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Triple Combination Therapy Using Metformin, Thiazolidinedione, and a GLP-1 Analog or DPP-IV Inhibitor in Patients with Type 2 Diabetes Mellitus

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Although there is no HbA1c threshold for cardiovascular risk, the American Diabetic Association-recommended goal of HbA1c < 7.0% appears to be unacceptably high. To achieve an optimal HbA1c level goal of 6.0% or less, a high dosage of sulfonylureas and insulin would be required; the trade-off would be the common adverse effects of hypoglycemia and weight gain. In contrast, hypoglycemia is uncommon with insulin sensitizers and GLP-1 analogs, allowing the physician to titrate these drugs to maximum dosage to reduce HbA1c levels below 6.0% and they have been shown to preserve β-cell function. Lastly, weight gain is common with sulfonylurea and insulin therapy, whereas GLP-1 analogs induce weight loss and offset the weight gain associated with TZDs. A treatment paradigm shift is recommended in which combination therapy is initiated with diet/exercise, metformin (which has antiatherogenic effects and improves hepatic insulin sensitivity), a TZD (which improves insulin sensitivity and preserves β-cell function with proven durability), and a GLP-1 analog (which improves β, α-cell function and promotes weight loss) or a dipeptidyl peptidase IV inhibitor in patients with type 2 diabetes mellitus.

Keywords: Diabetes mellitus; Glucagon-like peptide 1; Metformin; Thiazolidinediones

INTRODUCTION

Beta cell failure and peripheral insulin resistance are the basic pathophysiologic defects of type 2 diabetes mellitus. Many studies, including the United Kingdom Prospective Diabetes Study (UKPDS), Steno-2, Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Veterans Affairs Diabetes Trial (VADT) have demonstrated the limited efficacy of antidiabetic agents in terms of durability of blood glucose control and reduction in cardiovascular mortality. Antidiabetic agents also have their own treatment barriers, such as hypoglycemia and weight gain, which may be partly responsible for increased cardiovascular risk, especially in the late stages of type 2 diabetes mellitus.

An early and proactive approach to treating patients with type 2 diabetes mellitus using a triple combination of metformin, thiazolidinedione (TZD), and a glucagon-like peptide-1 (GLP-1) analog (or dipeptidyl peptidase IV [DPP-IV] inhibitor) is presented here. The goal of this treatment is to target insulin resistance in the liver and muscle and islet dysfunction, and to cover the basic defects and shortcomings of the stepwise American Diabetes Association (ADA)'s theoretical treatment algorithm. Basic clinical investigations and studies substantiating the suggestion of a paradigm shift in the treatment of type

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2 diabetes mellitus will also be discussed briefly.

LIMITED EFFICACY OF METFORMIN AND SULFONYLUREA

The UKPDS clearly demonstrated that sulfonylureas had no protective effect on progressive β-cell failure in newly-diagnosed type 2 diabetic patients over the 15-year study duration [1]. Moreover, sulfonylureas were shown not to have a significant protective effect against atherosclerotic cardiovascular complications, and some studies even gave notion that sulfonylureas may accelerate the atherogenic process [2]. Similarly, metformin-treated patients also experienced a progressive deterioration in glycemic control [3]. Although, metformin was shown to reduce macrovascular events in the UKPDS, evidence that metformin actually modifies β-cell deterioration or reduces cardiovascular risk is very limited. The relentless rise in hemoglobin A1c (HbA1c) levels observed with both sulfonylureas and metformin resulted from a progressive decline in β-cell function, and by 3 years, approximately 50% of diabetic patients required an additional pharmacological agent to maintain HbA1c levels below 7.0%. Although the add-on treatment improved glycemic control, after the initial decline in HbA1c concentrations, progressive β-cell failure continued and HbA1c values rose progressively. Thus, most clinical evidence shows that the glucose-lowering effect of sulfonylureas and metformin is not durable and that the loss of glycemic control is associated with progressive β-cell failure.

Metformin is traditionally known for its metabolic effects on the liver; and other metformin target tissues include skeletal muscle and adipose tissue. Metformin is a useful adjuvant to lifestyle modification in overweight and obese patients with type 2 diabetes mellitus, metabolic syndrome, or impaired glucose tolerance (IGT). AMP-activated protein kinase (AMPK), a serine–threonine kinase that functions as an intracellular energy sensor, has been involved in the molecular mechanisms of metformin's actions in the liver, muscle, endothelium, and the ovaries [4]. Although metformin failure may occur rapidly in clinical practice, initiating treatment soon after diabetes diagnosis and while HbA1c levels are low might preserve β-cell function, prolonging the effectiveness of metformin.

DURABILITY OF GLUCOSE CONTROL WITH THIAZOLIDINEDIONE

The best evidence that retardation or arrest of β-cell loss can be achieved comes from interventions that reduce excess body adiposity or change its biology. Weight loss in the Diabetes Prevention Program and the Finnish Diabetes Prevention Study was associated with ongoing reductions in the rate of type 2 diabetes mellitus each year. This pattern would be expected if weight loss were slowing, or even stopping, the progression of β-cell deterioration. The same phenomenon has been observed repeatedly with TZDs, which change lipid distribution and adipose-tissue biology to ameliorate some adverse metabolic effects of obesity, including insulin resistance.

There are five studies in subjects with IGT demonstrating that TZDs prevent the progression of IGT to type 2 diabetes mellitus. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication study showed a 62% decrease in the development of type 2 diabetes mellitus with rosiglitazone, while the Actos Now for Prevention of Diabetes study showed an 81% reduction in the conversion of IGT to type 2 diabetes mellitus with pioglitazone. All five of these studies showed that, in addition to their insulin sensitizing effect, TZDs have a major action to preserve β-cell function. Many *in vivo* and *in vitro* studies with human and rodent islets have shown that TZDs exert a protective effect on β-cell function. Direct measurement of β-cell function in the Troglitazone in Prevention of Diabetes and Pioglitazone in Prevention of Diabetes studies proved that TZDs can slow or even stop the loss of β-cell function. The mechanism appeared to be a reduction in the secretory demand for insulin that occurs when insulin resistance is treated [5].

In contrast to the sulfonylureas, eight long-term (> 1.5 years), active-comparator or double-blind placebo-controlled studies with TZDs present a very different picture [6-8]. After an initial decline in HbA1c levels, durability of glycemic control is maintained because of the preservation of β-cell function in type 2 diabetes mellitus patients.

EFFICACY AND SAFETY OF GLP-1 ANALOGS

Incretins have been shown to improve β-cell function and maintain durability of glycemic control. In addition, the GLP-1 analogs exenatide and liraglutide consistently lower body weight, and, in some studies, have favorable cardiovascular benefits, including lowering blood pressure, beneficial effects on serum lipids, and the potential to improve myocardial contractility and endothelial function (effects seen with GLP-1 infusions) (Table 1) [9]. Bunck et al. [10] demonstrated improved beta cell function in patients treated with exenatide compared with a glargine-treated group. First and second phase insulin

Table 1. Extraglycemic effects of glucagon-like peptide-1 receptor agonists (From Mudaliar S, Henry RR. Am J Med 2010;123(3 Suppl):S19-27, with permission from Elsevier.) [9]

Target tissue	Effects	Potential benefits
Pancreatic β-cell	↑ β-cell proliferation (seen so far only in animal/*in vitro* studies)	Long-term durability of glycemic effect
	↓ β-cell apoptosis (seen so far only in animal/*in vitro* studies)	Potential for prevention/delay of type 2 diabetes
Cardiovascular system	↑ Myocardial contractility Improved endothelial funtion	↓ Cardiovascular morbidity and mortality
	↓ Systolic and diastolic blood pressure Improved serum lipid levels	
Liver	↓ Gluconeogenesis and glycogenolysis (seen so far only in animal/*in vitro* studies)	Improved hepatic sensitivity
	↓ Lever fat	Improved glycemic control ↓ Progression/regression of nonalcoholic fatty liver disease
Body weight	↓ Body weight	Improvements in glycemia, blood pressure and serum lipids

secretion and C-peptide response to a hyperglycemic clamp were measured before and after 1 year of treatment; insulin secretion increased 1.5- and 2.9-fold, respectively, and glargine increased the ratio of the C-peptide response during the hyperglycemic clamp by 31%. In contrast, exenatide increased the ratio more than threefold.

The addition of exenatide to metformin and/or sulfonylurea treatment for 3 years in type 2 diabetes mellitus patients resulted in sustained improvements in glycemic control, cardiovascular risk factors, and hepatic biomarkers, coupled with progressive weight reduction. A subset of these subjects was followed-up on for 3.5 years, and the decline in HbA1c levels was shown to persist [11].

In addition to their effects on β- and α-cells, GLP-1 analogs reduce hepatic glucose production, appetite, and gastric motility, which are responsible for weight loss. More importantly, stimulation of insulin secretion and suppression of glucagon by exenatides is strictly dependent on plasma glucose concentrations, thereby minimizing the adverse effect of hypoglycemia. The expectation that incretin therapy may not only improve β-cell function but also increase β-cell mass in patients with type 2 diabetes mellitus was not substantiated, in marked contrast to findings in rodents [12].

SUGGESTIVE EXTRA-ISLET ACTION OF DPP-IV INHIBITORS

Although there are no studies of the long-term efficacy of DPP-IV inhibitors on β-cell function, in short-term studies ranging from several months to 1 year, both sitagliptin and vildagliptin

demonstrated a reduction in postprandial plasma glucose concentrations while maintaining plasma insulin response, indicating a positive effect on β-cell function [13-15]. But this enhancement in insulin secretion does not necessarily mean preservation of β-cell function on a long-term basis. DPP-IV inhibitors also decrease glucagon secretion, and in concert with a rise in plasma insulin, lead to a reduction in basal hepatic glucose production [16]. Hypoglycemia does not occur with the DPP-IV inhibitors, but they do not suppress appetite or cause weight loss.

It is well known that GLP-1 (7-36) (and GLP-1 [7-37]) is a primary insulinotropic hormone on the β-cell mediated by the G-protein coupled receptor, GLP-1R, which activates cAMP-dependent PKA and PI3 kinase-dependent Akt signal pathways. GLP-1 (9-36) amide (and GLP-1 [9-37]) is the cleavage product of GLP-1 (7-36) amide (and GLP-1 [7-37]) formed by DPP-IV within minutes. Those cleavage products (GLP-1 [7-36] amide) have only weak insulinotropic agonist activities on the GLP-1 receptor; however, they also have extra-islet actions, such as suppression of hepatic glucose production, antioxidant cardioprotection, and reduction of oxidative stress in vascular tissues through binding to another receptor. Tomas and Habener [17] recently suggested a dual receptor hypothesis, which describes two hypothetical cell signaling pathways by which GLP-1 and its cleavage product exert insulinomimetic actions on insulin-sensitive target tissues. Prolonged inhibition of DPP may prevent the formation of GLP-1 (9-36) amide, and might ultimately augment oxidative stress in the heart, vasculature, and liver, and promote hepatic glucose production,

which would be undesirable in the treatment of obesity-related diabetes. Therefore, potent, short-acting DPP-IV inhibitors taken at meal time might provide brief stimulation of insulin secretion by increasing levels of insulinotropic GLP-1 (7-36) amide, allowing escape from DPP-IV inhibition and the intermittent production of insulinomimetic GLP-1 (9-36) amide during interprandial periods. However, no clinical evidence exists demonstrating better outcomes using potent, short-acting DPP-IV inhibitors instead of longer-acting DPP-IV inhibitors, nor has there been a large study on the efficacy of the cleavage products of GLP-1 (7-36) (and GLP-1 [9-37]).

COMBINATION OF THIAZOLIDINEDIONE AND DPP-IV INHIBITOR (Table 2)

In 175 patients (placebo group, n = 178) with type 2 diabetes mellitus who had not achieved adequate glycemic control with pioglitazone alone, 100 mg Sitagliptin was added once daily

for 24 weeks. The addition resulted in effective glycemic control (between-treatment difference in least squares mean change from baseline, -0.70%) and the changes were well tolerated, with no increased risk of hypoglycemia compared with the placebo (2 vs. 0 patients, respectively) [18].

A 24-week, multicenter, double-blind, randomized, parallel-group study comparing the effects of vildagliptin (50 or 100 mg daily) with a placebo as an add-on therapy to pioglitazone (45 mg daily) was conducted with 463 patients with type 2 diabetes mellitus that was inadequately controlled by prior TZD monotherapy. The patients showed an adjusted mean change (AMΔ) in HbA1c levels, from baseline to endpoint, of −0.8 ± 0.1% (P = 0.001 vs. placebo) and −1.0 ± 0.1% (P < 0.001 vs. placebo), for daily dosages of 50 and 100 mg of vildagliptin, respectively. Mild hypoglycemia was reported by 0, 0.6, and 1.9% of patients receiving vildagliptin 50 mg/day, 100 mg/day, or a placebo, respectively [19].

Table 2. Summaries of selected clinical trials on combination of exenatide, liraglutide, sitaglipitin and vildagliptin with TZD/metformin (From Chia CW, Egan JM. J Clin Endocrinol Metab 2008;93:3703-16, with permission from The Endocrine Society.) [30]

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]

w/wo, with/without; PLB, placebo; RDPC, randomized, double-blind, placebo-controlled; RADC, randomized double-blind, active-controlled.
[a]Between-treatment difference vs. PLB group.

A previous study compared the efficacy and tolerability of an initial combination therapy with vildagliptin/pioglitazone to component monotherapy [20]. The first-line treatment with vildagliptin/pioglitazone (both high- and low-dose regimens) provided better glycemic control than each component monotherapy with minimal hypoglycemia. The high-dose combination (100/30 mg qd) allowed 65% of patients to achieve target HbA1c levels (< 7%), with a tolerability profile comparable with pioglitazone (30 mg qd) monotherapy. The low-dose combination (50/15 mg qd) provided both efficacy and tolerability benefits over pioglitazone 30 mg qd. By addressing complementary mechanisms, the initial combination of vildagliptin and pioglitazone appears to be an effective means of achieving good glycemic control while attenuating drug-related adverse effects.

Another study evaluated the efficacy and safety of alogliptin in type 2 diabetes mellitus patients with a mean duration of 7.6 years and inadequate glycemic control using therapy with a thiazolidinedione and metformin/sulfonylurea. This study demonstrated a significant improvement in glycemic control after 26 weeks without clinically significant effects on the incidence of hypoglycemia, which occurred most often in patients who also were taking a sulfonylurea [21].

Recently, Gupta et al. [22] observed that the GIP receptor contains a functional PPAR-γ response element in the promoter region of the gene in INS-1 cells. Interventions that decreased or increased PPAR-γ activity (including exposure to a thiazolidinedione) resulted in corresponding changes in GIP receptor expression in *in vivo* rat models. Solomon et al. [23] suggested improved beta cell function following lifestyle-induced weight loss may partly be mediated by enhanced GIP secretion and action in older, obese, diabetic subjects. Whether treating patients with type 2 diabetes mellitus with a thiazolidinedione will enhance incretin effects mediated by GIP is not known, but is an intriguing possibility [24].

TRIPLE COMBINATION - METFORMIN, THIAZOLIDINEDIONE AND GLP-1 ANALOGS (Table 2)

Exenatide 10 μg bid therapy for 6 weeks improved glycemic control (mean difference, −0.98%), reduced body weight (mean difference, −1.51 kg), and caused gastrointestinal symptoms more than placebo in 233 patients (exenatide group 121, placebo group 112) with type 2 diabetes mellitus that was suboptimally controlled with TZD ± metformin [25].

A triple combination therapy of liraglutide, metformin, and TZD for 26 weeks in 533 subjects (1:1:1) randomized to once-daily liraglutide (1.2 or 1.8 mg) or liraglutide placebo in combination with metformin (1 g twice daily) and rosiglitazone (4 mg twice daily) demonstrated significantly greater mean ΔHbA1c values in the liraglutide groups versus placebo (mean ± SE, −1.5 ± 0.1% for both 1.2 and 1.8 mg liraglutide and −0.5 ± 0.1% for placebo). Minor hypoglycemia occurred more frequently with liraglutide, but there was no major hypoglycemia. Gastrointestinal adverse events were more common with liraglutide, but most occurred early in the study period and were transient. Investigators concluded that the triple combination of liraglutide, metformin, and TZD is an effective and safe treatment for patients with type 2 diabetes mellitus [26]. In a 14-week extension study of Liraglutide Effect and Action in Diabetes 6 trial, patients switched from 10 μg twice-daily exenatide to 1.8 mg liraglutide once-daily or 40 weeks of continued liraglutide. Liraglutide improved HbA1c levels (Δ 0.32%), fasting plasma glucose, and homeostasis model of β-cell function values more so than exenatide, with less persistent nausea and hypoglycemia. Over 40 weeks, liraglutide reduced HbA1c levels by 1.3% [27].

A 20-week study to observe the effects of exenatide plus rosiglitazone on β-cell function and insulin sensitivity using hyperglycemic and euglycemic insulin clamp techniques in type 2 diabetes mellitus patients currently taking metformin has been conducted [28]. Exenatide and rosiglitazone significantly improved the *M* value at 20 weeks ($P < 0.05$), while exenatide had no significant effect on insulin-stimulated glucose disposal. After 80 to 90 minutes of the hyperglycemic clamp the disposition index increased significantly and similarly with exenatide and rosiglitazone (both $P < 0.001$) but not with rosiglitazone [28]. These results demonstrate that exenatide has a positive influence on β-cell function but does not exert any significant insulin–sensitizing action, as determined by the *M* value during the insulin clamp. Rosiglitazone, however, caused a two-fold increase in insulin sensitivity, measured as M/I during the euglycemic insulin clamp. Conclusively, therapy with exenatide and rosiglitazone, in addition to metformin, offset the weight gain observed with rosiglitazone and elicited an additive effect on glycemic control with significant improvements in β-cell function and insulin sensitivity.

CONCLUSION

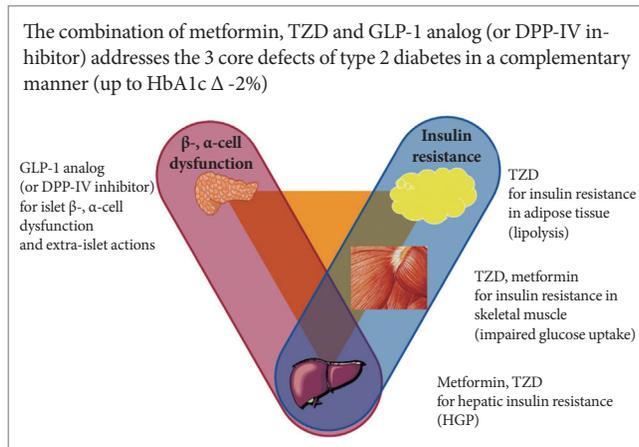The stepped ADA algorithm of metformin/sulfonylurea thera-

Fig. 1. Treatment of type 2 diabetes mellitus: a therapeutic approach based upon pathophysiology.

py in type 2 diabetes mellitus has been proven ineffective in achieving durable glycemic control even in newly-diagnosed patients. However, TZDs and GLP-1 analogs, when used as monotherapy, have been shown to have a more durable effect. When used in combination, one would expect an even more durable effect on preservation of β-cell function and reduction in HbA1c levels, although this remains to be proven in a longer-term study. In contrast to sulfonylurea and metformin, both TZDs and GLP-1 analogs have been shown to preserve β-cell function. Although there is no HbA1c threshold for cardiovascular risk, the ADA-recommended goal of HbA1c < 7.0% appears to be unacceptably high. To achieve an optimal HbA1c level goal of 6.0% or less, a high dosage of sulfonylureas and insulin would be required; the trade-off would be the common adverse effects of hypoglycemia and weight gain. In contrast, hypoglycemia is uncommon with insulin sensitizers and GLP-1 analogs, allowing the physician to titrate these drugs to maximum dosage to reduce HbA1c levels below 6.0%. Lastly, weight gain is common with sulfonylurea and insulin therapy, whereas GLP-1 analogs induce weight loss and offset the weight gain associated with TZDs.

A treatment paradigm shift is recommended in which combination therapy is initiated with diet/exercise, metformin (which has antiatherogenic effects and improves hepatic insulin sensitivity), a TZD (which improves insulin sensitivity and preserves β-cell function with proven durability), and a GLP-1 analog (which improves β, α-cell function and promotes weight loss) or a DPP-IV inhibitor (Fig. 1) [29,30].

REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

2. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia 2006;49:930-6.

3. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65.

4. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol 2010;162:193-212.

5. Buchanan TA, Xiang AH. Diabetes: preventing type 2 diabetes mellitus: is metformin the answer? Nat Rev Endocrinol 2010; 6:253-4.

6. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.

7. Hanefeld M, Pfutzner A, Forst T, Lubben G. Glycemic control and treatment failure with pioglitazone versus glibenclamide in type 2 diabetes mellitus: a 42-month, open-label, observational, primary care study. Curr Med Res Opin 2006;22:1211-5.

8. Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Komajda M, Curtis P; RECORD Study Group. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med 2007;24:626-34.

9. Mudaliar S, Henry RR. Effects of incretin hormones on beta-cell mass and function, body weight, and hepatic and myocardial function. Am J Med 2010;123(3 Suppl):S19-27.

10. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Jarvinen H, Heine RJ. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care 2009;32:762-8.

11. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Hol-

combe JH, Wintle ME, Maggs DG. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin 2008;24:275-86.

12. Menge BA, Tannapfel A, Belyaev O, Drescher R, Muller C, Uhl W, Schmidt WE, Meier JJ. Partial pancreatectomy in adult humans does not provoke beta-cell regeneration. Diabetes 2008; 57:142-9.

13. Drucker DJ. The biology of incretin hormones. Cell Metab 2006;3:153-65.

14. Ahren B, Pacini G, Foley JE, Schweizer A. Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. Diabetes Care 2005; 28:1936-40.

15. Deacon CF. Dipeptidyl peptidase 4 inhibition with sitagliptin: a new therapy for type 2 diabetes. Expert Opin Investig Drugs 2007;16:533-45.

16. Balas B, Baig MR, Watson C, Dunning BE, Ligueros-Saylan M, Wang Y, He YL, Darland C, Holst JJ, Deacon CF, Cusi K, Mari A, Foley JE, DeFronzo RA. The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. J Clin Endocrinol Metab 2007;92:1249-55.

17. Tomas E, Habener JF. Insulin-like actions of glucagon-like peptide-1: a dual receptor hypothesis. Trends Endocrinol Metab 2010;21:59-67.

18. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2006;28:1556-68.

19. Garber AJ, Schweizer A, Baron MA, Rochotte E, Dejager S. Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. Diabetes Obes Metab 2007;9:166-74.

20. Rosenstock J, Kim SW, Baron MA, Camisasca RP, Cressier F, Couturier A, Dejager S. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:175-85.

21. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q; Alo-gliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 2009;25:2361-71.

22. Gupta D, Peshavaria M, Monga N, Jetton TL, Leahy JL. Physiologic and pharmacologic modulation of glucose-dependent insulinotropic polypeptide (GIP) receptor expression in beta-cells by peroxisome proliferator-activated receptor (PPAR)-gamma signaling: possible mechanism for the GIP resistance in type 2 diabetes. Diabetes 2010;59:1445-50.

23. Solomon TP, Haus JM, Kelly KR, Rocco M, Kashyap SR, Kirwan JP. Improved pancreatic beta-cell function in type 2 diabetic patients after lifestyle-induced weight loss is related to glucose-dependent insulinotropic polypeptide. Diabetes Care 2010;33:1561-6.

24. Pratley RE. GIP: an inconsequential incretin or not? Diabetes Care 2010;33:1691-2.

25. Zinman B, Hoogwerf BJ, Duran Garcia S, Milton DR, Giaconia JM, Kim DD, Trautmann ME, Brodows RG. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2007;146: 477-85.

26. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, Hale PM, Zdravkovic M, Blonde L; LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+ TZD). Diabetes Care 2009;32:1224-30.

27. Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, Blonde L, Rosenstock J; Liraglutide Effect Action in Diabetes-6 Study Group. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care 2010;33: 1300-3.

28. DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Maggs D, Glass LC. Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. Diabetes Care 2010;33:951-7.

29. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773-95.

30. Chia CW, Egan JM. Incretin-based therapies in type 2 diabetes mellitus. J Clin Endocrinol Metab 2008;93:3703-16.