	6,42±0,69	<0,001	6,54±0,73	<0,001	0,56
Glucose variability					
MAGE, mmol\l					
start	3,05±1,10		3,11±0,68		
week 12	2,26±0,68	0,001	2,83±0,77	0,07	<0,01
SD, mmol\l					
start	1,46±0,68		1,60±0,71		
week 12	1,08±0,41	0,09	1,99±0,92	0,07	<0,001
LI					
start	1,33±0,81		1,46±0,78		
week 12	1,05±0,51	0,42	1,85±0,71	<0,001	<0,001
J index, (mmol\l)² /h					
start	26,55±11,60		27,21±13,67		
week 12	18,10±7,56	<0,001	37,80±12,82	<0,001	<0,001
LBGI					
start	0,81±0,86		0,95±0,77		
week 12	1,15±0,79	0,005	2,02±0,97	<0,001	<0,001
HBGI					
start	3,22±2,90		3,49±2,50		
week 12	1,76±2,14	0,01	4,54±3,20	0,01	<0,001
MAG, mmol\l *h					
start	1,09±0,28		1,20±0,45		
week 12	1,06±0,71	0,04	1,38±0,37	0,10	0,02
Oxidative status, mmol\l					
start	1,87±0,24		1,89±0,27		
week 12	2,39±0,63	<0,001	2,25±0,60	0,03	0,03

4. The Effect of Dipeptidyl Peptidase-4 Inhibitors on Fat Metabolism

In another study, we conducted a comprehensive study of fat metabolism, with visualization of fat dynamics, assessment of adipocytokine-adiponectin and leptin secretion during therapy with IDPP-4 (sitagliptin) combined with metformin for carbohydrate and fat metabolism in patients with type 2 diabetes and obesity.

4.1. Materials and Methods

The study included 82 patients with type 2 diabetes with excessive body weight of varying severity, dyslipidemia, not taking lipid-lowering therapy, who did not reach the target levels of HbA1c on metformin monotherapy and dietary treatment. The average age of the patients was 55.3±9.1 years. Group I included 42 patients with type 2 diabetes and obesity on combination therapy with metformin 2000 mg / day + Sitagliptin 100 mg / day. Before entering the study

patients in this group received monotherapy with metformin at a dose of 1500-2000 mg / day. Group II included 40 patients on metformin alone at a dose of 2000 mg / day. Before entering the study, patients were on dietary treatment. All patients were overweight and obese.

4.2. Results

According to the data obtained, after 24 weeks during combination therapy with sitagliptin and metformin, there was a significant decrease in HbA1c levels on average by 1.63±1.31% (18,52%), p<0.001. Body weight (BW) decreased by 4.97±3.22 kg (5.2%), p<0.001, waist circumference (WC) decreased by 6.52±4.71 cm (5.88%), p<0.001 The analysis of the lipid profile showed significant positive dynamics of TC, HDL and Apo B in both groups. The only difference between groups was in HDL and TG dynamics. MRI visualization of visceral fat dynamics demonstrated positive fat redistribution by lowering VFA by 20.62±13.54 cm^2 (7.52%), p<0.001. On Sitagliptin and Metformin therapy a more marked decrease in leptin level by 7.37±5.69 ng/ml (30.47%), p<0.001 was registered. After 6 months of therapy a more marked adiponectin level increase by 1.95±1.53 μg/mL (27.06%), p<0.001. Data from the analysis of pancreatic β-cells function condition have certain scientific and practical interest. For instance, in Sitagliptin and Metformin combined therapy group, a significant increase in HOMA-β index by 23.4±22.6 relative units (33.06%), p<0.0001 [12-14].

5. Discussion

The results of study indicate satisfactory glycemic control in both treatment groups for the parameter HbA1c. The FBGL reached the target level only in the 1st group. However in the 1st group (metformin + sitagliptin) MAGE significantly approached the level of this indicator in healthy people. In the 2nd group (metformin + gliclazide MB), this parameter did not significantly changed (2.83 mmol / l). It should be noted that the criterion of high variability is the MAGE>3, 9 mmol/l [15].

LBGI significantly increased in both groups, however LBGI was at an average level of indicators of persons without diabetes.

The level of total antioxidants in both groups has undergone changes in the direction of increasing of total antioxidant ability of blood plasma. There were no pronounced intergroup differences in this parameter. In previous studies with gliclazide MB, noted an increase in antioxidant activity, and authors attributed this fact to the presence of a ring structure in the drug molecule, an aminoazobicyclooctane group that acts as a free radical neutralizer [16].

In our study, it can be concluded that the glycemic control and OSA are more closely related. This positive correlation between improving glycemic control and increasing the body antioxidant ability is comparable with the results of other studies.

According to the study investigates the effect of Sitagliptin in data received, after 24 weeks, the positive dynamics of HbA1c was followed by a significant decrease in mean fasting glycemia and postprandial glycemia in group. An important advantage in our study was that, despite the common belief about the neutral effect that DPP-4 inhibitors have on weight, we demonstrated that with the addition of sitagliptin to metformin, there was a more marked weight loss and decrease of BMI and visceral fat depot. What was a "pure" contribution of DPP-4 inhibitor + metformin combination, and what was due to lifestyle changes in both groups could not be determined in this work, therefore further prospective studies including quantitative calculation of energy inputs are required. The study of adipokine status, specifically leptin and adiponectin, was of particular interest. During increased energy intake exceeding the body's requirements, the leptin level increases, which prevents further food consumption and increases energy expenditure, and that leads to negative energy balance and rebalancing of energy. In our work, on a background of combined Sitagliptin and Metformin therapy, the leptin level was reduced by 30.47%. We associate decrease in leptin level with weight loss as a decrease in the amount of fat. In both study groups the initial adiponectin levels were lower than reference values. After 24 weeks of therapy, adiponectin content in blood increased by 27.06% in the group receiving sitagliptin and metformin combination. In our study, an increase of adiponectin is most likely associated with a decrease of body weight and VFA, according to the data of the correlation analysis. However, there are publications which make it known that GLP-1 promotes an increase in adiponectin level [17, 18], the Sitagliptin therapy was followed by increase in adiponectin level [19, 20]. In addition, the study showed a significant improvement in the functional activity of pancreatic β-cells against combined sitagliptin and metformin therapy, which was confirmed by an increase in the HOMA-β index and a decrease in the ratio of proinsulin/insulin. A possible mechanism for improving the function of β-cells can be a decrease in lipotoxicity, against a background of a decrease in the level of TG inhibiting β cells function.

6. Conclusion

Despite a significant change in AOS in both groups after intensification of therapy, one can individualize the approach to the treatment of type 2 diabetes, taking into account the available data of daily monitoring for more effective treatment and reducing the progression of diabetes complications.

The work demonstrated the important role of correction of fat metabolism disorders in improving glycemic control in patients with diabetes and obesity. Regression of visceral fat according to the MRI results was accompanied by the recovery of levels of adipokine hormones, which led to an improvement in the parameters of carbohydrate and fat metabolism. Contrary to common belief, we consider Sitagliptin as a drug that promotes weight loss. The work

demonstrates that ultimately it is the reduction of the visceral depot that plays a key role in the correction of carbohydrate metabolism disorders. The parameters of the lipid profile and glycemic control are significantly improved as the pathogenetic effect on patient's body weight as well as on the structure of its adipose tissue. Recovery of such indicators as HOMA-IR and HOMA-β proves the possibility of disease management by correcting disorders of fat metabolism in patients with T2D and obesity in the early stages

References

[1] Nathan R. Hill, DPhil, Nick S. Oliver, Pratik Choudhary. Normal Reference Range for Mean Tissue Glucose and Glycemic Variability Derived from Continuous Glucose Monitoring for Subjects Without Diabetes in Different Ethnic Groups. Diabetes technology & therapeutics. 2011 Sep; 13 (9): 921–928. doi: 10.1089/dia.2010.0247.

[2] Bonora E, Calcaterra F, Lombardi S, Bonfante N, Formentini G, Bonadonna RC, Muggeo M. Plasma glucose levels throughout the day and HbA (1c) interrelationships in type 2 diabetes: implications for treatment and monitoring of metabolic control. Diabetes Care. 2001. Vol. 24. № 12. P. 2023–2029. doi.org/10.2337/diacare.24.12.2023.

[3] Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care? Diabetes Care. 2011 May; 34 Suppl. 2: S120-7. doi: 10.2337/dc11-s206.

[4] Kashiwagi AL, Asahina T, Nishio Y. Glycation, oxidative stress, and scavenger activity: glucose metabolism and radical scavenger dysfunction in endothelial cells. Diabetes. 1996 Jul; 45 Suppl. 3: S84-6.doi: https://www.ncbi.nlm.nih.gov/pubmed/8674901.

[5] Tonooka N, Oseid E, Zhou H, Harmon JS, Robertson RP. Glutathione peroxidase protein expression and activity in human islets isolated for transplantation. Clinical Transplantation. 2007 Nov-Dec; 21 (6): 767-72. doi 10.1111/j.1399-0012.2007.00736.x.

[6] Pankratova MA, Pirozhkov SV, Balabolkin MI, Litvicki PF. Oxidative stress in patients with type 2 diabetes mellitus with different duration of the disease and varying degrees of compensation for carbohydrate metabolism. Diabetes mellitus. 2/2006, P. 12-15. doi: http://dx.doi.org/10.14341/2072-0351-6113.

[7] Van Genugten R. Moller-Goede D., van Raatle D. et al Extrapancreatic effects of incretin-based therapies: potential benefit for cardiovascular-risk management in type 2 diabetes / Diabetes, Obesity and Metabolism-2013-№7: 593606.

[8] Jose T. Inzucchi S. Cardiovascular effects of the DPP-4 inhibitors. Diabetes and Vascular Disease Research-2012№2: 109-116.

[9] Satoh-Asahara N. Sasaki Y., Wada H. et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism-2013-№3: 347351.

[10] Derosa G. Ragonesi P., Fogaria E. at al. Sitagliptin added to previously taken anti-diabetic agents on insulin resistance and lipid profile: a two years study evaluation. Fundam Clin Pharmacol-2012-№2: 221-229.

[11] Nomura K, Saitoh T, Kim GU et al. Glycemic Profiles of Healthy Individuals with Low Fasting Plasma Glucose and HbA1c. ISRN Endocrinology. Volume 2011 (2011), Article ID 435047, 6 pages http://dx.doi.org/10.5402/2011/435047.

[12] Ametov A. S., Gusenbekova D. G. The role of DPP-4 inhibitors in the correction of fat metabolism disorders in patients with type 2 diabetes and obesity. Diabetes mellitus. 2015; 18 (3): 8592.

[13] https://www.intechopen.com/books/diabetes-and-its-complications/dpp-4-inhibitors-and-fatmetabolism-in-patients-with-type-2-diabetes.

[14] Ametov A. S., Gusenbekova D. G. International Journal of Clinical and Experimental Medical Sciences. Volume 4, Issue 6, November 2018, Pages: 78-86.

[15] Hill NR, Nick SO, Choudhary P et al. Normal Reference Range for Mean Tissue Glucose and Glycemic Variability Derived from Continuous Glucose Monitoring for Subjects Without Diabetes in Different Ethnic Groups Diabetes// Technology & Therapeutics. August 2011, 13 (9): 921-928. doi: 10.1089/dia.2010.0247.

[16] O'Brien R. C, Luo M, Balazs N. et al. In-vitro and in-vivo antioxidant properties of gliclazide. Journal of Diabetes and its Complications. 2000. Vol. 14. P. 201–206 doi: http://dx.doi.org/10.1016/S1056-8727(00)00084-2.

[17] Pocai A., Carrington P., Adams J., et al. Glucagon-Like Peptide 1/Glucagon Receptor Dual Agonism Reverses Obesity in Mice. Diabetes.-№10-2009: 2258–2266.

[18] Kim Ch., Hosaka T., Yoshida M. et al. Exendin-4, a GLP-1 receptor agonist, directly induces adiponectin expression through protein kinase A pathway and prevents inflammatory adipokine expression. Biochemical and Biophysical Research Communications - 2009-№3: 613–618.

[19] Nomura Sh., Omoto S., Taniura T. et al. Anti-atherosclerotic effects of sitagliptin in patients with type 2 diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy - 2015: 339.

[20] Nagao H., Kashine S., Nishizawa H., et al. Vascular complications and changes in body mass index in Japanese type 2 diabetic patients with abdominal obesity. Cardiovascular Diabetology - 2013-№1: 88.