Nat. Volatiles & Essent. Oils, 2020; 7(1): 53-60
https://doi.org/10.52783/nveo.5447

NVEO
Natural Volatiles & Essential Oils

Effect Of Monotherapy And Combined Therapy With Thiazolidinedione Dpp 4 Inhibitors

KOMAL CHANDRA

Department of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, India 248002

Abstract

The American Diabetes Association has set a HbA1c objective of 7.0%, which appears excessive given the lack of a well-established HbA1c threshold for CVD risk. Hypoglycemia and weight gain are common adverse effects of the large doses of sulfonylureas and insulin needed to achieve a HbA1c of 6.0% or less. However, it has been shown that insulin sensitizers and GLP-1 analogs may keep -cells working without greatly raising the risk of hypoglycemia, therefore they may be titrated to maximal dose in order to bring down HbA1c levels below 6.0%. Finally, Weight loss and protection against the weight gain linked with TZDs are both possible thanks to GLP-1 analogs, but sulfonylurea and insulin treatment often cause weight gain.

Key words: Diabetes, mellitus; Glucagon; Metformin; Thiazolidinediones

INTRODUCTION

Type 2 diabetes mellitus is a metabolic illness that has emerged as a global public health crisis. According to new estimates from the World Health Organization, diabetes is responsible for about 3 million deaths annually throughout the globe. By 2025, Type 2 diabetes mellitus (T2DM) is expected to account for 90-95% of all occurrences of diabetes mellitus, with an estimated 333 million individuals suffering from the condition. Multiple medical conditions, such as inadequate blood flow to the extremities, nerve damage, eye damage, and kidney failure, might develop as a result. Certain oral antihyperglycemic medications and insulin are used in the treatment of type 2 diabetes, in addition to changes in lifestyle.

Two key pathophysiologic problems define type 2 diabetes mellitus: Disrupted beta cells and impaired peripheral insulin sensitivity. Anti-diabetic drugs have been proven to be unsuccessful in a number of trials. Hypoglycemia and weight gain are two side effects of antidiabetic medications that may contribute to the increased cardiovascular risk seen in late-stage type 2 diabetes mellitus patients.

LITERATURE REVIEW

Salahuddheen, K (2012), Alpha-glucosidase inhibitor acarbose and DPP-4 inhibitor vildagliptin, with and without biguanide derivative metformin, should be studied. Evaluate the performance and safety of the DPP4 inhibitor vildagliptin in comparison to the Sulfonylurea derivative glibenclamide, with and without the Biguanide derivative metformin. Vildagliptin, a DPP4 inhibitor, was compared to the thiazolidinedione derivative pioglitazone for its effectiveness and safety, both alone and in combination with the biguanide derivative metformin. Vildagliptin, a DPP4 inhibitor, was compared to another DPP4 inhibitor, pioglitazone, and the results showed that the combination of Vildagliptin and pioglitazone was both effective and safe. Inhibiting dipeptidyl peptidase-4 (DPP-

4) has the potential to reduce levels of glycated hemoglobin (HbA1c), fasting blood sugar (FBS), and postprandial glucose (PG). DPP-4 has been shown to have a positive effect on body mass index (BMI), serum lipid profile (HDL), and total cholesterol (TC) when used as monotherapy across a wide range of ages and sexes, with reductions of between 0.5-0.35 in HbA1c, 35-22.8 points in fasting blood sugar, and 79-42.2 points in resting blood sugar. DPP-4 inhibition has shown promise as a potential combination treatment, and it has shown promise when used in conjunction with metformin and TZDs. Combination trials have shown that adding a DPP-4 inhibitor to an existing monotherapy treatment results in comparable rates of side effects compared to monotherapy, which is encouraging. In addition, the combo therapies seldom cause hypoglycemia. To prove its effectiveness and safety in treating type 2 diabetes, further long-term studies are needed.

Xiaocai Cai, Xiaocai Gao, Wenjing Yang, et al (2018), To determine if first combination therapy with hypoglycemic medications is more effective than monotherapy. Only studies that matched the predetermined criteria were considered for this meta-analysis. Differences in weighted means and relative risks were computed. The meta-analysis comprised data from 36 research. First-time combination therapy with another anti-diabetes medicine significantly lowered glycated hemoglobin (HbA1c) levels, in comparison to metformin monotherapy. Except for sulfonylurea/glinide and metformin and thiazolidinedione and metformin, most combinations of diabetic medicines showed a comparable risk of hypoglycemia.

A.J. Scheen in 2011, Studies have revealed that DPP-4 inhibitors reduce glucose levels similarly to thiazolidinediones while causing a somewhat smaller drop in hemoglobin A1c compared to metformin. Gliptins were associated with comparable HbA1c reductions in those on metformin as they were in those taking a sulphonylurea or a thiazolidinedione (TZD). Saxagliptin was shown to be non-inferior to sitagliptin in just one head-to-head study. There is obviously a need for more studies that directly compare various incretin-based medicines to one another. DPP-4 inhibitors are rapidly increasing in importance as we learn more about their benefits and drawbacks via controlled clinical research for the management of type 2 diabetes.

Alam, F., et al. (2019), Pioglitazone, the only thiazolidinedione drug now in clinical use, is being explored for its unique insulin sensitizing potential despite its association with a variety of undesirable side effects. Alterations in homeostasis model assessment-insulin resistance, body weight, and fasting blood sugar levels were secondary goals, but increases in glycated hemoglobin were the primary focus. The safety outcomes were changes in biomarkers and the incidence of unwanted side effects. The studies were performed using the R program's Metafor package and the random-effects model-based RevMan program. 16 randomized controlled trials were included. HbA1c was lowered by 0.05% and FBS was down by 0.24 mmol/l, both of which are equivalent to reductions reported with pioglitazone monotherapy. In addition to lowering HOMA-IR by 0.05, pioglitazone also boosted HDL by 0.02 mmol/l. As a monotherapy, pioglitazone was superior than placebo in lowering both blood pressure and triglycerides. Pioglitazone was linked to increased weight gain and oedema risk, but lowered hypoglycemia risk. Patients with type 2 diabetes who are experiencing hyperglycemia, poor lipid metabolism, or high blood pressure may benefit from pioglitazone, according to a meta-analysis. Pioglitazone dosing recommendations should be based on each patient's unique circumstances.

Yoshinori Nishida, Yoshinori Takahashi, Kenji Tezuka, et al (2017), The purpose of this study was to compare the physiological and biochemical reactions of people with type 2 diabetes mellitus treated with five different DPP-4 inhibitors. We compared the effects of five different DPP-4 inhibitors on a variety of laboratory parameters, over the course of 12 months using a multivariate regression model. Comparing baseline and exposure periods, our research showed that the five DPP-4 inhibitors studied improved hepatic markers and lowered HbA1c.

DURABILITY OF GLUCOSE CONTROL WITH THIAZOLIDINEDIONE

Interventions that reduce excess body adiposity or affect its biology provide the strongest evidence that -cell loss may be postponed or avoided. Both the Diabetes Prevention Program and the Finnish Diabetes Prevention Study found that yearly incidence of type 2 diabetes mellitus decreased in tandem with weight loss. If losing weight slowed or stopped the decline of beta cells, we would anticipate this trend. Taking a TZD has been shown in five studies to minimize the risk of acquiring type 2 diabetes in patients with IGT. All five trials demonstrated that TZDs do more than only increase insulin sensitivity; they also significantly protect -cell function. Both Pioglitazone and Troglitazone were studied for their potential to prevent diabetes, direct evaluation of -cell function demonstrated that TZDs may reduce or halt the loss of -cell function. Treatment of insulin resistance seems to work by decreasing the secretory demand for insulin.

DPP-4 INHIBITORS VERSUS GLP-1 RECEPTOR AGONISTS

As there haven't been many studies comparing GLP-1 receptor agonists with DPP-4 inhibitors, it may be difficult to tell which patients will have the best results with either class of medication. Tolerance to and oral bioavailability of small molecule DPP IV inhibitors are generally high. It is safe to use them in patients with renal and hepatic impairment, as well as the elderly, the frail, the vulnerable, and those with a history of alcohol or drug misuse since they are easy to give. They have been demonstrated to have no effect on weight gain or loss, and they are connected to a decrease in hypoglycemia rates and HbA1c levels (0.6 to 0.7%). They may be taken whenever convenient, regardless of mealtimes, since they do not produce hypoglycemia and hence do not need dosage titration. Moreover, they seldom if ever cause negative interactions with other prescriptions, meaning you may take them with other drugs without adjusting the dosage of either. In clinically meaningful ways, DPP-4 inhibitors do not alter the pharmacokinetic profiles or exposure to other routinely used drugs that influence the CYP system. Since diabetes is a common complication of diseases like TB and HIV, DPP-4 inhibitors may be of use in these situations.

Subcutaneous injections of incretin mimetics, also known as GLP1 R agonists, protect the drug from degradation by digestive hormones. As a result of the 6–10-fold rise in concentration upon injection, these inhibitors are more effective than DPP IV inhibitors for lowering HbA1 c levels, leading to considerable weight loss, particularly in extremely obese people. DPP4 inhibitors and GLP-1R agonists may be differentiated most noticeably in the eyes of patients by the former's oral, once-daily dose and the latter's injection schedule. Evidence shows that patients may be more open to injectable medications if they are more effective than those that have previously been tried.

Table 1: Comparison of action of DPP-4 inhibitors and GLP-1 receptor agonists

Action	DPP-4 inhibitors	GLP-1 receptor agonists
Insulin secretion	Increased	Increased
Glucagon Secretion	Decreased	Decreased
PPPG	Reduced	Reduced
Appetite	No effect	Suppressed
Satiety	No effect	Induced
Gastrointestinal adverse effects	Rare to none	Often Nausea
Gastric emptying	No effect	Slowed
Body weight	Neutral	Reduced

Glycemic control, cardiovascular risk factors, and liver biomarkers all improved in type 2 diabetes mellitus patients who took exenatide in conjunction with metformin and/or sulfonylurea for 3 years, as well as gradual weight loss. After 3.5 years of following up with some of these patients, we found that their HbA1c levels continued to drop.

Weight reduction is the result of GLP-1 analogs' effects on - and -cells as well as on hepatic glucose synthesis, appetite, and stomach motility. To further reduce the risk of hypoglycemia, exenatides tightly rely on plasma glucose level to stimulate insulin production while suppressing glucagon. In contrast to what was seen in rats, there was no evidence that incretin treatment for type 2 diabetes mellitus humans would lead to an increase in -cell bulk in addition to an improvement in -cell function.

COMBINATION OF THIAZOLIDINEDIONE AND DPPIV INHIBITOR

After 24 weeks of pioglitazone monotherapy, patients with type 2 diabetes mellitus who still had uncontrolled blood sugar levels were given Sitagliptin 100 mg once daily. No additional risk of hypoglycemia was seen in comparison to the placebo group, and effective glycemic control was accomplished with the adjustments. From baseline to endpoint, HbA1c levels changed by an AM of 0.8% in individuals receiving 50 mg of vildagliptin daily and 1.0% in those receiving 100 mg. Mild hypoglycemia occurred in 0% of patients on vildagliptin 50 mg/day, 0.6% of patients taking vildagliptin 100 mg/day, and 1.9% of patients taking a placebo.

Table 2. Summaries of selected clinical trials

Prior Rx.	Weeks	Trial design	Intervention	No. of subjects	Baseline HbA1c	Δ HbA1c	≤ 7% Achieved	Δ Weight kg, baseline
Exenatide TZD w/wo MET	16	RDPC	PLB + TZD w/wo MET	112	7.9	+0.1 ± 0.1	16	-0.2 ± 0.26
			EXE10 μ bid w/wo MET	121	7.9	-0.9 ± 0.1	62	-1.75 ± 0.25
Liraglutide TZD + MET	26	RDPC, parallel group	PLB	177	8.4	-0.54		+0.6 ± 0.3
			Lira 1.2 mg qd	178	8.5	-1.48		-1.0 ± 0.3
			Lira 1.8 mg qd	178	8.6	-1.48		-2.0 ± 0.3
Sitagliptin PIO	24	RDPC, parallel group	PLB + PIO 30-45 mg qd	173	8.0	-0.2	23	+1.5
			SITA 100 mg qd + PIO 30-45 qd	175	8.1	-0.9	45	+1.8
Vildagliptin Drug naive	24	RDAC, prallel group	PIO 45 mg qd	161	8.7	-1.4 ± 0.1	43	+1.5 ± 0.3
			VILD 50 mg qd + PIO 15 mg qd	144	8.8	-1.7 ± 0.1	54	+1.4 ± 0.3
			VILD 100 mg qd + PIO 30 mg qd	148	8.8	-1.9 ± 0.1	65	+2.1 ± 0.3
			VILDA 100 mg qd	154	8.6	-1.1 ± 0.1	43	+0.2 ± 0.3
TZD	24	RDPC, parallel group	PLB + PIO 45 mg qd	158	8.7	-0.3 ± 01	15	+1.4± 0.3
			VILD 50 mg qd + PIO 45 mg qd	147	8.6	-0.8 ± 0.1	29	0.1 ± 0.4[a]
			VILD 50 mg qd + PIO 45 mg qd	158	8.7	-1.0 ± 0.1	36	1.3 ± 0.4[a]

Effectiveness and safety of first vildagliptin/pioglitazone combination therapy were compared to those of component monotherapy in a previous experiment. Compared to individual component monotherapy, glycemic control was better with the combination of vildagliptin and pioglitazone in the first line of treatment. The high-dose combination was well tolerated and helped 65% of patients achieve their HbA1c goals, equivalent to pioglitazone alone. The low-dose combination was more efficient and well-tolerated than pioglitazone 30 mg qd.

TRIPLE COMBINATION

Improvements in glycemic control and weight loss were seen in 233 individuals with type 2 diabetes mellitus who were using TZD metformin but not getting ideal results from their treatment. However, compared to placebo, it was linked with more severe gastrointestinal side effects.

After 26 weeks of therapy with liraglutide, metformin, and TZD, the mean HbA1c levels in the liraglutide groups were substantially higher than placebo. Liraglutide once daily or a placebo was administered to subjects in a randomized controlled trial. More cases of mild hypoglycemia were seen with liraglutide, although no severe cases were seen. The incidence of gastrointestinal adverse events was greater with liraglutide, although they were often minor and transient. Liraglutide was associated with fewer episodes of persistent nausea and hypoglycemia than exenatide, and HbA1c levels (0.32%) and fasting plasma glucose were improved more so. HbA1c readings were lowered by 1.3% after being on liraglutide for 40 weeks.

The insulin clamp M value was used to determine, these data show that exenatide has a beneficial effect on -cell activity but has no appreciable insulin-sensitizing effects. Nonetheless, Rosiglitazone resulted in an increase in insulin sensitivity that was twice as big as that seen with placebo during the euglycemic insulin clamp (as

evaluated by M/I). When exenatide and rosiglitazone were combined with metformin, weight gain from rosiglitazone was averted, and glycemic control, -cell performance, and insulin sensitivity were all significantly improved.

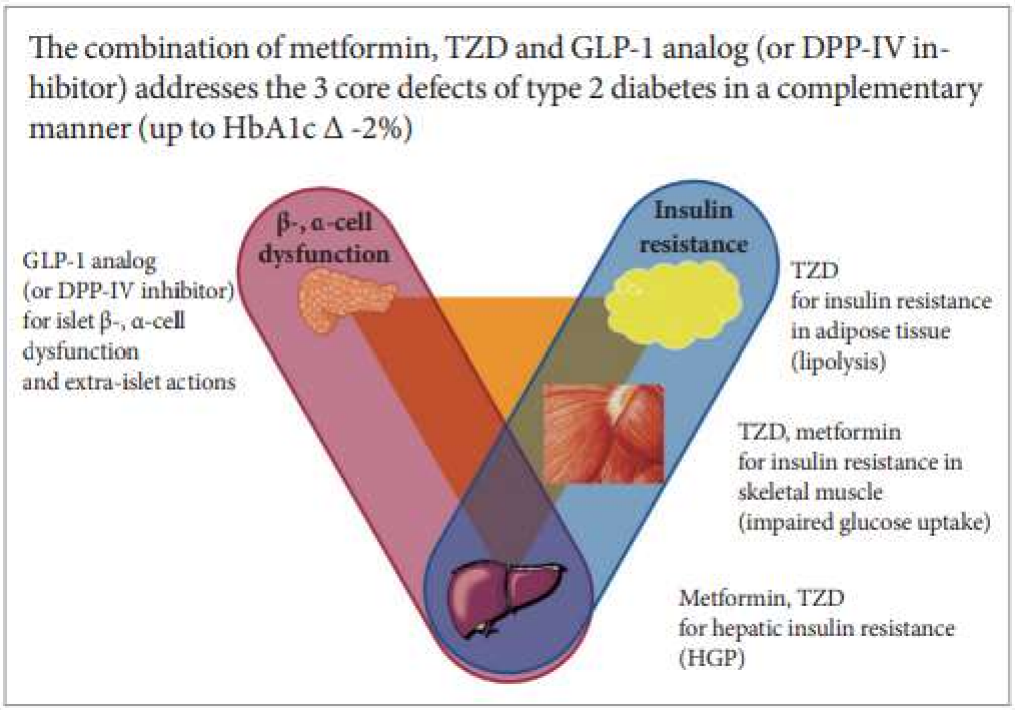

Fig. 1: Treatment of type 2 diabetes mellitus

Monotherapy

The initial clinical trial of vildagliptin compared it to a placebo over the course of 4 weeks and included patients with moderate T2DM. The results indicated that glucagon levels were reduced, which led to better metabolic management as a result of DPP inhibition. Despite the reduced glycemia, insulin levels did not change. Two hundred and seventy-nine individuals with fasting plasma glucose(FPG) between 6.1 and 15 mmol/L and a mean hemoglobin A1c between 6.8 and 10.0% were randomly assigned to receive vildagliptin at varying dosages for 12 weeks in a double-blind, dose-ranging research (25-100 mg daily). Both 50 mg and 100 mg once-daily showed statistically significant decreases in HbA1c compared to placebo. Patients with diabetes who took 100 mg of vildagliptin twice daily for four weeks had improvements in both GLP-1 degradation and -cell function.

A randomized, double-masked study compared vildagliptin monotherapy to placebo in those whose HbA1c was 8.0% on average at baseline. Researchers found that vildagliptin improved glycemic management, with a HbA1c drop of 0.6%. In a 24-week trial, vildagliptin monotherapy at 100 mg qd or 50 mg bid was safe and similarly effective in treating type 2 diabetes in persons who were previously untreated. After 50 mg of vildagliptin once daily, there was a substantial reduction in HbA1c, fasting plasma glucose, and postprandial plasma glucose compared to the placebo group. Patients with impaired fasting glucose were given a placebo for 2 weeks, then vildagliptin for 6 weeks, and finally the placebo for 2 weeks to assess the efficacy of vildagliptin treatment. Those with IFG who took 100 mg of vildagliptin once day saw improvements in cell function and insulin sensitivity.

Combination therapy

Vildagliptin is an effective addition to other treatments for lowering blood sugar levels. On average, the patients had been taking metformin for 29 months before to the study. During a 40-week extension period, those using placebo and metformin had a monthly rise in HbA1c of 0.066%, whereas those on vildagliptin and metformin saw an increase of just 0.013%. Adding vildagliptin to metformin treatment successfully prevented glycemic control from worsening, the research found In order to evaluate vildagliptin's impact on -cell function and insulin sensitivity, researchers needed more than a year. There were a total of 57 individuals who saw the research through to its conclusion; took vildagliptin and metformin, and 26 took metformin and a placebo. In addition, the vildagliptin/metformin group had considerably higher post-meal insulin sensitivity than the placebo/metformin group.

Adding 50 or 100 mg of vildagliptin to pioglitazone 45 mg once day was compared to placebo in a separate trial of 463 individuals with an average baseline HbA1c of 8.7%. HbA1c decreased by 1.1% in the 100mg group, 0.8% in the 50mg group, and only 0.3% in the placebo group after 12 weeks of daily vildagliptin treatment. Over the course of 24 weeks, the effects of insulin therapy, vildagliptin, and placebo were compared. Insulin did not effectively control the patients' blood sugar levels. Researchers found that whereas insulin alone lowered HbA1c by 0.2%, adding vildagliptin decreased it by 0.7%.

CONCLUSION

In newly diagnosed individuals with type 2 diabetes mellitus, therapy with metformin/sulfonylurea according to the ADA's stepwise approach has been demonstrated to be ineffective in achieving sustained glucose control. When taken alone, however, TZDs and GLP-1 analogs have shown to be more effective than combination therapies. While more research is needed, it is reasonable to assume that the combination will have an even more long-lasting impact on preserving -cell activity and lowering HbA1c levels. TZDs and GLP-1 analogs, in contrast to sulfonylurea and metformin, have been demonstrated to maintain -cell function. Nevertheless, insulin sensitizers and GLP-1 analogs seldom cause hypoglycemia, enabling doctors to use higher doses of these medicines to bring down HbA1c levels to below 6.0%. Finally, sulfonylurea and insulin treatment are both linked with weight increase, whereas GLP-1 analogs not only prevent the weight gain associated with TZDs, but also produce weight loss.

REFERENCES

1) Nishida, Y., Takahashi, Y., Tezuka, K. et al. (2017), Comparative effect of dipeptidyl-peptidase 4 inhibitors on laboratory parameters in patients with diabetes mellitus. BMC Pharmacol Toxicol **21**, 28. https://doi.org/10.1186/s40360-020-00407-4
2) Alam, F., Islam, M.A., Mohamed, M. et al. (2019), Efficacy and Safety of Pioglitazone Monotherapy in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Sci Rep **9**, 5389. https://doi.org/10.1038/s41598-019-41854-2
3) A.J. Scheen (2011), DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials, Diabètes & Métabolism, vol. 15
4) Cai, X., Gao, X., Yang, W. et al. (2018), Efficacy and Safety of Initial Combination Therapy in Treatment-Naïve Type 2 Diabetes Patients: A Systematic Review and Meta-analysis. Diabetes Ther **9**, 1995–2014. https://doi.org/10.1007/s13300-018-0493-2
5) Salahuddheen, K (2012) Emerging Role of Mono & Combination Therapy of Vildagliptin in Assessing the Safety & Efficacy in Type-2 Diabetic Patients. Masters thesis, College of Pharmacy, JKK Munirajah Medical Research Foundation, Komarapalayam.

6) Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee on behalf of the LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes [published online June 13, 2016]. N Engl J Med. 2016. doi:10.1056/NEJMoa1603827.
7) Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. Cardiovascular Therapeutics 2014; 32:147-58.
8) Chen C, Yu Q, Zhang S, Yang P, Wang C-Y. Assessing the efficacy and safety of combined DPP-4 inhibitor and insulin treatment in patients with type 2 diabetes: a meta-analysis. International Journal of Clinical and Experimental Pathology 2015; 8:14141-50
9) Gross JL, Kramer CK, Leitão CB, et al; Diabetes and Endocrinology Meta-analysis Group (DEMA). Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med. 2011;154(10):672-679.
10) Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154(9):602-613.
11) Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128.
12) Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-784.
13) Schernthaner G, Barnett AH, Patel S, Hehnke U, von Eynatten M, Woerle HJ. Safety and efficacy of the dipeptidyl peptidase-4 inhibitor linagliptin in elderly patients with type 2 diabetes: a comprehensive analysis of data from 1331 individuals aged >/= 65 years. Diabetes Obes Metab 2014; 16:1078-86.
14) Arjona Ferreira JC, Marre M, Barzilai N, Guo H, Golm GT, Sisk CM, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderateto-severe chronic renal insufficiency. Diabetes Care 2013; 36:1067-73.
15) Liu Y, Hong T. Combination therapy of dipeptidyl peptidase-4 inhibitors and metformin in type 2 diabetes: rationale and evidence. Diabetes Obes Metab 2014; 16:111-7.