Chapter 4

DPP-4 Inhibitors and Fat Metabolism in Patients with Type 2 Diabetes

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Additional information is available at the end of the chapter

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Abstract

Objective. To evaluate the influence of combined therapy of Sitagliptin and metformin on fat metabolism in patients with T2 DM.

Methods. The study included 82 patients with obesity. The following were evaluated at base line and after 6 months of therapy: fasting glucose, postprandial glucose, glycated hemoglobin, weight, waist circumference, lipid profile, proinsulin, leptin,adiponectin, HOMA-β,HOMA-IR, MRI of visceral fat.

Results. After 6 months, HbA1c decreased by 18.52% ($p < 0.001$) in-group 1 and by 8.17% ($p < 0.001$) in-group 2. HOMA-β increased by 33% in group 1 ($p < 0.001$) and by 11% in group 2 ($p > 0.05$). Adiponectin levels increased by 27.06% ($p < 0.001$) in group 1 and by 7.16% in group 2 26 ($p < 0.001$). Leptin levels were reduced by 30.47% ($p < 0.001$) in group 1 and by 5.41% in group 2 ($p < 0.001$). MRI showed a 7.52% reduction in visceral fat for group 1 ($p < 0.001$) and a 1.76% reduction for group 2 ($p < 0.01$).

Conclusion. Sitagliptin and metformin combination therapy had a prominent effect on nonglycemic parameters, with more marked decreases in visceral fat and leptin and increases in adiponectin levels.

Keywords: Sitagliptin, visceral fat, fat metabolism, type 2 diabetes, adiponectin, leptin

1. Introduction

Diabetes mellitus (DM) occupies a prominent place among chronic diseases due to the rapid spread, tendency to increase in the number of patients, high disability due to numerous macro- and microvascular complications and the leading position among the main causes of death [1]. The relationship between epidemics of type 2 diabetes and obesity initiated conducting research studying the adipose tissue as an endocrine organ that plays

a crucial role in the development of metabolic disorders in patients suffering from obesity. Due to excessive accretion of visceral adipose tissue, there is an imbalance of adipokines, lipid metabolism, hyperinsulinemia, which lead to the development and progression of insulin resistance (IR), DM 2. 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 a class of inhibitors of dipeptidyl peptidase-4 (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 nonglycemic effects, among which, a positive effect on body weight (BW), lipid profile and blood pressure (BP) [2–5]. One of the first approved representatives of iDPP-4 (registered by the FDA in 2007) is Sitagliptin. According to the literature, the use of Sitagliptin has been studied both in the form of monotherapy, and in double, triple combinations of hypoglycemic drugs combined with insulin [6–12]. Particular attention is drawn to the possibility of the combination of iDPP-4 with a first line drug-metformin. It is important to note that metformin can lead to an increase in total GLP-1 and potentially enhance the effects of the inhibitor DPP-4 [13]. The combination of metformin and iDPP-4 suggests an impact on all the major pathogenetic mechanisms of development of type 2 diabetes type [14]. A number of studies [15, 16] reported the identification of DPP-4 as a new adipokine, which can be a link between an increase in adipose tissue mass and obesity-associated diseases. The excessive content of DPP-4 in visceral adipose tissue may be a marker of inflammation of adipose tissue, which is associated with insulin resistance. Conversely, animal studies have shown that suppression of DPP-4 prevents the development of inflammation and impaired glucose tolerance, which develops on the background of obesity, in adipose tissue.

Thus, due to poor knowledge, a comprehensive study of lipid metabolism, with the visualization of fat dynamics, the evaluation of adipocytokine-adiponectin and leptin secretion, and the possibility of disease management by changing the parameters of lipid metabolism, on the background of iDPP-4 therapy in combination with metformin, the best variant of physiological intervention mobilizing the body's own resources, is of the scientific and practical interest, which determined the relevance of the study. The solution of this problem will allow us to expand our understanding of the nonglycemic effects of iDPP-4, to improve the effectiveness of therapy in patients with type 2 diabetes and obesity. The study was conducted at the Department of Endocrinology of the Russian Medical Academy of Postgraduate Education.

The aim of our study was to evaluate the effect of combined therapy with Sitagliptin and metformin on the parameters of fat metabolism in patients with type 2 diabetes and obesity.

The study protocol was 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 14.11.2013 (Minutes № 8 of 14.11.2013).

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. A brief description of the groups by main parameters is presented in **Table 1**.

After the formation of comparable clinical groups, all patients underwent clinical, instrumental and laboratory tests. Methods of examination included the collection of anamnesis, measurement of anthropometric parameters (height, body weight (BW), waist circumference (WC), hip circumference (HC) and their ratio).

To evaluate the carbohydrate metabolism, the levels of fasting plasma glycemia (GH), postprandial glycemia (PPG) and glycated hemoglobin (HbA1c) were determined.

For the study of fat and lipid metabolism, the concentrations of leptin, adiponectin, total cholesterol (OX), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and apolipoprotein β (apo β protein) were determined.

The quantity and nature of the distribution of adipose tissue were assessed by MRI of visceral fat at L4 level. The area of visceral fat (VFA) ≥ 130 cm^2 and the ratio of VFA/SFA > 0.4 were interpreted as visceral obesity.

Insulin resistance and functional activity of β-cells were determined using the HOMA IR and HOMA β indices. The calculation was carried out according to the following formulas:

HOMA IR = Fasting insulin (μE/ml) X Fasting plasma glucose (mmol/L)/22.5.

Index of HOMA-IR <2.77 was considered normal. IRI-immunoreactive insulin.

HOMA β = 20X IRI (μU/ml)/fasting glycemia (mmol/L) −3.5.

A biochemical blood test was performed on Advia 1800 automatic analyzers from Bayer (Germany) and Olympus AU 2700 from Beckman Coulter (USA). The level of HbA1c was determined by capillary electrophoresis on a Capillaris 2 device from Sebia (France). The study of the content of adiponectin was carried out by ELISA (immunoenzyme method) with Bio Vendor test systems (Germany). The levels of leptin and proinsulin were evaluated using DRG kits for enzyme immunoassay on the Multiscan Labsystems analyzer (Finland). Insulin level in serum of venous blood was evaluated by the method of chemiluminescent immunoassay on the automatic device Architect i2000 (Abbot, USA). The level of C-peptide was determined in the serum of venous

Group characteristics by main parameters			
Parameters	**Group 1**	**Group 2**	**P**
Total number of patients, abs%	42 (100)	40 (100)	—
Men's, abs. (%)	10 (23.8)	8 (20)	—
Women, abs. (%)	32 (76.1)	32 (80)	—
Average age, years	55.3 ± 9.1	56.1 ± 5.4	>0.05
Duration of DM type 2, years	2.4 ± 2.0	2.4 ± 1.5	>0.05
Fasting glycemia, mmol/l	9.7 ± 279	9.6 ± 2.1	>0.05
Postprandial glycemia, mmol/l	11.01 ± 3.19	9.45 ± 1.96	<0.05
HbA1c, %	8.3 ± 1.66	8.35 ± 1.7	>0.05
Total cholesterol, mmol/l	6.85 ± 0.95	7.11 ± 6.39	>0.05
Adiponectin, μkg/ml	7.63 ± 2.56	7.41 ± 2.43	>0.05
Leptin, ng/ml	23.87 ± 13.43	23.84 ± 9.61	>0.05
BMI, kg/m^2	34.78 ± 4.87	35.45 ± 4.3	>0.05
Visceral fat area (VFA, L4), sm^2	300.73 ± 80.88	334.62 ± 70.55	>0.05
Subcutaneous fat area (SFA, L4), sm^2	375.88 ± 91.55	431.25 ± 54.13	>0.05
Proinsulin, pmol/l	9.66 ± 10.49	10.02 ± 12.65	>0.05
Insulin, μU/ml	14.24 ± 9.3	14.72 ± 8.51	>0.05
C-peptide, ng/ml	3.3 ± 1.6	3.2 ± 1.7	>0.05
HOMA-β	40.63 ± 25.99	57.05 ± 35.43	>0.05
HOMA-IR	5.85 ± 4.15	6.32 ± 5.0	>0.05

Table 1. Characteristics of groups by main parameters.

blood by the method of chemiluminescent immunoassay on the Immulite 2000 automatic analyzer (Siemens, USA). To assess the lipid profile, the levels of OX, HDL cholesterol, LDL cholesterol and TG in serum were determined after 12 h of fasting by enzymatic colorimetry on automatic Advia 1800 analyzers. Apolipoprotein β (apo-β-protein) was determined by immunoturbidimetry using an Olympus AU 400 automatic analyzer, manufactured by Beckman Coulter (USA).

Before entering the study, patients provided written informed consent, were trained in the school of diabetes, were secured by means of self-control and self-monitoring diaries.

The statistical analysis of the data was carried out using the Statistica 8 software package. The Wilcoxon test was used to assess the difference in the parameters before and after treatment. The difference in dynamics between the groups was determined by the Mann–Whitney U test. The pair relationships of the indicators were determined by the Spearman rank correlation coefficient.

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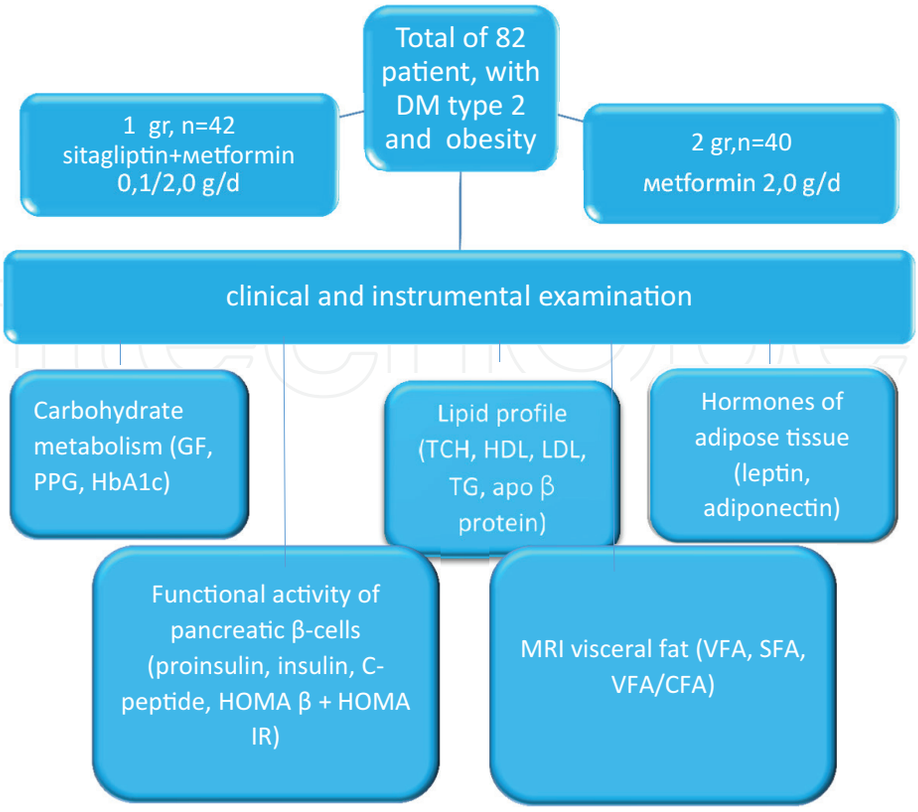

Figure 1. Study design.

To test the statistical hypotheses on the type of distribution, the Shapiro-Wilks criterion was applied. The significance level of p was set at 0.05.

The design of the study is shown in **Figure 1**.

2. Anthropometric measures

After 24 weeks of therapy, a significant decrease in all anthropometric measures was observed in both groups, but more statistically significant differences were observed in group I. BMI decreased on average by 1.81 ± 1.33 (5.29%), $p < 0.001$ in group I, and by 0.68 ± 0.35 (1.96%), $p < 0.001$ in group II. Body weight (BW) decreased by 4.97 ± 3.22 kg (5.2%), $p < 0.001$ in group I, and by 2 ± 0.94 kg (2.07%), $p < 0.001$ in group II. Waist circumference (WC) decreased by 6.52 ± 4.71 cm (5.88%), $p < 0.001$ in group I and by 2.42 ± 1.06 (2.18%), $p < 0.001$ in group II. Accordingly, WC/HC ratio decreased from 0.95 ± 0.06 to 0.91 ± 0.05 (3.28%), $p < 0.001$ in group I, and from 0.94 ± 0.03 to 0.93 ± 0.03 (0.98%), $p < 0.001$ in group II (**Figure 2**). The decrease in WC as well as in the WC/HC ratio indicates a decrease in the amount of visceral fat, which means a decrease in insulin resistance and hyperinsulinemia, the underlying basis of the metabolic syndrome.

The decrease of body weight on Sitagliptin and metformin combined therapy is likely associated with an integrated effect from caloric restriction of the diet, a synergistic effect of iDPP-4 and metformin on GLP-1, which has an anorectic effect.

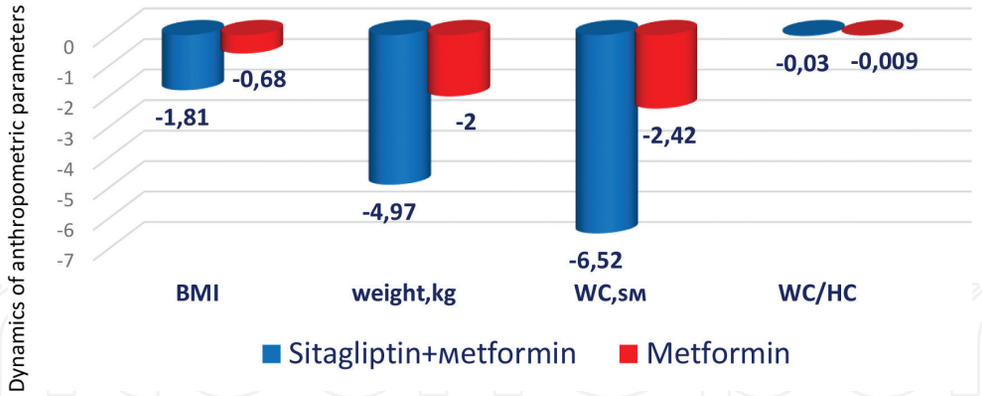

Figure 2. Dynamics of anthropometric parameters. P < 0.001 for all values; P between groups <0.001 for all value.

3. Carbohydrate metabolism

After 24 weeks, a significant decrease in all parameters of carbohydrate metabolism was observed in group I. Level of FPG in group I decreased by 2.67 ± 2.37 mmol/L (21%), p <0.001, FPG decrease in group II has not reached statistical significance with the mean decrease of 0.33 ± 1.6 mmol/L (1.45%), p > 0.05. Postprandial glucose (PPG) decreased by 3.26 ± 2.54 mmol/L (26.35%), p <0.001 in group I and by 0.64 ± 1.2 mmol/L (5.31%), p < 0.05 in group II. HbA1c level decreased by 1.63 ± 1.31% (18.52%), p <0.001 in group I, and by 0.72 ± 0.47% (8.17%) in group II (**Figure 3**).

The largest success in achieving glycemic control in patients on combined treatment is associated with complimentary action of the therapy components. Metformin lowers insulin resistance and hepatic glucose production, while Sitagliptin delays inactivation of GLP-1, thus enhancing glucose-dependent insulin secretion and decreasing glucagon secretion [17]. In addition, it was demonstrated that metformin leads to increase in overall GLP-1 and can

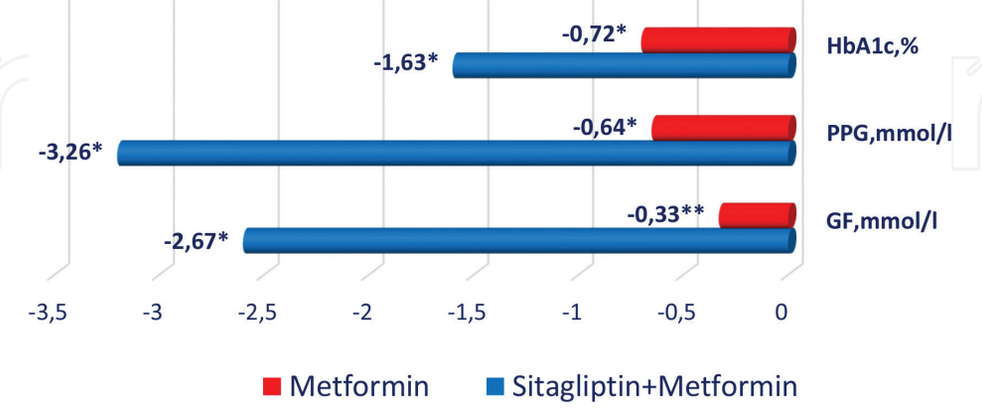

Figure 3. Dynamics of carbohydrate metabolism in the groups. GF-glucose fasting, PPG-postprandial glycemia; *P < 0.05; ** P > 0.05.

potentially enhance the effects of DPP-4 inhibitor. It is notable that the study achieved a significant PPG decrease in metformin monotherapy group, which is potentially associated with metformin ability to increase GLP-1 level and to slow down carbohydrate absorption in the intestine.

4. Lipid profile

Lipid profile parameters belong to the improvement indices of the metabolic health.

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. HDL level decreased by 0.78 ± 0.5 mmol/L (17.43%), $p < 0.001$ in group I, and by 0.37 ± 0.17 mmol/L (9.63%), $p < 0.001$ in group II; TG decreased by 1.33 ± 1.16 mmol/L (28.15%), $p < 0.001$ in group I, and by 0.63 ± 0.39 mmol/L (15.19%), $p < 0.001$ in group II. **Figure 4** displays parameter dynamics in both groups.

Possible mechanisms partaking in the positive effect on lipid profile from therapy by DPP-4 inhibitor in combination with metformin could be weight loss, lowering of glucose level, decrease in visceral fat (VF), which is accompanied by improvement in metabolic status.

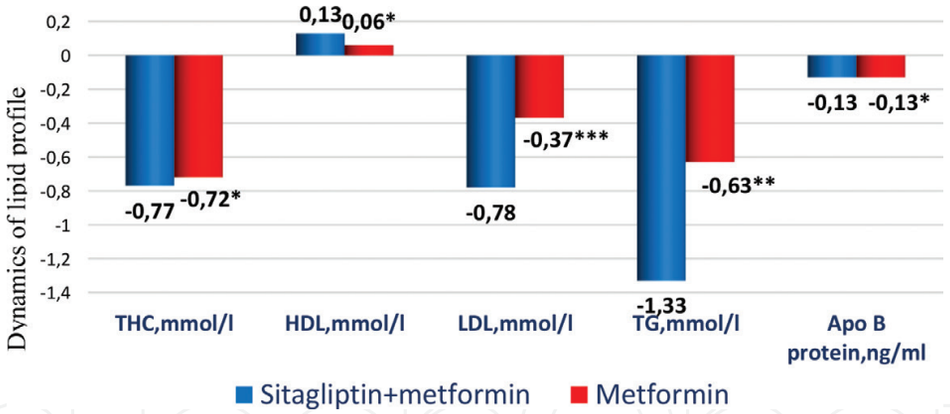

Figure 4. Dynamics of lipid profile. *** $P < 0.001$; **$P < 0.05$; *$P > 0.05$ between groups.

5. Subcutaneous and visceral fat

MRI visualization of visceral fat dynamics demonstrated positive fat redistribution by lowering VFA in group I by 20.62 ± 13.54 cm^2 (7.52%), $p < 0.001$. In group II of metformin monotherapy, VFA decreased by 5.77 ± 3.75 cm^2 (1.76%), $p < 0.001$. SFA decreased by 4.51 ± 14.43 cm^2 (1.69%), $p < 0.05$ in group I, and by 1.95 ± 1.05 cm^2 (0.46%), $p < 0.05$ in group II. Significant improvement in SFA dynamic was observed in both groups; however, we have not detected

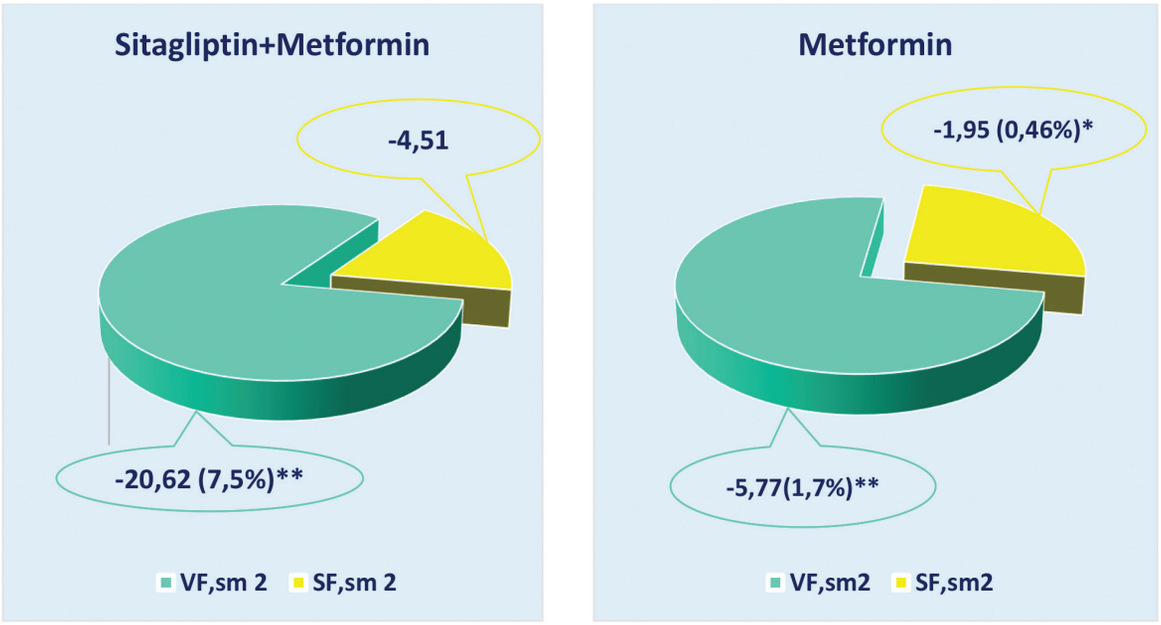

Figure 5. Dynamics of visceral and subcutaneous fat by results MRI. VF-visceral fat, SF- subcutaneous fat; *P between groups >0.05; **P between groups <0.05.

statistically significant difference between the groups (**Figure 5**). VFA/SFA ratio significantly lowered by 0.18 ± 0.24 (15.26%), $p < 0.001$ in group I; and by 0.008 ± 0.008 (1.14%), $p < 0.001$ in group II, which is also indicative of more marked lowering of visceral fat in group I.

6. Adipose tissue hormones

Of note, decrease in VFA and improvement in anthropometric measures were associated to change in secretion of adipose tissue hormones. 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, while on metformin monotherapy, leptin level decreased by 1.21 ± 1.34 ng/ml (5.41%), $p < 0.001$.

The study also indicates dynamics of another adipokine-adiponectin that plays a significant role in glucose and lipid metabolism. The initial adiponectin levels in both groups were lower than reference values. After 6 months of therapy, a more marked adiponectin level increase by 1.95 ± 1.53 μg/mL (27.06%), $p < 0.001$ was observed in group I compared to group II, where it is increased by 0.49 ± 0.26 μg/mL, (7.16%), $p < 0.001$. It is known that this hormone secretion is diminished at T2D. The recovery of secretion is accompanied by the improvement in carbohydrate metabolism indicators, lowering of atherogenesis and slowing down of the progression of diabetes vascular events [18].

Adipose tissue hormones dynamics is displayed in **Figure 6**.

Thus, visceral fat area increased on the background of increasing concentration of adiponectin and decreasing leptin content.

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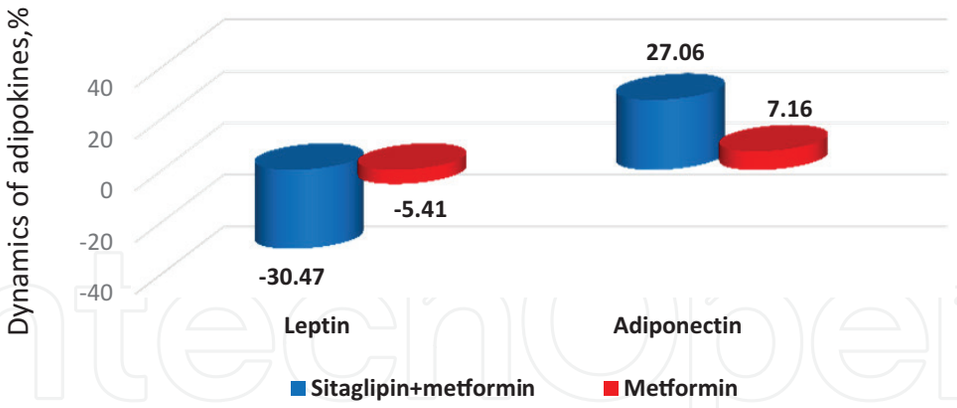

Figure 6. Dynamics of adipokines.

7. Functional activity of β-cells and HOMA-IR

Data from the analysis of pancreatic β-cell function condition have certain scientific and practical interest. For instance, in the Sitagliptin and metformin combined therapy group, a significant increase in HOMA-β index by 23.4 ± 22.6 relative units (33.06%), $p < 0.0001$ was observed compared to the group that receiving metformin monotherapy, where increase in this index has not reached a statistical significance and equaled 4.86 ± 1.63 relative units (11.08%), $p > 0.05$.

Furthermore, the work has obtained statistically significant insulin level lowering in both groups. For instance, on a background of Sitagliptin therapy in combination with metformin therapy, insulin level decreased by 15.68%, ($p < 0.001$), and on metformin monotherapy, insulin level decreased by 7.57%, ($p < 0.001$).

Before treatment, both groups showed increase in proinsulin level, after 6 months of therapy, we achieved significant decrease in the proinsulin level in group I (Sitagliptin + metformin) by 29.17%, ($p < 0.001$), and in group II (metformin) by 13.79%, ($p < 0.001$). Proinsulin/insulin ratio is increased when the functional activity of β-cells is decreased and is an indication of more marked apoptosis in pancreatic β-cells. We established that on Sitagliptin therapy in combination with metformin, a significant decrease by 10.38%, ($p < 0.05$) was observed in proinsulin/insulin ratio, while in metformin monotherapy group, a decrease in this ratio was insignificant, by 2.84%, ($p > 0.05$) (**Figure 7**). This should be considered as a long-term positive effect of Sitagliptin on the function of pancreatic β-cells.

It is important to note that on combined therapy C-peptide level increased by 55.83%, ($p < 0.0001$); and by 6.3%, ($p < 0.05$) in metformin monotherapy group. HOMA-IR significantly lowered in both groups. However, we have not detected statistically significant difference between the groups' dynamics. It decreased by 32% ($p < 0.0001$) in group I, and by 11.05% ($p < 0.0001$) in group II. The decrease in homeostasis model assessment of insulin resistance is the evidence of improvement in peripheral glucose disposal. Positive effect on β-cell function is associated with lowering of glucotoxicity, weight loss, insulin resistance, and improvement

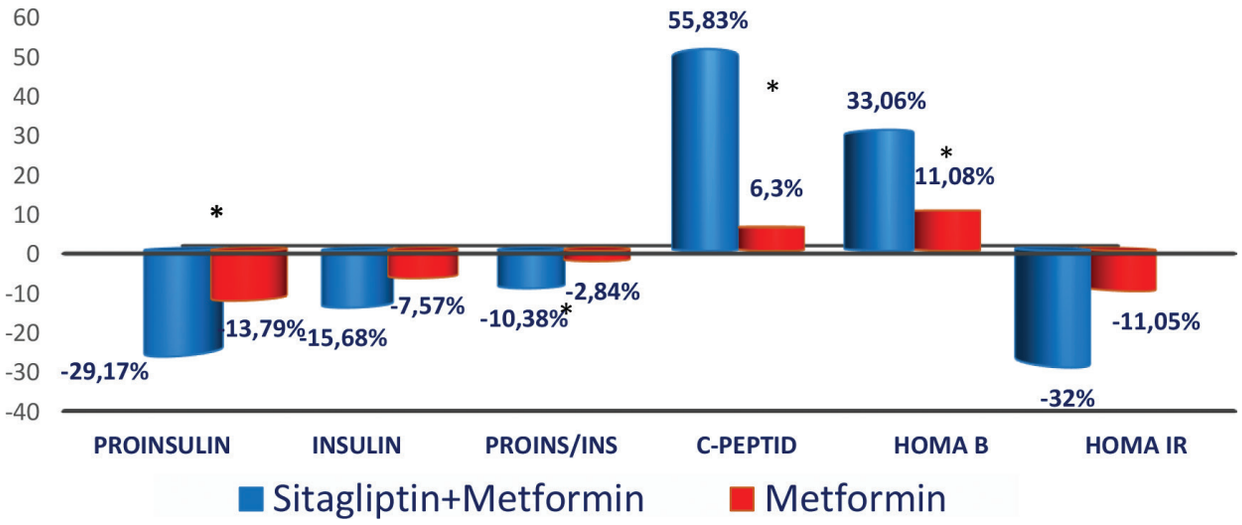

Figure 7. Function of β-cells of the pancreas and HOMA IR in dynamics. *P between groups <0.05.

in metabolic health, which promoted lowering of the "stress" on the insular apparatus of the pancreas. β-cell function improvement is promising in stabilization of T2D progression.

The results of the correlation analysis are displayed in **Table 2** and in **Figure 8**.

Thus, as can be seen from the correlation analysis, an additional therapeutic effect on glycemic control in patients with T2D and obesity is associated with a decrease in the amount of visceral fat and a change in the secretion of adipose tissue hormones. **Table 3** presents a comparative analysis of the main parameters, depending on the type of therapy.

Показатели, динамика	**Адипонектин**	***Лептин***
HbA1c	r = −0.39*	r = 0.32*
VF	r = −0.54*	r = 0.33*
body mass	r = −0.75**	r = 0.45**
BMI	r = −0.74**	r = 0.45**
WC	r = −0.62**	r = 0.43**
LDL	r = −0.29**	r = 0.3**
TG	r = −0.33**	r = 0.16
HOMA IR	r = −0.53**	r = 0.37**
HOMA β	r = 0.29**	r = −0.33**
Leptin	r = −0.63*	—

*p < 0.01 significance of correlation coefficient at p < 0.01.
**p < 0.05 significance of correlation coefficient at p < 0.05.

Table 2. Correlation analysis.

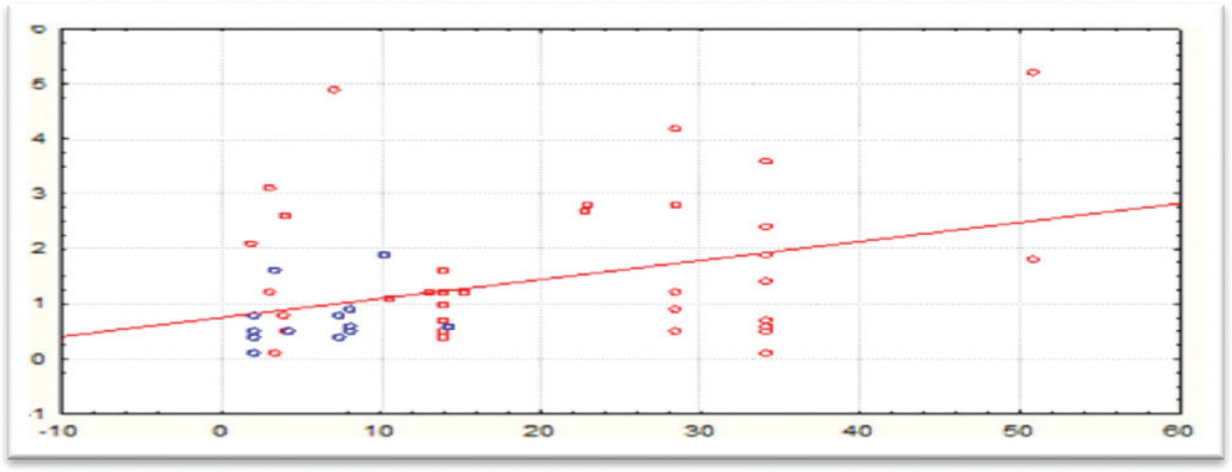

Figure 8. Correlation between the dynamics of the VF and HbA1c.

Parameters	Group 1, Sitagliptin + metformin		Group 2, Metformin		P between groups
	Before treatment	After treatment	Before treatment	After treatment	
HbA1c	8.3 ± 1.66	6.66 ± 1.24	8.35 ± 1.75	7.62 ± 1.39	<0.001
BMI, kg/m^2	34.78 ± 4.87	32.96 ± 5.04	35.45 ± 4.3	34.76 ± 4.33	<0.001
Adiponectin, mkg/ml	7.63 ± 2.56	9.59 ± 3.03	7.41 ± 2.43	7.9 ± 2.44	<0.001
Leptin, ng/ml	23.87 ± 13.43	16.49 ± 9.63	23.87 ± 9.61	22.66 ± 9.61	<0.001
VF, sm^2	300.73 ± 80.88	280.11 ± 84.16	334.62 ± 70.55	328.85 ± 70.4	<0.001
SF, sm2	375.88 ± 91.55	371.37 ± 98.04	431.25 ± 54.13	429.3 ± 54.52	>0.05
LDL, mmol/l	4.31 ± 0.73	3.53 ± 0.58	3.89 ± 0.61	3.51 ± 0.61	<0.001
TG, mmol/l	4.28 ± 2.4	2.95 ± 1.73	4.31 ± 2.04	3.68 ± 1.86	<0.05
HOMA-IR	5.85 ± 4.15	3.49 ± 2.44	6.32 ± 5.0	4.32 ± 2.77	>0.05
HOMA-β	40.63 ± 25.99	64.04 ± 29.01	57.05 ± 35.43	61.91 ± 30.82	<0.005

Table 3. Comparative characteristics of the main parameters depending on the type of therapy.

8. Discussion

The study investigates the effect of Sitagliptin in combination with metformin as well as of metformin monotherapy on carbohydrate and fat metabolism in patients who required their therapy to be intensified. According to the 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 I, while in group II (on metformin monotherapy), the

decrease in glycemia did not reach statistical significance. An important advantage in our study was that, despite the common belief about 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, compared to the group of patients on metformin monotherapy. 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. The main function of leptin is forming a communication pathway link between adipocytes and the brain [19]. Leptin secretion positively correlates with the amount of adipose tissue, which we also demonstrated in our work. In addition to the anorectic effect in the adjustment of eating behavior, leptin also stimulates energy intake. 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. Most obese patients have high leptin levels, but this does not lead to weight loss, which confirms the fact that obese patients may develop resistance to leptin. Leptin's effect disorder in obesity can be a leading factor in the development of insulin resistance and fat and glucose metabolism disorder. In our work, on a background of combined Sitagliptin and metformin therapy, the leptin level was reduced by 30.47% and in the metformin monotherapy group by 5.41%. We associate decrease in leptin level with weight loss and 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, and by 7.16% in the group receiving metformin monotherapy. Adiponectin with its effect on the reduction of insulin resistance, which is characteristic of patients with T2D and obesity, and also its anti-inflammatory, antidiabetic and antisclerotic effects make it an additional therapeutic target. 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 [20, 21], the Sitagliptin therapy was followed by increase in adiponectin level [22, 23].

Correlational analysis demonstrated correlation of glycemic control in T2D obese patients with reducing visceral fat amount and with recovery of secretion of adipose tissue hormones.

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, a decrease in the ratio of proinsulin/insulin, in contrast to metformin monotherapy, where the change in these indices did not reach statistical significance. 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-cell function.

9. Conclusion

Our study 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 chapter 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.

Information regarding funding and conflict of interest

The study has been performed at the personal expense of the authors. The authors claim that there is no conflict of interest regarding data disclosed in the article.

List of abbreviations

DM	diabetes mellitus
IR	insulin resistance
DPP-4	dipeptidyl peptidase type 4
GLP	glucagon-like peptide
BM	body mass
BMI	body mass index
HbA1c	glycated hemoglobin
GF	glucose fasting
PPG	postprandial glycemia
VF	visceral fat
VFA	visceral fat area
SFA	subcutaneous fat area
MRI-MPT	

WC	waist circumference
HC	hip circumference
TCH	total cholesterol
LDL	low-density lipoproteins
HDL	high-density lipoproteins
TG	triglycerides

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