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BRIEF ARTICLE

Comparison between sitagliptin and nateglinide on postprandial lipid levels: The STANDARD study

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Abstract

AIM: To assess the effects of sitagliptin and nateglinide on lipid metabolism.

METHODS: In a parallel group comparative open trial, patients with type 2 diabetes mellitus under treatment at the Japanese Red Cross Medical Center were randomly assigned to receive either sitagliptin (50 mg once daily) or nateglinide (90 mg three times daily before meals). Eligible patients met the following criteria: age ⩾ 20 years; hemoglobin A_{1c} (HbA_{1c}) > 6.5% despite diet and exercise; HbA_{1c} between 6.5% and 8.0%; fasting glucose < 7.77 mmol/L; diet and exercise therapy for more than 3 mo; and ability to read and understand the information for written informed consent. Exclusion criteria were contraindications to sitagliptin, contraindications to nateglinide, pregnancy or possible pregnancy, and severe liver/renal failure. Patients who were considered to be unsuitable by the attending physician for other reasons were also excluded. Blood samples were collected at one and three hours after intake of a test meal. The primary outcome measure was the area under the curve (AUC) of apolipoprotein (Apo) B48 at three hours postprandially.

RESULTS: Twenty patients were randomly assigned to the sitagliptin group and sixteen patients were randomized to the nateglinide group. All 36 patients took the medication as directed by the physician in both groups, and they all were analyzed. Apart from antidiabetic drugs, there was no difference between the two groups with respect to the frequency of combined use of lipid-lowering, antihypertensive, and/or antiplatelet drugs. The doses of these medications were maintained during 12 wk of treatment. Detailed dietary advice, together with adequate exercise therapy, was given to the patients so that other factors apart from the two test drugs were similar in the two groups. There were no significant differences of the baseline characteristics between the two groups, except for body mass index (the sitagliptin group: 25.14 ± 3.05 kg/m^2; the nateglinide group: 21.39 ± 2.24 kg/m^2). Fasting levels of HbA_{1c}, glycated albumin, 1.5-anhydroglucitol, and blood glucose, as well as the blood glucose levels at one and three hours postprandially, improved in both groups after 12 wk of treatment, and there were no significant differences between the two groups. However, the glucagon level at one hour postprandially (P = 0.040) and the diastolic blood pressure (P < 0.01) only showed a significant decrease in the sitagliptin group. In the nateglinide group, there was no significant change in the AUC of Apo B48, the glucagon level at one hour postprandially, the fasting triglyceride level, or the diastolic blood pressure. Body weight was unchanged in both groups. However, the AUC of Apo B48 at three hours postprandially showed a significant decrease in the sitagliptin group from 2.48 ± 0.11 at baseline to 1.94 ± 0.78 g/L per hour after 12 wk (P = 0.019). The fasting triglyceride level also decreased significantly in the sitagliptin group (P

= 0.035). With regard to lipid-related markers other than Apo B48 and fasting triglycerides, no significant changes were observed with respect to Apo A1, Apo B, or Apo C3 in either group. No adverse events occurred in either group.

CONCLUSION: Sitagliptin significantly improves some lipid parameters while having a comparable effect on blood glucose to nateglinide. A large-scale prospective study of sitagliptin therapy is warranted.

Key words: Dipeptidyl-peptidase 4 inhibitors; Type 2 diabetes mellitus; Sitagliptin; Nateglinide; Blood glucose; Lipid metabolism

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INTRODUCTION

When treating diabetes mellitus, prevention of major vascular disorders is an important objective[1-9]. Several studies have demonstrated that postprandial hyperglycemia (PPHG) is significantly linked to major vascular disorders[10-16]. In an *in vitro* study of human vascular endothelial cells, the cellular death rate was increased by repeated fluctuation between normoglycemia and hyperglycemia compared with that due to persistent hyperglycemia[17]. These findings suggest that inhibition of circadian glycemic changes may prevent vascular disorders[18,19].

Postprandial hyperlipidemia (PPHL) has been noted in patients with type 2 diabetes. Inhibition of lipoprotein lipase activity due to impaired insulin action on adipocytes and an increase of exogenous lipoproteins due to overeating are considered to be the underlying causes of PPHL. PPHL may trigger progression of arteriosclerosis with the accumulation of chylomicron remnants in the vessel walls. An epidemiological study of Japanese patients has shown that hypertriglyceridemia is an independent risk factor for coronary artery disorders[20].

Nateglinide, a *D*-phenylalanine derivative, rapidly stimulates insulin secretion to exert an antihyperglycemic effect and treatment with nateglinide inhibits carotid artery intima-media thickening, which is a surrogate marker of arteriosclerosis[21]. On the other hand, the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin increases insulin secretion by inhibiting breakdown of incretins, thereby exerting an antihyperglycemic effect. The efficacy of sitagliptin for PPHL has also been reported[22,23]. However, it is unknown whether this improvement of PPHL is due to suppression of postprandial glycemia or an increase of incretin secretion secondary to inhibition of DPP-4.

In the present study, we treated type 2 diabetic patients with nateglinide or sitagliptin for 12 wk. The response to a test meal was assessed to compare the effects of the two drugs on PPHG and PPHL.

MATERIALS AND METHODS

Study population

Patients with type 2 diabetes attending the Japanese Red Cross Medical Center (JRCMC) between July 2010 and June 2011 were enrolled in this parallel group comparative open trial. Eligible patients met the following criteria: age ⩾ 20 years; hemoglobin A_{1c} (HbA_{1c}) > 6.5% despite diet and exercise; HbA_{1c} between 6.5% and 8.0%; fasting glucose < 7.77 mmol/L; diet and exercise therapy for more than 3 mo; and ability to read and understand the information for written informed consent. Exclusion criteria were contraindications to sitagliptin, contraindications to nateglinide, pregnancy or possible pregnancy, and severe liver/renal failure. We also excluded patients who were considered to be unsuitable by the attending physician for other reasons. As many patients as possible were registered because it was difficult to set a specific sample size for this exploratory clinical study and relevant information was limited.

Randomization

Random allocation of patients to either treatment group was performed centrally by using our registration system, with the random allocation sequence being generated by Kojima Y. Enrollment was done by Kojima Y, Kaga H and Kitazawa T, while assignment of participants to interventions was carried out by Iimura Y, Ohno M, Yoshitsugu M and Hiyoshi T.

Study treatment

Sitagliptin was administered at a dose of 50 mg once daily before breakfast to one group, while nateglinide was administered at a dose of 90 mg three times daily (immediately before each meal) to the other group. Doses of antihypertensive and lipid-lowering drugs were not changed during the study.

Data collection

Blood samples were collected before and one and three hours after eating a test meal (total energy: 1925 kJ; protein: 18.0 g, fat: 18.0 g, carbohydrate: 56.5 g), both before treatment and after the 12-wk treatment period (final date: September 30, 2011). Then the levels of various parameters of glucose and lipid metabolism were measured.

Outcome measures

The primary outcome was the area under the concentration *vs* time curve (AUC) of apolipoprotein (Apo) B48 at three hours postprandially after 12 wk of treatment. The secondary outcomes were postprandial blood glucose, HbA_{1c}, glucagon at one hour postprandially, fasting triglycerides, and blood pressure.

Table 1 Baseline patient profile and post-treatment data

	Sitagliptin group		Nateglinide group	
	Before treatment	After 3 mo of treatment	Before treatment	After 3 mo of treatment
Age (yr)	63.85 ± 12.92	-	66.44 ± 9.02	-
Sex: M/F (*n*)	15/5	15/5	12/4	12/4
Body weight (kg)	68.79 ± 12.89[1]	69.30 ± 13.18	58.36 ± 8.54	58.75 ± 8.52
Systolic blood pressure (mmHg)	134.3 ± 19.3	126.5 ± 11.1	129.1 ± 13.9	122.7 ± 14.8
Diastolic blood pressure (mmHg)	81.5 ± 12.9	73.3 ± 7.4[b]	76.9 ± 8.8	74.3 ± 10.2
HbA_{1c} (%)	7.2 ± 0.7	7.0 ± 0.8[b]	7.2 ± 0.4	6.8 ± 0.5[b]
Glycated albumin (%)	19.3 ± 3.6	17.7 ± 2.6[b]	19.9 ± 3.4	18.1 ± 2.8[b]
1.5-AG (μmol/L)	65.5 ± 45.8	81.6 ± 46.2[b]	51.0 ± 22.7	69.5 ± 29.3[b]
Fasting blood glucose (mmol/L)	7.8 ± 1.7	7.3 ± 1.6	8.1 ± 1.0	7.6 ± 1.5
Blood glucose 1 h postprandially (mmol/L)	12.0 ± 3.0	10.6 ± 3.1[b]	13.6 ± 2.3	11.0 ± 2.8[b]
Blood glucose 3 h postprandially (mmol/L)	7.6 ± 2.5	6.6 ± 2.0[b]	7.6 ± 2.5	6.5 ± 1.9[a]
Apo-B48 AUC (g/L per hour)	2.48 ± 0.11	1.94 ± 0.78[a]	3.14 ± 0.29	2.29 ± 0.16
Apo-A1 AUC (g/L per hour)	4.64 ± 0.73	4.50 ± 0.76	4.59 ± 0.73	4.67 ± 0.76
Apo-B AUC (g/L per hour)	2.73 ± 0.47	2.91 ± 0.46	2.60 ± 0.46	2.64 ± 0.40
Apo-C3 AUC (g/L per hour)	0.30 ± 0.07	0.28 ± 0.06	0.31 ± 0.11	0.28 ± 0.09
Fasting insulin (pmol/L)	53.3 ± 26.9	58.4 ± 34.4	41.3 ± 29.0	40.4 ± 31.5
Insulin 1 h postprandially (μU/mL)	279.3 ± 115.7	275.1 ± 143.4	230.1 ± 104.2	248.7 ± 112.2
Fasting glucagon (ng/L)	67.2 ± 15.9	66.6 ± 16.0	65.1 ± 16.4	70.1 ± 16.0
Glucagon 1 h postprandially (ng/L)	80.3 ± 17.0	70.3 ± 16.9[a]	79.0 ± 13.4	81.5 ± 20.6
Fasting triglycerides (mmol/L)	1.26 ± 0.81	1.09 ± 0.61[a]	1.54 ± 1.44	1.11 ± 0.60

[1]This parameter showed a significant between-group difference ($P < 0.05$) before treatment. Data are shown as the mean ± SD ([a]$P < 0.05$, [b]$P < 0.01$ *vs* time curve). Area under the concentration *vs* time curve (AUC) data were obtained from before to three hours after the test meal. The *t* test was used for statistical analysis. M: Male; F: Female; 1.5-AG: 1.5-anhydroglucitol; Apo: Apolipoprotein; HbA_{1c}: Hemoglobin A_{1c}.

Ethical considerations

This study was approved by the Ethical Committee of the JRCMC and was conducted according to the principles specified in the Helsinki Declaration. Prior to its initiation, we registered this study with the UMIN Clinical Trials Registry (www.umin.ac.jp; registration number UMIN000006278), as the sitagliptin and nateglinide randomized clinical trial (STANDARD study). All patients provided informed consent and participated in the study on a voluntary basis.

Statistical analysis

For intragroup and intergroup comparisons, we employed the paired *t* test and *t* test, respectively. All analysis were carried out by using SAS software version 8.02 (SAS Institute, Cary, NC, United States), and $P < 0.05$ was considered statistically significant.

RESULTS

Twenty patients were randomly assigned to the sitagliptin group and sixteen patients were randomized to the nateglinide group. All 36 patients took the medication every day as directed by the physician in both groups, and they all were available for analysis. Apart from antidiabetic drugs, there was no difference between the two groups with respect to the frequency of combined use of lipid-lowering, antihypertensive, and/or antiplatelet drugs (statins in 6 and 7 patients from the sitagliptin group and the nateglinide group, respectively; angiotensin receptor blockers in 6 and 3 patients; and calcium channel blockers in 1 and 2 patients). The doses of these medications were maintained during 12 wk of treatment. Detailed dietary advice, together with adequate exercise therapy, was given to the patients by diabetologists, nurses, and dieticians who belonged to the JRCMC, so that other factors apart from the two test drugs were similar in the two groups.

Table 1 summarizes the baseline and post-treatment data. There were no significant differences of the mean age, sex ratio, HbA_{1c}, 1.5-anhydroglucitol (1.5-AG), glycated albumin, Apo A1, Apo B, Apo B48, Apo C3, fasting triglycerides, postprandial blood glucose, insulin, and glucagon levels. However, the baseline body mass index was higher in the sitagliptin group than in the nateglinide group (25.14 ± 3.05 kg/m^2 *vs* 21.39 ± 2.24 kg/m^2).

Fasting levels of HbA_{1c}, glycated albumin, 1.5-AG and blood glucose, as well as the blood glucose levels at one and three hours postprandially, improved in both groups after 12 wk of treatment, and there were no significant differences between the two groups. However, the glucagon level at one hour postprandially ($P = 0.040$) and the diastolic blood pressure ($P < 0.01$) only showed a significant decrease in the sitagliptin group. In the nateglinide group, there was no significant change in the AUC of Apo B48, the glucagon level at one hour postprandially, the fasting triglyceride level, or the diastolic blood pressure. Body weight was unchanged in both groups. However, the AUC of Apo B48 at three hours postprandially showed a significant decrease in the sitagliptin group from 2.48 ± 0.11 g/L at baseline to 1.94 ± 0.78 g/L per hour after 12 wk ($P = 0.019$). The fasting triglyceride level also decreased significantly in the sitagliptin group ($P = 0.035$). With regard to lipid-related markers other than Apo B48 and fasting triglycerides, no significant changes were observed with respect to Apo A1, Apo B, or Apo C3 in either group.

No adverse events, including hypoglycemia, gastrointestinal side effects, pancreatitis, infection, immune abnormalities, liver dysfunction, renal dysfunction, and cardiac dysfunction, occurred in either group.

DISCUSSION

The present study showed that two oral antidiabetic drugs with different mechanisms of action similarly improved postprandial glycemia and significantly decreased the levels of HbA_{1c}, glycated albumin, and 1.5-AG. With regard to lipid metabolism, however, a significant decrease of fasting triglycerides and of the postprandial AUC for Apo B48, a marker of chylomicrons and chylomicron remnants (exogenous lipids), only occurred in the sitagliptin group. There was no change of the AUC for Apo B (endogenous lipids) in either group.

Tremblay *et al*[23] investigated postprandial changes of lipoproteins after administration of sitagliptin for 6 wk and reported a significant decrease of triglyceride-rich lipoproteins (both Apo B and Apo B48), suggesting that sitagliptin reduced the levels of endogenous and exogenous lipids. In contrast, our study showed that Apo B did not decrease after 12 wk of treatment with sitagliptin, while Apo B48 decreased significantly. This difference may be explained by different conditions of the two studies, including the lipid and calorie contents of the test meals. Apo C3 is related to inhibition of lipoprotein lipase activity in hepatic cells, and it showed no significant change in either group, which suggests that the Apo C3-related pathway for synthesis of endogenous lipids was not affected by either medication. In the sitagliptin group, it is thought that inhibition of gastrointestinal peristalsis leads to reduced absorption of triglycerides and decreased Apo B48 synthesis.

Lee *et al*[24] investigated the serum glucagon levels of healthy individuals and patients with impaired glucose tolerance or type 2 diabetes and reported that the differences between these groups were maximal at one hour postprandially. In the present study, a significant decrease of the serum glucagon level at one hour postprandially was only noted in the sitagliptin group, suggesting that sitagliptin and nateglinide have differing effects on glucagon. In addition, the influence of glucagon on postprandial lipid levels requires further investigation.

Nateglinide has been reported to improve PPHG through its insulinotropic action, and nateglinide treatment caused no appreciable changes of serum lipid levels in this study. The emphasis of treatment for type 2 diabetes has shifted from simple correction of fasting and PPHG to management of dyslipidemia as well. Because sitagliptin inhibits both PPHG and PPHL, it may be useful for the prevention of macrovascular disease in patients with diabetes[25-29], but a large-scale prospective study would be required for confirmation.

This study had the following limitations: (1) small sample sizes (20 and 16 per group, respectively); (2) unequal baseline body weights of the two groups; and (3) a short follow-up period of 3 mo. Accordingly, our results have limited generalizability and a large-scale long-term study is needed to verify our findings.

In conclusion, our randomized controlled trial showed that suppression of triglycerides and postprandial Apo B48 only occurred in the sitagliptin group, although PPHG was similarly improved in both the sitagliptin and nateglinide groups. To best of our knowledge, this is the first report to confirm the efficacy of a DPP-4 inhibitor for improving postprandial hyperlipidemia while achieving a comparable improvement of blood glucose to the control drug. A large-scale prospective study of sitagliptin therapy is needed.

COMMENTS

Background

There have been some reports about the efficacy of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, for postprandial hyperlipidemia in patients with type 2 diabetes. However, it is unknown whether this improvement of postprandial hyperlipidemia is due to suppression of postprandial glycemia or an increase of incretin secretion secondary to inhibition of DPP-4.

Research frontiers

Nateglinide, a *D*-phenylalanine derivative, rapidly stimulates insulin secretion to exert its antihyperglycemic effect. Sitagliptin was the first incretin enhancer approved in Japan (in 2009) and it increases insulin secretion by inhibiting the breakdown of incretins, unlike nateglinide. It remains unclear which of these two drugs is more effective for improving postprandial hyperlipidemia and hyperglycemia.

Innovations and breakthroughs

This is the first study to demonstrate that sitagliptin significantly improves some lipid parameters while having a comparable effect on blood glucose to nateglinide, with a decrease of triglycerides and apolipoprotein (Apo) B48 only being observed in patients receiving sitagliptin.

Applications

By understanding and utilizing the response to sitagliptin demonstrated in this study, treatment of diabetes could be better tailored and macrovascular disease may also be prevented because sitagliptin inhibits both postprandial hyperglycemia and postprandial hyperlipidemia.

Terminology

DPP-4 inhibitors, of which sitagliptin was the first to be released in Japan, inhibit the enzyme DPP-4 and are used to treat type 2 diabetes. Apo B is the major component of the apolipoproteins, which serve as enzyme cofactors, receptor ligands, and lipid carriers that regulate the metabolism of lipoproteins and their tissue uptake.

Peer review

In this 12-wk trial, the authors tested the effects of sitagliptin and nateglinide on metabolic markers in 36 patients with type 2 diabetes (n = 20 and n = 16, respectively). While postprandial blood glucose and hemoglobin A_{1c} improved in both groups, only sitagliptin improved the lipid profile at 1 or 3 h postprandially. Although its small size is a major limitation of this study, the results provide some interesting information about the metabolic effects of these two drugs in diabetic patients.

REFERENCES

1 **Ohkubo Y**, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; **28**: 103-117 [PMID: 7587918 DOI: 10.1016/0168-8227(95)01064-K]

2 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk

of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837-853 [PMID: 9742976 DOI: 10.1016/S0140-6736(98)07019-6]

3 **Holman RR**, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577-1589 [PMID: 18784090 DOI: 10.1056/NEJMoa0806470]

4 **Gerstein HC**, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545-2559 [PMID: 18539917 DOI: 10.1056/NEJMoa0802743]

5 **Duckworth W**, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129-139 [PMID: 19092145 DOI: 10.1056/NEJMoa0808431]

6 **Patel A**, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560-2572 [PMID: 18539916 DOI: 10.1056/NEJMoa0802987]

7 **Griffin SJ**, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbæk A, Sharp SJ, Simmons RK, van den Donk M, Wareham NJ, Lauritzen T. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 2011; **378**: 156-167 [PMID: 21705063 DOI: 10.1016/S0140-6736(11)60698-3]

8 **Ray KK**, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; **373**: 1765-1772 [PMID: 19465231]

9 **Mannucci E**, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis* 2009; **19**: 604-612 [PMID: 19427768]

10 Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 1999; **354**: 617-621 [PMID: 10466661 DOI: 10.1016/S0140-6736(98)12131-1]

11 **Mukai N**, Doi Y, Ninomiya T, Hata J, Yonemoto K, Iwase M, Iida M, Kiyohara Y. Impact of metabolic syndrome compared with impaired fasting glucose on the development of type 2 diabetes in a general Japanese population: the Hisayama study. *Diabetes Care* 2009; **32**: 2288-2293 [PMID: 19729523 DOI: 10.2337/dc09-0896]

12 **Cavalot F**, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, Anfossi G, Trovati M. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 2011; **34**: 2237-2243 [PMID: 21949221 DOI: 10.2337/dc10-2414]

13 **Sorkin JD**, Muller DC, Fleg JL, Andres R. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care* 2005; **28**: 2626-2632 [PMID: 16249530 DOI: 10.2337/diacare.28.11.2626]

14 **Shiraiwa T**, Kaneto H, Miyatsuka T, Kato K, Yamamoto K, Kawashima A, Kanda T, Suzuki M, Imano E, Matsuhisa M, Hori M, Yamasaki Y. Post-prandial hyperglycemia is an important predictor of the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients. *Biochem Biophys Res Commun* 2005; **336**: 339-345 [PMID: 16140262 DOI: 10.1016/j.bbrc.2005.08.158]

15 **Esposito K**, Giugliano D, Nappo F, Marfella R. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 2004; **110**: 214-219 [PMID: 15197140 DOI: 10.1161/01.CIR.0000134501.57864.66]

16 **Hanefeld M**, Koehler C, Schaper F, Fuecker K, Henkel E, Temelkova-Kurktschiev T. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis* 1999; **144**: 229-235 [PMID: 10381296 DOI: 10.1016/S0021-9150(99)00059-3]

17 **Risso A**, Mercuri F, Quagliaro L, Damante G, Ceriello A. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. *Am J Physiol Endocrinol Metab* 2001; **281**: E924-E930 [PMID: 11595647]

18 **Chiasson JL**, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care* 1998; **21**: 1720-1725 [PMID: 9773737 DOI: 10.2337/diacare.21.10.1720]

19 **Hanefeld M**, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke* 2004; **35**: 1073-1078 [PMID: 15073402 DOI: 10.1161/01.STR.0000125864.01546.f2]

20 **Iso H**, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M, Komachi Y. Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol* 2001; **153**: 490-499 [PMID: 11226981 DOI: 10.1093/aje/153.5.490]

21 **Mita T**, Watada H, Shimizu T, Tamura Y, Sato F, Watanabe T, Choi JB, Hirose T, Tanaka Y, Kawamori R. Nateglinide reduces carotid intima-media thickening in type 2 diabetic patients under good glycemic control. *Arterioscler Thromb Vasc Biol* 2007; **27**: 2456-2462 [PMID: 17872451 DOI: 10.1161/ATVBAHA.107.152835]

22 **Hsieh J**, Longuet C, Baker CL, Qin B, Federico LM, Drucker DJ, Adeli K. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. *Diabetologia* 2010; **53**: 552-561 [PMID: 19957161 DOI: 10.1007/s00125-009-1611-5]

23 **Tremblay AJ**, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. *Diabetes Obes Metab* 2011; **13**: 366-373 [PMID: 21226820 DOI: 10.1111/j.1463-1326.2011.01362.x]

24 **Lee S**, Yabe D, Nohtomi K, Takada M, Morita R, Seino Y, Hirano T. Intact glucagon-like peptide-1 levels are not decreased in Japanese patients with type 2 diabetes. *Endocr J* 2010; **57**: 119-126 [PMID: 19881250 DOI: 10.1507/endocrj.K09E-269]

25 **Monami M**, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011; **27** Suppl 3: 57-64 [PMID: 22106978]

26 **Monami M**, Lamanna C, Desideri CM, Mannucci E. DPP-4 inhibitors and lipids: systematic review and meta-analysis. *Adv Ther* 2012; **29**: 14-25 [PMID: 22215383 DOI: 10.1007/s12325-011-0088-z]

27 **Gallwitz B**, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, Dugi KA, Woerle HJ. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* 2012; **380**: 475-483 [PMID: 22748821 DOI: 10.1016/S0140-6736(12)60691-6]

28 **Frederich R**, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, Chen R, Wolf R, Mahaffey KW. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med* 2010; **122**: 16-27 [PMID: 20463410 DOI: 10.3810/pgm.2010.05.2138]

29 **Williams-Herman D**, Engel SS, Round E, Johnson J, Golm GT, Guo H, Musser BJ, Davies MJ, Kaufman KD, Goldstein BJ. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. *BMC Endocr Disord* 2010; **10**: 7 [PMID: 20412573]

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