European Review for Medical and Pharmacological Sciences 2017; 21: 3490-3495

The effect of sitagliptin on obese patients with insulin treatment-induced diabetes mellitus

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Abstract. – OBJECTIVE: The objective of the present study was to observe the effect of sitagliptin on obese patients with insulin treatment-induced diabetes mellitus.

PATIENTS AND METHODS: A total of 120 obese patients with insulin treatment-induced diabetes mellitus were consecutively selected and divided into the control group (n=35), observation group 1 (n=40), and observation group 2 (n=45). The control group received different types or doses of insulin, observation group 1 received insulin combined with metformin, and observation group 2 received insulin combined with sitagliptin. The therapeutic effects were compared at the 6-month follow-up visit.

RESULTS: Body mass index (BMI) was lower in observation group 1 and observation group 2, and higher in the control group compared with before treatment; the occurrence of hypoglycemia in observation group 2 was lower than in the other two groups, and the differences were statistically significant ($p<0.05$). After treatment, the fasting insulin (FINS) and homeostatic model assessment insulin-resistance (HOMA-IR) in observation group 2 were significantly lower than in the other two groups ($p<0.05$). Adiponectin levels were increased and leptin and visfatin levels were decreased in observation group 2 after treatment, and the differences were statistically significant ($p<0.05$). The levels of fasting blood glucose, hemoglobin A1c, total cholesterol, triglyceride, and low-density lipoprotein in the three groups were not significantly different ($p>0.05$).

CONCLUSIONS: Sitagliptin can reduce BMI and the occurrence of hypoglycemia in obese patients with insulin treatment-induced diabetes mellitus, and the effect may be related to decreased HOMA-IR, decreased leptin and visfatin levels, and increased adiponectin levels.

Key Words
Sitagliptin, Insulin, Diabetes mellitus obesity, Insulin resistance index, Leptin, Visfatin, Adiponectin.

Introduction

Diabetes mellitus is a common chronic disease with a high rate of disability and mortality in our country[1,2]. The main mechanism of type-2 diabetes mellitus is insulin resistance. Clinical treatment includes oral administration of hypoglycemic drugs and insulin[3]. According to numerous studies[4], insulin treatment can shorten the treatment course, improve the success rate of treatment and stability of blood glucose, and reduce the risk of hypoglycemia in diabetic patients diagnosed for the first time. However, it was found at follow-up visits[5] that insulin treatment can increase the occurrence of obesity, and that on average, about 30-50% of patients suffer from obesity for 3.5 years after insulin treatment, with decreased hypoglycemic effect and increased complications. This may be attributed to the fact that insulin interferes with the metabolism of blood glucose and blood lipids, increases insulin resistance, and affects a variety of active endocrine substances, such as adiponectin, leptin, and visfatin[6]. Metformin has good therapeutic effect on diabetic patients. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which inhibits DPP-4 from degrading endogenous intestinal incretins, increases the levels of insulin glucagon-like peptide (GLP-1), promotes β-cells to release insulin, inhibits the secretion of insulin, and inhibits α-cells from secreting glucagon, thus reducing blood glucose level[7] with few effects on body weight and hypoglycemia[8]. The aim of the present study was to analyze the effects of sitagliptin on obese patients with insulin treatment-induced diabetes mellitus.

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Patients and Methods

Patients

A total of 120 obese patients with diabetes mellitus who received insulin treatment between January 2013 and January 2016 in our hospital were consecutively selected. The inclusion criteria were as follows: 1. Patients who were not obese before insulin treatment (the reference range for body mass index (BMI) in Chinese people was 18.5-23.9 kg/m^2, overweight implied the range was from 24.0-27.9 kg/m^2, and obesity implied BMI above 28.0 kg/m^2); 2. Patients who preferably received insulin treatment after being diagnosed with diabetes mellitus, without combination with other oral hypoglycemic drugs; 3. Insulin treatment could regulate blood glucose within a normal range without hypoglycemia and complications; 4. BMI $\geq$ 24.0 kg/m^2 within 1 year after insulin treatment; 5. Patients who provided informed consent, had good compliance, and complete medical history. The exclusion criteria were as follows: 1. Patients who had severe diabetic complications, complications with other underlying diseases, such as of the heart, liver, lung, kidney, and brain, and autoimmune diseases; 2. Patients who failed to tolerate treatment with metformin or sitagliptin combined with insulin; 3. Patients who abandoned the study voluntarily or participated in other studies. According to different treatment methods, patients were divided into the control group (n=35), observation group 1 (n=40), and observation group 2 (n=45). The baseline parameters of patients in the three groups were comparable. See Table I.

Methods

Patients in the control group received different types or doses of insulin, patients in observation group 1 received insulin combined with metformin (0.85 g/d, once per day), and patients in observation group 2 received insulin combined with sitagliptin (100 mg/d, once per day). The BMI; occurrence of hypoglycemia; fasting insulin (FINS); homeostatic model assessment insulin-resistance (HOMA-IR); adiponectin, leptin, and visfatin levels; fasting blood glucose (FBG); hemoglobin A1c (HbA1C), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) levels were compared at the 6-month follow-up visit. FINS was measured using a Centaur XP chemiluminescence immunity analyzer from Siemens (München, Germany), and FBG, HbA1C, TC, TG, and LDL levels were measured using an ADVIA 2400 fully automatic biochemical analyzer from Siemens, HOMA-IR = (FINS) × BG/22.5. The radioimmunoassay kit from Beijing North Biotechnology Research Institute was used to measure adiponectin, leptin, and visfatin levels in strict accordance with the instructions.

Statistical Analysis

SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Measurement data are presented as mean ± standard deviation. Single-factor ANOVA analysis was used for inter-group comparisons, LSD-t test was used for pairwise comparisons, and paired *t*-test was used for intra-group comparisons. Enumeration data are presented as a number of cases or percentage (%), and χ^2-test was used for inter-group comparison. $p<0.05$ was taken as statistically significant.

Table I. Comparison of baseline parameters of the three groups.

Group	Control group (n=35)	Observation group 1 (n=40)	Observation group 2 (n=45)	F/χ^2	*p*
Male/female	20/15	22/18	21/24	1.017	0.601
Age (y)	52.6±11.3	53.1±12.2	53.4±14.5	0.162	0.954
Duration of insulin treatment (months)	10.8±3.5	11.3±3.6	12.4±3.7	0.242	0.825
BMI (kg/m^2)	26.5±2.4	26.6±2.5	26.8±2.5	0.085	0.962
FBG (mmol/l)	6.2±1.3	6.3±1.2	6.4±1.3	0.185	0.864
HbA1C (%)	6.8±0.9	7.0±1.1	7.2±1.3	0.321	0.764
TC (mmol/l)	6.2±1.3	6.3±1.4	6.3±1.5	0.174	0.869
TG (mmol/l)	1.2±0.3	1.3±0.4	1.3±0.4	0.114	0.857
LDL (mmol/l)	4.5±0.8	4.4±0.7	4.6±0.6	0.094	0.932

Note: FBG: fasting blood-glucose; HbA1C: hemoglobin A1C; TC: total cholesterol; TG: triacylglycerol; LDL: low density lipoprotein.

Table II. Comparison of BMI and occurrence of hypoglycemia.

Group	Cases	BMI (kg/m^2)	Hypoglycemia [cases (%)]
Control group	35	28.5±3.4	7 (20.0)
Observation group 1	40	24.2±2.1	8 (20.0)
Observation group 2	45	24.3±2.2	2 (4.4)
F/χ^2		6.532	6.490
p		0.000	0.039

Results

Comparison of BMI and occurrence of hypoglycemia

BMI was lower in observation group 1 and observation group 2, and higher in the control group compared with before treatment; the occurrence of hypoglycemia in observation group 2 was lower than in the other two groups, and the differences were statistically significant ($p<0.05$). See Table II.

Comparison of FINS and HOMA-IR

After treatment, FINS and HOMA-IR in observation group 2 were significantly lower than in the other two groups ($p<0.05$). See Table III.

Comparison of adiponectin, leptin, and visfatin levels

Adiponectin levels were increased and the levels of leptin and visfatin were decreased in observation group 2 after treatment, and the differences were statistically significant ($p<0.05$). See Table IV.

Comparison of FBG, HbA1C, TC, TG, and LDL levels

The levels of FBG, HbA1C, TC, TG, and LDL in the three groups were not different after treatment ($p>0.05$). See Table V.

Discussion

Many tests confirmed the safety and efficacy of single-drug or combined treatment with sitagliptin. Aschner et al[9], Raz et al[10], Mohan et al[11], and Nonaka et al[12] performed randomized and double-blind studies with large sample-sizes to test the effects of sitagliptin and placebo for the treatment of diabetes mellitus, with an observation time of 12-24 weeks. In a separate study,

Table III. Comparison of FINS and HOMA-IR.

Group	Pre-treatment FINS(μU/ml)	Post-treatment FINS	Pre-treatment HOMA-IR	Post-treatment HOMA-IR
Control group	36.8±5.5	41.2±4.2	3.5±0.7	3.8±0.9
Observation group 1	37.2±5.6	38.5±4.6	3.6±0.9	3.7±0.8
Observation group 2	37.5±5.4	26.9±3.5	3.6±0.8	3.1±0.5
F	0.125	5.632	0.095	5.432
p	0.864	0.009	0.923	0.012

Table IV. Comparison of adiponectin, leptin, and visfatin levels (ng/ml).

Group	Adiponectin		Leptin		Visfatin	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	16.5±3.6	13.2±3.3	6.5±1.4	7.3±1.6	45.6±12.3	51.6±14.5
Observation group 1	15.8±3.7	14.4±3.5	6.8±1.5	7.1±1.8	48.7±12.6	52.2±15.2
Observation group 2	15.7±3.2	18.2±3.5	6.6±1.3	4.5±1.2	51.2±13.3	32.3±10.5
F	0.152	5.124	0.063	4.685	0.322	6.235
p	0.912	0.019	0.958	0.025	0.635	0.003

Table V. Comparison of FBG, HbA1C, TC, TG, and LDL levels.

Group	FBG (mmol/l)	HbA1C (%)	TC (mmol/l)	TG (mmol/l)	LDL (mmol/l)
Control group	6.3±1.2	6.7±0.6	6.3±1.2	1.3±0.5	4.4±0.8
Observation group 1	6.2±1.3	6.8±0.7	6.2±1.3	1.4±0.6	4.5±0.7
Observation group 2	6.4±1.3	6.6±0.8	6.4±1.5	1.2±0.4	4.3±0.6
F	0.124	0.065	0.085	0.212	0.174
p	0.823	0.925	0.878	0.769	0.802

FBG (Fasting blood glucose), HbA1C (Hemoglobin A1c), TC (Total cholesterol), TG (Triglyceride), and LDL (Low-density lipoprotein).

Aschner et al[13] compared the single-drug treatment of sitagliptin and metformin, and Iwamoto et al[14] compared the single-drug treatment of sitagliptin and voglibose. Williams et al[15] analyzed 1091 diabetic patients from 140 centers among 18 countries in a clinical double-blind placebo study, and compared the treatment effects of sitagliptin combined with metformin, with an observation time of 24-54 weeks. Vilsboll et al[16] analyzed 641 patients with poorly controlled type-2 diabetes mellitus using insulin alone or insulin + metformin in a double-blind placebo-controlled study, and randomly divided patients into the sitagliptin group and placebo group, with an observation time of 24 weeks.

In the present study, we aimed to determine the clinical effects of combined treatment with sitagliptin on obese patients with insulin treatment-induced diabetes mellitus. Insulin-induced obesity not only increased the difficulty of reducing blood glucose, but also might increase the complications of diabetes mellitus (such as target-organ damage of the heart, brain, and kidney) and the adverse reactions of insulin (such as the hypoglycemia or hyperglycemia) [17]. There has been no unified understanding of how to manage such patients at present, and there is little relevant clinical research. Therefore, the effects of treatment methods based on clinical experience remain inconclusive. We made the following conclusions: BMI was lower in observation group 1 and observation group 2, and higher in the control group compared with before treatment. Also, the occurrence of hypoglycemia in observation group 2 was lower than in the other two groups, and the differences were statistically significant. Using sitagliptin alone did not increase the body weight and the occurrence of hypoglycemia, but reduced the body weight of patients with insulin resistance and obesity. The effect of sitagliptin may therefore be associated with the degree of insulin resistance. Sitagliptin reduces the body weight of patients with obesity, but does not increase the occurrence of hypoglycemia, thus its effect is better than metformin. After treatment, FINS and HOMA-IR levels in observation group 2 were significantly lower than in the other two groups. Additionally, adiponectin levels were increased, and leptin and visfatin levels were decreased in observation group 2, and the differences were statistically significant. The improved effect of sitagliptin on obesity may be related to improvements in the levels of various active endocrine substances. Increased FINS level is associated with increased insulin resistance. HOMA-IR is stable, and is an objective and accurate index of insulin resistance. Adiponectin, leptin, and visfatin are active substances secreted by adipocytes. Some studies[18] confirmed that adiponectin and leptin are mutual antagonistic factors that jointly control blood lipid level, blood glucose, and protein metabolism, and are closely related to cardiac-cerebral vascular disease and atherosclerosis. Furthermore, they are closely related to the treatment and prognosis of diabetes mellitus. Under the condition of insulin resistance, adiponectin levels decrease and leptin levels increase. Visfatin is a newly discovered hormone that is also related to obesity. Visfatin is the pre-B cell colony-enhancing factor, and plays an important role in immune regulation[19]. Also, visfatin is mainly secreted by visceral adipose tissue, although the relationship between it and subcutaneous fat remains unclear[20]. Visfatin has a hypoglycemic effect and its effect is dose-dependent. Its hypoglycemic mechanism can act independently from insulin adjustment[21]. The levels of FBG, HbA1C, TC, TG, and LDL in the three groups were not different. Therefore, weight control mediated by sitagliptin may be unrelated to blood glucose and blood lipid metabolism.

Conclusions

Sitagliptin can reduce BMI and the occurrence of hypoglycemia of obese patients with insulin treatment-induced diabetes mellitus, which may be related to decreased HOMA-IR, leptin and visfatin levels, and increased adiponectin levels.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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