Effects of saxagliptin add-on therapy to insulin on blood glycemic fluctuations in patients with type 2 diabetes

A randomized, control, open-labeled trial

Feng-fei Li, PhDa, Lan-lan Jiang, MDa, Reng-na Yan, MDa, Hong-hong Zhu, MDa, Pei-hua Zhou, MDa, Dan-feng Zhang, MDa, Xiao-fei Su, MDa, Jin-dan Wu, MDa, Lei Ye, MD, PhDb, Jian-hua Ma, MD, PhDa,∗

Abstract

Background: To investigate whether saxagliptin add-on therapy to continuous subcutaneous insulin infusion (CSII) further improve blood glycemic control than CSII therapy in patients with newly diagnosed type 2 diabetes (T2D).

Methods: This was a single-center, randomized, control, open-labeled trial. Newly diagnosed T2D patients were recruited between February 2014 and December 2015. Subjects were divided into saxagliptin add-on therapy to CSII group (n=31) and CSII therapy group (n=38). The treatment was maintained for 4 weeks. Oral glucose tolerance test was performed at baseline. Serum samples were obtained before and 30 and 120 minutes after oral administration for glucose, insulin, and C-peptide determination. Continuous glucose monitoring (CGM) was performed before and endpoint.

Results: A total of 69 subjects were admitted. After 4-week therapy, CGM data showed that patients with saxagliptin add-on therapy exhibited further improvement of mean amplitude glycemic excursion (MAGE), the incremental area under curve of plasma glucose >7.8 and 10mmol/L compared with that of control group. In addition, the hourly mean blood glucose concentrations, especially between 0000 and 0600 in patient with saxagliptin add-on therapy, were significantly lower compared with that of the control patients. Furthermore, patients in saxagliptin add-on group needed lower insulin dose to maintain euglycemic control. In addition, severe hypoglycemic episode was not observed from any group.

Conclusion: Saxagliptin add-on therapy to insulin had the ability of further improve blood glycemic controlling, with lower insulin dose required by patients with T2D to maintain euglycemic controlling.

Abbreviations: aGAD = antiglutamic acid decarboxylase, AUC = area under curve, CGM = continuous glucose monitoring, CSII = continuous subcutaneous insulin infusion, CVD = cerebrovascular disease, DPP-4 = dipeptidyl peptidase-4, GIP = glucose-dependent insulinotropic polypeptide, GLP-1 = glucagon-like peptide-1, MAGE = mean amplitude glycemic excursion, MBG = mean blood glucose, MDI = multiple daily injections, MODY = maturity onset diabetes in the young, OGTTs = oral glucose tolerance tests, PPG = postprandial glucose, SD = standard deviation, SURs = sulfonylureas, T2D = type 2 diabetes.

Keywords: add-on therapy, blood glycemic fluctuation, saxagliptin, type 2 diabetes

1. Introduction

Intensive insulin therapy has become common practice in the world to keep blood glucose values in target range in patients with type 2 diabetes (T2D). Intensive insulin therapy consists of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI). Use of CSII therapy is now regarded as a safe and valuable alternative in patients with newly diagnosed...
T2D. Several studies have demonstrated that early implementation of a short course of intensive insulin therapy may dramatically improve beta-cell function in most patients with newly diagnosed T2D. This improvement of beta-cell function might be responsible for the remission described in newly diagnosed T2D patients.[1,2] We recently observed that patients with newly diagnosed or longstanding T2D treated with CSII therapy confers a greater improvement of mean amplitude glycemic excursion (MAGE) as detected by continuous glucose monitoring (CGM).[6] It is now believed that glucose fluctuations may be an important independent risk factor for cardiovascular disease in patients with onset T2D.[7,8] Large glucose fluctuations may cause the overproduction of superoxide by the mitochondrial electron-transport chain, which induces a subsequent nitrosative stress.[9] Postprandial glucose (PPG) is an independent risk factor for cardiovascular disease.[10]

Saxagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, is a novel glucose-lowering agent in patients with T2DM.[11,12] Saxagliptin as a monotherapy in drug-naive T2D patients,[11-15] and add-on therapy in patients with inadequate glycemic control with oral antidiabetic agents or insulin were generally well tolerated and demonstrate significant improvements in glycemic control and a low risk of hypoglycemia.[11] Very recently, saxagliptin add-on metformin plus glitazide therapy achieved further improvement of MAGE in patients with advanced T2DM.[11] Moreover, saxagliptin is associated with the improvement of pancreatic beta-cell function in patients with T2D.[21] The improvement of pancreatic beta-cell function might depend on the reduction of DPP4 activity, which improves insulin signaling.[22]

With this background, a therapy saxagliptin combination with insulin seems to be a promising approach for subjects with T2D to control blood glycemic fluctuations. We therefore performed a single-center, randomized, control, open-labeled trial using CGM to assess the blood glucose fluctuations in T2DM patients, in whom treated with saxagliptin add-on therapy to insulin.

2. Patients and methods

This was a single-center, randomized, control, open-labeled trial. Between January 2014 and December 2015, a total of 69 patients with newly diagnosed T2DM were recruited in the Department of Internal Medicine of the First Hospital, Nanjing Medical University, China. The inclusion criteria were patients aged between 18 and 80 years; 9.0% ≤ HbA1c ≤ 12% at diagnosis. Patients were excluded from analysis if they had ketoacidosis, chronic kidney disease, positive for anti-glutamic acid decarboxylase (aGAD) antibody, or if they had maturity onset diabetes in the young (MODY), or mitochondria diabetes mellitus.[11] Patients with known cancers, known allergies to insulin were excluded.[24] The study was approved by the ethics committee of Nanjing First Hospital. Written informed consent was obtained from the patients before the study.

All patients were randomly assigned into saxagliptin add-on therapy to CSII group and CSII alone group. Subjects underwent oral glucose tolerance tests (OGTTs) using 75 g of glucose (dissolved in 200 mL water) before and after treatment. Serum samples were obtained before and 30 and 120 minutes after oral administration for glucose, insulin, and C-peptide determination. After the baseline parameters were assessed, patient blood concentrations were monitored by CGM (Medtronic Incorporated, Northridge, Minnesota, USA) for 3 days, as we before described.[6,25] After CGM data were collected, enrolled subjects received saxagliptin (5 mg once daily, Bristol-Myers Squibb, Indiana, USA) add-on CSII or CSII treatment, without any oral antidiabetic drugs except metformin. The total daily insulin (Aspart, Novo Nordisk, Bagsværd, Denmark) dose was 0.5 IU/kg which was given in 2 injection modes: 1/3 of total daily dose was equally given as boluses within 3 meals, the remaining insulin was given as basal dose. Investigators titrated insulin doses on an individual-patient basis at the titration algorithm (if the fasting blood glucose level was less than 4.4 mmol/L, the insulin dose was reduced 2 units; if the fasting blood glucose level was within 4.4 to 6.1 mmol/L, the insulin dose was unchanged; if the fasting blood glucose level was within 6.2 to 7.8, 7.9 to 10.0, and >10.0 mmol/L, the insulin dose was increased subsequently by 2, 4, and 6 units, respectively), as we described before.[6] The saxagliptin dose was unchanged during the study period. At the last 3 days of the 4-week treatment period, patients were received another CGM for 3 days.

All patients received the same energy intake during the study period. All subjects were instructed to maintain a similar level of physical activity and received meals consisting of the same nutritional value, and equivalent carbohydrate intake during the study.

The days for euglycemic control (the fasting capillary blood glucose was less than 6.1 mmol/L and capillary blood glucose at 2 hours after each of 3 meals was less than 8.0 mmol/L), were recorded within groups and compared between the groups.[12,26] Changes in insulin dosed and body weight before and after treatments were analyzed. The 24-hour mean blood glucose (MBG), 24-hour MAGE, and the incremental area under curve (AUC) of plasma glucose >10.0 mmol/L, >7.8 mmol/L, and <3.9 mmol/L was calculated by software given by Medtronic Incorporated, and hypoglycemia episodes were also recorded. MAGE was calculated for each patient by measuring the arithmetic mean of the ascending and descending excursions between consecutive peaks and nadirs for the same 24-hour period, and only absolute excursion values >1 SD were considered, as we described before.[6,25]

The primary endpoint was the changes of MAGE before and after therapies between groups. Secondary endpoints were changes of insulin doses, of body weight from baseline to the completion of treatments. The hourly MBG concentrations, the 24-hour MBG and the AUC of hypoglycemia and hyperglycemia were also analyzed.

This study was registered with ClinicalTrials.gov, number ChiCTR-PPR-15007045 (http://www.chictr.org.cn/showproj.aspx?proj=8321).

2.1. Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL). Shapiro–Wilk test was used to assess the distribution of data. Normally distributed and continuous variables are presented as mean (standard deviation, SD). The mixed ANOVA model (2 × 2) test was used to compare differences within group. A 2-way ANOVA was used in the comparisons between groups. Bonferroni correction was followed. P values were 2-tailed with a significance level of 5%.

3. Results

3.1. Baseline characteristics

A total of 69 patients were recruited to the study. The patients with age 47.79 ± 10.09 years, body-mass index 25.12 ± 2.29 kg/m², HbA1c 9.46 ± 1.52%, mean fasting plasma glucose...
10.32 ± 2.15 mmol/L, mean fasting plasma insulin 7.56 ± 4.50 μU/mL, mean fasting plasma C-peptide 2.31 ± 0.74 ng/mL. Subjects were randomized allocated into saxagliptin plus CSII group (31) and CSII group (38). There were no significant demographic differences between groups at baseline (Table 1). All patients completed the study.

3.2. Glucose, insulin, body weight, and insulin secretion profiles

Patients in saxagliptin add-on group reached glycemic control in less days than those of control group (3.62 ± 1.82 vs 4.54 ± 1.72 days, P = 0.042). The daily total insulin dose required by subjects to maintain euglycemic controlling in saxagliptin add-on group was statistically significant lower than that of the control group at the endpoint [16.16 ± 5.93 vs 21.12 ± 7.22 U, P = 0.004]. Consistently, the basal and bolus insulin doses were also decreased in saxagliptin add-on therapy group [8.23 ± 3.47 vs 10.63 ± 3.97 U, P = 0.013 and 7.93 ± 3.22 vs 10.49 ± 4.09 U, P = 0.008, respectively] (Table 2). Body weight of subjects was numerable but not significantly reduced within groups from baseline to the completion of treatments (saxagliptin add-on therapy group from 73.93 ± 10.85 to 71.97 ± 8.86, P = 0.429, control group from 71.55 ± 9.24 to 69.89 ± 8.92, P = 0.467). Moreover, changes of body weight in patients in saxagliptin add-on group did not differ with control group [2.38 ± 3.04 vs 2.09 ± 1.27 kg, P = 0.605] (Table 2). We also observed significantly increased insulin secretion levels, measured by C-peptide concentrations, at 0, 30, and 120 minutes after oral administration for glucose in saxagliptin add-on group compared with patients in control group after therapy [3.38 ± 1.06 vs 2.48 ± 1.33 ng/mL, P = 0.005, 6.58 ± 2.18 vs 5.29 ± 2.14 ng/mL, P = 0.022, 8.99 ± 2.10 vs 7.75 ± 2.30 ng/mL, P = 0.030, respectively).

3.3. Glycemic fluctuation profiles

Subjects in saxagliptin plus CSII group had lower MAGE (2.47 ± 0.79 vs 3.37 ± 2.17 mmol/L, P = 0.041), the incremental AUC >10 mmol/L [0.02 ± 0.07 vs 0.15 ± 0.28 mmol/L per day, P = 0.036], the incremental AUC >7.8 mmol/L [0.16 ± 0.23 vs 0.61 ± 0.65 mmol/L per day, P = 0.016] compared with that of control group (Table 3). The differences within groups were not significantly in the 24-hour MBG (6.54 ± 1.20 vs 6.98 ± 1.33 mmol/L, P = 0.301), and the incremental AUC <3.9 mmol/L [0.019 ± 0.062 vs 0.003 ± 0.018 mmol/L per day, P = 0.210] (Table 3). Although CGM data showed that patients of 2 groups had similar hourly blood glucose concentrations per hour at baseline (Fig. 1). After 4-week therapy, the hourly MBG concentrations, especially between 0000 and 0600 in patient with saxagliptin add-on therapy to CSII, was significantly lower compared with that of the control patients [6.08 ± 1.45 vs 7.11 ± 1.73, 5.87 ± 1.37 vs 6.74 ± 1.38, 5.73 ± 1.48 vs 6.73 ± 1.55, 5.83 ± 1.48 vs 6.78 ± 1.76, 5.79 ± 1.58 vs 6.87 ± 1.72, 5.84 ± 1.60 vs 6.80 ± 1.75, P < 0.05, respectively] (Fig. 2).

3.4. Safety and tolerance

We also compared the risk of severe hypoglycemia (glucose <2.8 mmol/L) between the 2 groups. Saxagliptin add-on therapy did not increase the severe hypoglycemic episodes as compared with CSII group [0.41 ± 0.20 vs 0.47 ± 0.21 mmol/L per day, P = 0.044] (Table 3). All subjects were well tolerated with therapies during the study, and no adverse events were reported from any group.

4. Discussion

We have conducted a prospective study on patients with newly diagnosed T2D and demonstrated that saxagliptin add-on insulin therapy provided better glucose control with smaller blood glycemic fluctuations compared to aspart based CSII treatment using CGM. We also demonstrated that saxagliptin combination therapy provides shorter term to achieve the euglycemic control, and the reduce insulin doses. Furthermore, saxagliptin add-on therapy did not increase the risk of hypoglycemia in patients with newly diagnosed T2D in China population.

Our data demonstrated that patients in both groups achieved euglycemic control after treatment. However, saxagliptin add-on

---

### Table 1

| Characteristics in patients at baseline. | Saxa + CSII | CSII | *P* |
|------------------------------------------|------------|------|-----|
| N                                        | 31         | 38   | /   |
| Age, y                                   | 48.65 ± 10.48 | 47.11 ± 8.85 | 0.532 |
| Male/female                              | 25/6       | 25/13 | 0.189 |
| Weight, kg                               | 73.68 ± 10.96 | 70.16 ± 9.33 | 0.292 |
| BMI, kg/m²                               | 25.36 ± 2.38  | 24.93 ± 2.23  | 0.441 |
| Waist-hip ratio, %                       | 0.93 ± 0.04 | 0.95 ± 0.06 | 0.102 |
| Glc 0 min, mmol/L                       | 10.73 ± 2.50 | 9.99 ± 1.79 | 0.163 |
| Glc 30 min, mmol/L                      | 15.93 ± 5.14 | 15.50 ± 3.34 | 0.57 |
| Glc 120 min, mmol/L                     | 21.53 ± 5.24 | 20.51 ± 4.17 | 0.373 |
| Cp 0 min, ng/mL                         | 2.43 ± 0.67 | 2.21 ± 0.78 | 0.209 |
| Cp 30 min, ng/mL                        | 3.52 ± 1.57 | 3.57 ± 1.90 | 0.951 |
| Cp 120 min, ng/mL                       | 5.61 ± 1.99 | 5.90 ± 2.64 | 0.62 |
| Ins 0 min, μU/mL                        | 7.38 ± 3.79 | 7.70 ± 5.06 | 0.775 |
| Ins 30 min, μU/mL                       | 16.17 ± 14.29 | 18.01 ± 19.40 | 0.667 |
| Ins 120 min, μU/mL                      | 27.09 ± 16.18 | 30.30 ± 23.41 | 0.527 |
| HbA1c, %                                 | 9.52 ± 1.88 | 9.42 ± 1.16 | 0.788 |

### Table 2

| Changes in weight gain and insulin doses in patients within groups before and after therapy. | Before therapy | After therapy | *P* |
|------------------------------------------------------------------------------------------|----------------|---------------|-----|
| Change in weight gain, kg                                                                 | Saxa + CSII    | 73.93 ± 10.85 | CSII | 71.97 ± 8.86 | 0.429 |
| Change in daily total insulin, U                                                         | Saxa + CSII    | 31.64 ± 10.27 | CSII | 31.51 ± 8.6   | 0.953 |
| Change in bolus insulin, U                                                               | Saxa + CSII    | 15.21 ± 5.07  | CSII | 15.77 ± 4.89  | 0.653 |
| Change in basal insulin, U                                                               | Saxa + CSII    | 16.44 ± 6.31  | CSII | 15.73 ± 5.00  | 0.620 |

Baseline = basal insulin dose, bolus = bolus insulin dose, CSII = continuous subcutaneous insulin infusion, daily total = daily total insulin dose.
treatment provided further improvement of MAGE, and the decrease in the incremental AUC of plasma glucose >7.8 and 10.0 mmol/L compared with insulin alone therapy. Saxagliptin is a specific inhibitor of the DPP-4 enzyme, which prevents the degradation of incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The increased active GLP-1 and GIP levels provide the increase in plasma insulin concentration released from pancreatic β-cells and decrease in glucagon level secreted from pancreatic α cells. In patients with T2D, saxagliptin is associated with the improvement of pancreatic β-cell function. The improvement of pancreatic β-cell function might depend on the reduction of DPP4 activity, which improves insulin signaling. Saxagliptin as a monotherapy in drug-naive T2DM patients and add-on therapy in patients with inadequate glycemic control with oral antidiabetic agents or insulin were generally well tolerated and demonstrated significant improvements in glycemic control and a low risk of hypoglycemia. In agreement with these studies, our data demonstrated that 5 mg saxagliptin add-on insulin therapy provided further improvement of glycemic fluctuations, decrease in time to achieve euglycemic control, insulin doses, and insignificant weight gain. The incidence of hypoglycemic episodes were relatively increased with saxagliptin in patients taking sulfonylureas (SURs) and add-on therapy with other selected antihyperglycemic agents in a large cohort study. However, in this study, we did not observe the increase risks of hypoglycemia compared with that of control group.

Our data also indicated that patients in saxagliptin add-on therapy to insulin group gained further improvement of MAGE. It is now believed that glucose fluctuation may be an important and independent risk factor for cardiovascular disease in patients with onset T2DM. Large glucose fluctuations may cause the overproduction of superoxide by the mitochondrial electron-transport chain, which induces a subsequent nitrosative stress. PPG is an independent risk factor for cardiovascular disease. Monnier et al. reported that acute glucose fluctuations during postprandial periods played a crucial role on oxidative stress. By reducing postprandial excursions, oxidative and nitrosative stress can be diminished. The smoothed blood glycemic executions might confer a protective profile to cerebrovascular disease (CVD). However, we have no data to support these concept, we now address this as our one limitation.

Insulin therapy confers an increase in risks of hypoglycemia and weight gain. However, in this study, subjects within groups exhibited small decreases in body weight from baseline to the completion of treatment. This might because that patients were received the less energy intake than usually consumed during the study period. All subjects were instructed to maintain a similar level of physical activity and received meals consisting of the same nutritional value, and equivalent carbohydrate intake during the study. Changes of body weight in patients with saxagliptin add-on therapy did not increase compared with that of insulin only therapy in this study. Our data agree with previous study showing saxagliptin added to insulin has no clinically significant weight gain.

With regard to the intensive insulin therapy used to newly diagnosed patients in this study, the patients recruited to our study had mean HbA1c levels of 9.6%. According to China
Guideline for Type 2 Diabetes,[36,37] newly diagnosed T2DM, with HbA1c > 9.0% or fasting blood glucose higher than 11.1 mmol/L, could be treated with intensive insulin therapy. Furthermore, Weng et al[32] found that early intensive insulin therapy in patients with newly diagnosed T2D has favorable outcomes on recovery and maintenance of β-cell function and protracted glycemic remission compared with treatment with oral hypoglycemic agents in Chinese population.

In this study, we also observed a significant induction in insulin secretion levels, measured by C-peptide concentrations, at 0, 30, and 120 minutes after oral administration for glucose in saxagliptin add-on group compared with patients in control group after therapy. This might partially be the reason that patients in saxagliptin add-on group had more improvement of blood glycemic variations compared with subjects in control group.

Our study still has other limitations. First, the study only observed Chinese population, so the situation might not be the same for other populations. Second, the sample size was relatively modest. Third, we did not observe for a long time period.

In conclusion, saxagliptin add-on therapy to insulin had the ability of further improve blood glycemic controlling, with lower insulin doses required by patients with T2D to maintain euglycemic control.

References
[1] Retnakaran R, Drucker DJ. Intensive insulin therapy in newly diagnosed type 2 diabetes. Lancet 2008;371:1725–6.
[2] Ilkova H, Glaser B, Tunckale A, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. Diabetes Care 1997;20:1533–6.
[3] Li Y, Xu W, Liao Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β-cell function. Diabetes Care 2004;27:2597–602.
[4] Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care 2004;27:1028–32.
[5] Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371:1753–60.
[6] Li FF, Fu LY, Zhang WL, et al. Blood glucose fluctuations in type 2 diabetes patients treated with multiple daily injections. J Diabetes Res 2016;2016:1028045.
[7] Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A metagression analysis of published data from 20 studies of 95,783 individuals followed for 12-4 years. Diabetes Care 1999;22:233–40.
[8] DECODE Study Group. European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397–405.
[9] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615–25.
[10] Nakagami T. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. Diabetologia 2004;47:385–94.
[11] Auger DJ, Robibe JA, Bettenbaumer DA, et al. Discovery and preclinical profile of saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 2005;48:5025–37.
[12] Dhillon S, Weber J. Saxagliptin. Drugs 2009;69:2103–14.
[13] Frederich R, McNell R, Berglund N, et al. The efficacy and safety of the dipeptidyl peptidase-4 inhibitor saxagliptin in treatment-naive patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetol Metab Syndr 2012;4:36.
[14] Pan CY, Yang W, Tou C, et al. Efficacy and safety of saxagliptin in drug-naive Asian patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Metab Res Rev 2012;28:628–75.
[15] Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment of patients with type 2 diabetes. Curr Med Res Opin 2009;25:2401–11.
[16] Jain R. Utility of saxagliptin in the treatment of type 2 diabetes: review of efficacy and safety. Adv Ther 2015;32:1063–84.
[17] DeFronzo RA, Hsia MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009;32:1649–55.
[18] Hermans MP, Delibasi T, Farmer I, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with up titration of metformin in type 2 diabetes: the PROMPT study. Curr Med Res Opin 2012;28:1635–45.
[19] Yang W, Pan CY, Tou C, et al. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract 2011;94:217–24.
[20] Barnett AH, Charbonnel B, Donovon M, et al. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Curr Med Res Opin 2012;28:513–23.
[21] Xiaoany C, Jing W, Xiao churn H, et al. Effects of vildagliptin versus saxagliptin on daily acute glucose fluctuations in Chinese patients with T2DM inadequately controlled with a combination of metformin and sulfonylurea. Curr Med Res Opin 2016;32:1131–6.
[22] Henry RR, Smith SR, Schwartz SL, et al. Effects of saxagliptin on beta-cell stimulation and insulin secretion in patients with type 2 diabetes. Diabetes Obes Metab 2011;13:830–8.
[23] Rohrborn D, Bruckner J, Sell H, et al. Reduced DPP4 activity improves insulin signaling in primary human adipocytes. Biochem Biophys Res Commun 2016;471:348–54.
[24] Ziegler R, Tubili C, Chico A, et al. ProAct study: new features of insulin pumps improve diabetes management and glycemic control in patients after transition of continuous subcutaneous insulin infusion systems. Diabetes Technol Ther 2013;15:37–43.
[25] Li FF, Xu XH, Fu LY, et al. Influence of acarbose on plasma glucose fluctuations in insulin-treated patients with type 2 diabetes: a pilot study. Int J Endocrinol 2015;2015:903524.
[26] Schnell O, Mertes G, Standl E. Acarbose and metabolic control in patients with type 2 diabetes with newly initiated insulin therapy. Diabetes Obes Metab 2007;9:853–8.
[27] Barnett A, DPP-4 inhibitors and their potential role in the management of type 2 diabetes, Int J Clin Pract 2006;60:1454–70.
[28] Drucker DJ. The role of gut hormones in glucose homeostasis. J Clin Invest 2007;117:24–32.
[29] Cahn A, Ray I, Mosenzon O, et al. Prescribing factors for any and major hypoglycemia with saxagliptin versus placebo and overall: analysis from the SAVOR-TIMI 53 trial. Diabetes Care 2016;39:1329–37.
[30] Toh S, Hamp C, Reichman ME, et al. Risk for hospitalized heart failure among new users of saxagliptin, sitagliptin, and other antihyperglycemic drugs: a retrospective cohort study. Ann Intern Med 2016;164:703–14.
[31] Monnier L, Mas E, Giner C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681–7.
[32] Ceriello A, Quagliaro L, Catone B, et al. Role of hyperglycemia in nitrotyrosine postprandial generation. Diabetes Care 2002;25:1439–43.
[33] Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203.
[34] Charbonnel B, Carou B. Pharmacological management of type 2 diabetes: the potential of incretin-based therapies. Diabetes Obes Metab 2011;13:99–117.
[35] Barnett AH, Craddock S, Fisher M, et al. Key considerations around the risks and consequences of hyperglycaemia in people with type 2 diabetes. Int J Clin Pract 2010;64:1121–9.
[36] Chen W, Jiang H, Tao YX, et al. [Development and interpretation of Chinese medical nutrition therapy guideline for diabetes (2010)]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2011;33:253–6.
[37] Lu QG, Tong NW. Integration of Chinese medicine therapy of Endocrinology consensus statement on hyperglycaemia management target in adult inpatients in China. J Diabetes 2013;5:416–20.