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Effect of Linagliptin on Glycemic Control in Chinese Patients with Newly-Diagnosed, Drug-Naïve Type 2 Diabetes Mellitus: A Randomized Controlled Trial

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Background: This study aimed to evaluate the efficacy and safety of linagliptin (a novel dipeptidyl peptidase (DPP)-4 inhibitor) on glucose metabolism and β-cell function in Chinese patients with newly-diagnosed, drug-naïve type 2 diabetes mellitus (T2DM).

Material/Methods: Newly-diagnosed and drug-naïve T2DM patients were enrolled. After 4-week lifestyle modulation and 2-week placebo run-in, 57 patients were randomized to double-blind treatment with linagliptin (n=34) or placebo (n=23). The primary endpoint was the change from baseline in glycosylated hemoglobin A1c (HbA1c) after 24 weeks. Fasting plasma glucose (FPG), 2-h postprandial plasma glucose (2h-PPG), fasting insulin, proinsulin-to-insulin ratio, homeostasis model assessment of insulin resistance (HOMA-IR), and homeostasis model assessment of β-cell function (HOMA-β) were also evaluated.

Results: Baseline characteristics were similar between the 2 groups. Compared with placebo, linagliptin therapy resulted in a significant decrease in HbA1C (–1.2±0.7% *vs.* –0.4±0.4%, P<0.001), FBG (–0.98±1.17 *vs.* –0.32±0.51 mmol/L, P=0.011, and 2h-PPG (–2.02±0.94 *vs.* –0.97±0.63 mmol/L, P<0.001). Significant differences were observed for the proinsulin/insulin ratio (P<0.001) and HOMA-β index (P=0.001). Rates of adverse events were similar between the 2 groups (30.3% *vs.* 27.3%). All adverse events were mild. One patient discontinued participation due to pregnancy.

Conclusions: Linagliptin treatment resulted in a significant and clinically meaningful improvement of glycemic control in drug-naïve Chinese patients with T2DM, as well as improved parameters of β-cell function. Linagliptin had an excellent safety profile.

MeSH Keywords: Diabetes Mellitus, Type 2 • Patients • Randomized Controlled Trial

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Background

Diabetes imposes a high burden on modern society, and type 2 diabetes mellitus (T2DM) accounts for 90% of all cases [1]. T2DM affects about 380 million people worldwide [1], including about 100 million individuals in China, where the prevalence in people >20 years old is estimated to be up to 9.7% [2]. Many patients with T2DM remain inadequately managed, which results in progressively declining glycemic control [3].

Oral antidiabetic drugs (OADs) present multiple drawbacks such as treatment-limiting adverse effects, including hypoglycemia, gastrointestinal (GI) disorders, edema, and weight gain [4]. In addition, sulfonylureas may also lead to declined estimated glomerular filtration rate (eGFR), end-stage renal disease (ESRD), or even death [5].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are the most recently developed OADs, with a unique mechanism of action that increases endogenous glucagon-like peptide (GLP)-1 levels, thereby promoting glucose-dependent insulin secretion via pancreatic β-cells, reducing glucagon secretion via α-cells, suppressing appetite, and delaying gastric emptying [6].

Linagliptin is a new DPP-4 inhibitor that is primarily excreted via the bile, improving its renal safety [7]. Several large studies from Asia and other continents have demonstrated clinically meaningful improvements in glycemic control, enhanced β-cell function, and a good safety profile of linagliptin 5 mg alone or in combination with other OADs [8–12]. In a Chinese study, when combined with sulfonylureas and metformin, placebo-corrected changes in HbA1c induced by linagliptin were –0.7±0.14%, and changes in fasting plasma glucose (FPG) reached –1.0 mmol/L [13]. When combined with metformin in Chinese patients, placebo-corrected changes in HbA1c induced by linagliptin were –0.52±0.09% [12]. In Chinese patients with T2DM, high postprandial plasma glucose (PPG) levels are frequent because the traditional Chinese diet is rich in carbohydrates (rice and flour) [14]. Metformin mainly decreases FPG, while DPP-4 mainly inhibits PPG [15]. Therefore, DPP-4 inhibitors could be more efficient in Chinese patients consuming a traditional Chinese diet.

However, there is a lack of data about linagliptin monotherapy in Chinese patients with newly diagnosed T2DM. Therefore, this randomized, double-blind, parallel-group trial was carried out to examine the efficacy and safety of linagliptin as initial therapy in treatment-naïve Chinese patients with newly-diagnosed T2DM.

Material and Methods

Study design

This randomized, placebo-controlled, double-blind study was carried out in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice, the Declaration of Helsinki, and relevant Chinese laws/regulations. The trial was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and all patients provided written informed consent before participation. This study was carried out at the First Affiliated Hospital of Wenzhou Medical University (China).

Patients

Fifty-seven individuals diagnosed with T2DM at the outpatient department were enrolled in this trial from September 2013 to January 2014. All patients were treatment-naïve before enrollment except for diet and physical exercise therapy. T2DM was diagnosed according to the WHO T2DM diagnostic criteria: FPG ≤13.3 mmol/L, baseline HbA1c 7.0–10.0%, body mass index (BMI) of 20–35 kg/m^2, and age 18–80 years. Patients with type 1 diabetes, secondary diabetes, acute complications of diabetes, myocardial infarction, stroke, unstable angina, and coronary artery bypass graft (CABG) in the past 6 months were excluded from the trial. Patients with congestive heart failure (CHF), impaired hepatic function (serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase level exceeding twice the upper limit of normal), thyroid disorders, chronic intestinal tract disorders, and a history of acute pancreatitis or pancreatic tumor were also excluded from the study, as well as fertile women not using contraceptives.

Design and methods

All patients received health education before run-in. Patients were randomized to linagliptin (n=34) or placebo (n=23) after a 2-week placebo run-in period using a computer-generated random sequence and sealed envelopes prepared in advance. The assigned medication number was entered in the case report form, and the corresponding medication kit was given to the patient. The kits were prepared by the pharmacists, who had no contact with the patients. Using this procedure, both the participants and investigators were blinded to treatment allocation. The patients took 1 tablet per day, either linagliptin (Boehringer Ingelheim, Germany) or linagliptin-matching placebo. The placebo tablets were identical in appearance to the linagliptin 5 mg tablet. In the event of a medical emergency requiring the identification of an individual patient's treatment, investigators were able to have access to the information. The efficacy and tolerability of the treatment were assessed at 6, 12, 18, and 24 weeks.

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Physical examination was performed on all patients by medical professionals at each follow-up. Vitals, height, weight, waist circumference, and hip circumference were recorded at each visit. HbA1c and FPG levels were assessed at each visit. At 0, 12, and 24 weeks, tests evaluating liver and kidney functions, blood lipid profiles, uric acid, urine, and blood amylase were performed. At 0 and 24 weeks, electrocardiogram (ECG), 2-h PPG (2h-PPG) levels, fasting insulin levels, and proinsulin were assessed. In addition, we evaluated the plasma proinsulin/insulin ratios, the homeostasis model assessment indices for insulin resistance (HOMA-IR), and homeostasis model assessment indices for beta-cell function (HOMA-β). HOMA-IR=FPG (mmol/L)× fasting insulin (mIU/L)/22.5 [16]. HOMA-β=20× fasting insulin (mmol/L)/[FPG (mmol/L)–3.5].

All test results were provided by the Clinical Laboratory Center of the First Affiliated Hospital of Wenzhou Medical University. Patients were also invited to disclose any discomfort they may have been suffering from. Thereafter, based on the physical examinations, laboratory tests, and patients' discomforts, AEs were defined and categorized.

All medication bottles were returned to assess patient medication compliance: medication compliance%=(dispensed medication-returned medication)/ dispensed medication ×100.

Study endpoints

The primary endpoint was the change from baseline in HbA1c levels with linagliptin *vs.* placebo treatments at week 24. Secondary endpoints included changes from baseline FPG and 2h-PPG values. Exploratory endpoints included changes in fasting plasma proinsulin/insulin ratio, HOMA-IR, HOMA-β, body weight, blood pressure, plasma lipid levels, plasma creatinine and aminotransferase amounts, and amylase levels. Safety and tolerability were assessed by the incidence of adverse events (AEs) throughout the study period, and clinically relevant changes or findings in physical, vitals, ECG, and laboratory assessments. Hypoglycemia was defined according to American Diabetes Association guidelines [17].

Statistical analyses

A sample size of 50 randomized patients was planned (25 subjects in each group), assuming a 15% drop-out rate. This would provide 80% power to detect a mean difference of 0.7% [standard deviation (SD) of 0.8%] in the change from baseline in HbA1c levels between the linagliptin and placebo groups at week 24, at a 2-sided significance level of 0.05.

Data are presented as mean ±SD. Analysis of covariance (ANCOVA) was used to assess the differences between the 2 groups. The χ^2 test was used to assess the difference in clinical adverse events. Data analysis was carried out using SPSS 19.0 (IBM, Armonk, NY, USA). P values <0.05 were considered significant.

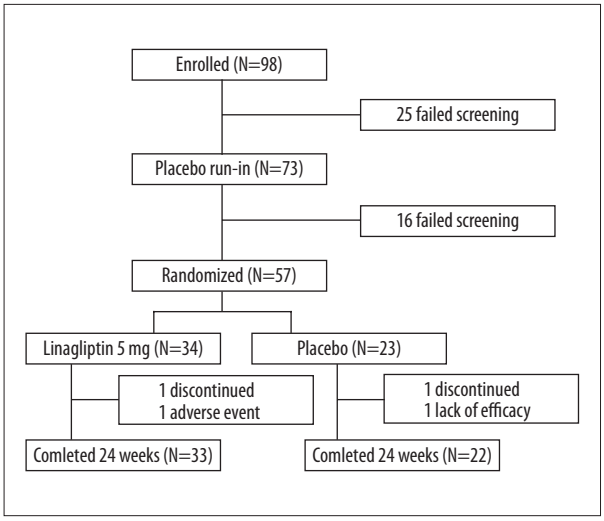

Figure 1. Patient flowchart.

Results

Characteristics of the patients

A total of 98 patients were screened; 73 entered the placebo run-in period and 57 were randomized to study treatment (linagliptin 5 mg, n=34; placebo, n=23). Thirty-three patients completed treatment in the linagliptin group and 22 in the placebo group. One patient discontinued treatment with linagliptin for incidental pregnancy, and 1 withdrew for lack of efficacy in the placebo group (Figure 1). Table 1 presents the demographic and baseline characteristics of the patients. There was no difference in any of the variables between the 2 groups.

Primary endpoint

Table 2 presents the biochemical variables after 24 weeks of treatment. HbA1c levels in the placebo group were 7.59±0.53%, and there were lower in the linagliptin group (6.77±0.67%; P<0.001) (Table 2).

Secondary endpoints and exploratory endpoints

After 24 weeks of treatment, compared with the placebo group, those who received linagliptin showed lower levels of FPG (linagliptin: 6.75±0.86 mmol/L; placebo: 7.43±1.00 mmol/L; P=0.001), 2h-PPG (linagliptin: 8.32±0.68 mmol/L; placebo: 9.24±0.63 mmol/L; P<0.001), and the proinsulin-to-insulin ratio (0.21±0.03 *vs.* 0.22±0.03, P=0.002) (Table 2). There was no

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Table 1. Baseline characteristics and parameters between the two study groups.

	Placebo	Linagliptin	*P*
Age (years)	51.2±7.5	52.5±11.0	0.610
Male (%)	50	65.7	0.239
Body weight (kg)	65.24±8.45	67.05±8.12	0.422
BMI (kg/m^2)	24.11±2.28	24.37±2.09	0.668
FPG (mmol/L)	7.75±1.32	7.79±1.52	0.859
PPG (mmol/L)	10.21±0.84	10.34±1.23	0.563
HbA1c (%)	8.00±0.69	7.97±0.68	0.884
TC (mmol/L)	4.41±0.72	4.67±0.79	0.364
HDL-C (mmol/L)	1.07±0.12	1.09±0.15	0.650
LDL-C (mmol/L)	2.46±0.56	2.63±0.60	0.091
TG (mmol/L)	1.71±0.59	1.75±0.43	0.778
HOMA-IR	2.91±0.92	2.76±1.01	0.595
HOMA-β	42.11±26.42	41.41±13.13	0.800
SBP (mmHg)	133.65±11.91	136.60±13.55	0.465
DBP (mmHg)	81.39±6.96	81.00±5.69	0.818
AST (U/L)	25.61±4.33	24.18±4.56	0.312
ALT (U/L)	26.13±6.55	26.15±6.87	0.878
sCr (μmol/L)	68.59±10.35	72.56±11.07	0.160
Amylase (U/L)	67.25±12.56	69.09±16.99	0.454
P/I	0.23±0.03	0.24±0.04	0.102

BMI – body mass index; FPG – fasting plasma glucose; PPG – postprandial plasma glucose; HbA1c – hemoglobin A1c; TC – total cholesterol; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglyceride; HOMA-IR – homeostasis model assessment insulin resistance; HOMA-β – homeostasis model assessment β-cell index; SBP – systolic blood pressure; DBP – diastolic blood pressure; AST – aspartate aminotransferase; ALT – alanine aminotransferase, sCr – serum creatine.

difference in the other variables such as body weight, lipid profile, blood pressure, liver markers, and amylase.

Safety

The rates of AEs with linagliptin were comparable to those of placebo after 24 weeks (linagliptin: 30.3%; placebo: 27.3%) (Table 3). No serious adverse events (SAEs) occurred during the study. In the linagliptin group, 3 hypoglycemic events occurred in 1 patient, with self-reported capillary blood glucose levels of 3.5 mmol/L, 3.7 mmol/L, and 3.7 mmol/L. The symptoms were relieved after eating. No hypoglycemic events occurred in the placebo group.

The most common type of AE was upper respiratory tract infections (URTI). There were 3 cases of URTI with linagliptin 5 mg and 2 with the placebo, all of which were mild. No significant difference was found in weight or BMI in either group at baseline and after 24 weeks (P>0.05). In addition, there was no difference in abnormal laboratory tests between the 2 groups. No meaningful difference between treatment groups was observed in changes in serum creatinine, alanine aminotransferase, aspartate aminotransferase, blood amylase, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels (all P>0.05). There was no clinically meaningful change in ECG or vitals after linagliptin treatment. No patients discontinued the trial medication due to AEs.

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Table 2. Outcomes after 24 weeks of treatment with linagliptin or placebo.

	Placebo	Linagliptin	*P*
HbA1c (%)	7.59±0.53	6.77±0.67	<0.001*
Body weight (kg)	64.55±7.60	66.79±8.36	0.399
FPG (mmol/L)	7.43±1.00	6.75±0.86	0.001*
PPG (mmol/L)	9.24±0.63	8.32±0.68	<0.001*
TC (mmol/L)	4.65±0.62	4.63±0.74	0.231
HDL-C (mmol/L)	1.06±0.13	1.08±0.14	0.805
LDL-C (mmol/L)	2.45±0.58	2.61±0.63	0.231
TG (mmol/L)	1.74±0.45	1.77±0.60	0.933
HOMA-IR	2.91±0.88	2.61±1.10	0.284
HOMA-β	46.10±21.50	52.49±16.58	0.090
SBP (mmHg)	130.09±10.18	129.06±13.09	0.556
DBP (mmHg)	79.85±4.44	78.42±4.94	0.134
AST (U/L)	25.52±8.10	24.22±7.05	0.954
ALT (U/L)	24.05±6.40	26.51±7.19	0.172
sCr (μmol/L)	69.56±7.31	73.34±13.90	0.395
Amylase (U/L)	69.33±14.38	71.06±17.11	0.916
P/I	0.22±0.03	0.21±0.03	0.002*

BMI – body mass index; FPG – fasting plasma glucose; PPG – postprandial plasma glucose; HbA1c – hemoglobin A1c; TC – total cholesterol; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglyceride, HOMA-IR – homeostasis model assessment insulin resistance; HOMA-β – homeostasis model assessment β-cell index; SBP – systolic blood pressure; DBP – diastolic blood pressure; AST – aspartate aminotransferase; ALT – alanine aminotransferase; sCr – serum creatine.

Table 3. Adverse effects in the linagliptin and placebo groups over 24 weeks.

	Linagliptin 5 mg (n=33)		Placebo (n=22)	
Number of patients having ≥1 AE	10	(30.3)	6	(27.3)
AEs (any cause)				
Hypoglycemia	1	(3.0)	0	(0.0)
Upper respiratory infection	3	(9.1)	2	(9.1)
GI	3	(9.1)	1	(4.5)
Renal or urinary	1	(3.0)	0	(0.0)
Musculoskeletal and connective tissue	1	(3.0)	1	(4.5)
Nervous system	0	(0.0)	1	(4.5)
Skin and subcutaneous tissue	1	(3.0)	1	(4.5)

AE – adverse event; GI – gastrointestinal. All data are presented as n (%). * Determined by the investigator as possibly, probably or definitely drug-related.

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Discussion

In this 24-week study assessing newly-diagnosed T2DM and drug-naïve Chinese patients, linagliptin monotherapy achieved significantly higher reductions in HbA1c levels than placebo, and showed an overall safety profile similar to that of the placebo. The absolute change in HbA1c was more pronounced than that observed in previous linagliptin studies conducted in Chinese and other Asian populations, in which linagliptin was often used in combination [10–13]. This may be because the subjects included in the present study were all drug-naïve. These results are consistent with other results of DPP-4 inhibitors' effects on HbA1c levels in Asian patients with T2DM inadequately controlled by diet and exercise [18].

Linagliptin was shown to modulate the fasting proinsulin-to-insulin ratio, indicative of β-cell function. The findings corroborated the increased availability of endogenous GLP-1, as observed with other DPP-4 inhibitors [19,20].

Blood pressure was reduced in the linagliptin group, with systolic blood pressure decreasing from 136.60±13.55 mmHg to 129.06±13.09 mmHg, while diastolic pressure ranged from 81.00±5.69 mmHg to 78.42±4.94 mmHg. These differences at 24 weeks were significant compared with baseline (data not shown). However, the reduction in blood pressure was similar between the 2 groups. Reduction in systolic and diastolic pressure was likely caused by persistent control of diet and physical exercise in both groups. In addition, the recruitment was conducted in winter, with most participants last observed in summer, and the change in seasons and climate might have contributed to blood pressure reduction [21]. Increases in GLP-1 decreases salt intake and therefore blood pressure [22,23], but the present study was not powered to provide an answer to this issue.

Linagliptin was well tolerated in the present study, with an AE profile similar to that of placebo. Only 1 in 33 patients showed mild hypoglycemia in the linagliptin group. Given the mechanism of action of this agent, linagliptin monotherapy was not associated with an increased risk of hypoglycemia or clinically significant changes in body weight. The common AEs observed in this study were upper respiratory tract infections and GI disorders, consistent with a previous study in Chinese individuals [13]. Pancreatitis is a possible AE with GLP-1 or DPP-4 inhibitor therapy strategies. After 24 weeks of observation, no significant increase in liver and pancreatic enzymes was found, and no patients complained of acute abdominal pain. Therefore, occurrence of pancreatitis is not associated with treatment with linagliptin, in accordance with published reports [24]. However, studies with larger samples are required to correctly assess this issue.

A few limitations of this study need to be addressed. First, the sample size was small, and the age range was wide; this was because we aimed to recruit patients with newly-diagnosed T2DM, and because the prevalence of T2DM in Chinese adults >20 years old is of about 10%. Second, drug-naïve patients with newly-diagnosed T2DM were enrolled, and the results cannot be generalized to individuals who are already being treated. Third, 24 weeks of follow-up does not allow assessment of long-term glycemic control or comprehensive AEs. Finally, this study was carried out in China, and cannot be generalized to the global population. Therefore, linagliptin efficacy on hyperglycemia and prevention of β-cell function deterioration needs to be further investigated in large-scale and long-term studies.

Conclusions

In conclusion, linagliptin 5 mg taken once daily provides superior glycemic control compared with placebo, and has a comparable safety profile in Chinese drug-naïve patients with T2DM. β-cell function improvement makes this molecule a new option for Chinese patients with inadequate control of T2DM and who never received hypoglycemic agents.

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Disclosure

The authors declare that they have no conflicts of interest.

References:

1. Guariguata L, Whiting DR, Hambleton I et al: Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract, 2014; 103: 137–49
2. Yang W, Lu J, Weng J et al: Prevalence of diabetes among men and women in China. N Engl J Med, 2010; 362: 1090–101
3. Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA, 1999; 281: 2005–12
4. Hauber AB, Mohamed AF, Johnson FR, Falvey H: Treatment preferences and medication adherence of people with Type 2 diabetes using oral glucose-lowering agents. Diabet Med, 2009; 26: 416–24
5. Hung AM, Roumie CL, Greevy RA et al: Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int, 2012; 81: 698–706
6. LeRoith D: TSI neLWW, 2000. In: OJM, (ed.), Diabetes Mellitus: A Fundamental and Clinical Text. Philadelphia: Lippincott Williams & Wilkins, 2000
7. Gallwitz B: Linagliptin-a novel dipeptidyl peptidase inhibitor for type 2 diabetes therapy. Clin Med Insights Endocrinol Diabetes, 2012; 5: 1–11

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8. Gallwitz B, Rosenstock J, Rauch T et al: 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: 475–83
9. Barnett AH, Patel S, Harper R et al: Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. Diabetes Obes Metab, 2012; 14: 1145–54
10. Kawamori R, Inagaki N, Araki E et al: Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study. Diabetes Obes Metab, 2012; 14: 348–57
11. Bajaj M, Gilman R, Patel S et al: Linagliptin improved glycaemic control without weight gain or hypoglycaemia in patients with type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: a 24-week randomized, double-blind study. Diabet Med, 2014; 31: 1505–14
12. Wang W, Yang J, Yang G et al: Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: A multinational 24-week, randomized clinical trial. J Diabetes, 2015 [Epub ahead of print]
13. Zeng Z, Yang JK, Tong N et al: Efficacy and safety of linagliptin added to metformin and sulphonylurea in Chinese patients with type 2 diabetes: a sub-analysis of data from a randomised clinical trial. Curr Med Res Opin, 2013; 29: 921–29
14. Villegas R, Liu S, Gao YT et al: Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med, 2007; 167: 2310–16
15. Doupis J, Veves A: DPP4 inhibitors: a new approach in diabetes treatment. Adv Ther, 2008; 25: 627–43
16. Matthews DR, Hosker JP, Rudenski AS et al: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985; 28: 412–19
17. Seaquist ER, Anderson J, Childs B et al: Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care, 2013; 36: 1384–95
18. Mohan V, Yang W, Son HY et al: Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India, and Korea. Diabetes Res Clin Pract, 2009; 83: 106–16
19. Del Prato S, Barnett AH, Huisman H et al: Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab, 2011; 13: 258–67
20. Rosenstock J, Aguilar-Salinas C, Klein E et al: Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. Curr Med Res Opin, 2009; 25: 2401–11
21. Modesti PA: Season, temperature and blood pressure: a complex interaction. Eur J Intern Med, 2013; 24: 604–7
22. Mistry GC, Maes AL, Lasseter KC et al: Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. J Clin Pharmacol, 2008; 48: 592–98
23. Ogawa S, Ishiki M, Nako K et al: Sitagliptin, a dipeptidyl peptidase-4 inhibitor, decreases systolic blood pressure in Japanese hypertensive patients with type 2 diabetes. Tohoku J Exp Med, 2011; 223: 133–35
24. Monami M, Dicembrini I, Mannucci E: Dipeptidyl peptidase-4 inhibitors and pancreatitis risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab, 2014; 16: 48–56

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