

Comparison of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed type 2 diabetes mellitus

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Abstract

Background: We aimed to compare the effect of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed type 2 diabetes mellitus (T2DM).

Patients and methods: In this 15-week, open-labelled, parallel-controlled, randomised study, 60 Chinese drug-naïve patients with newly diagnosed T2DM were randomised (2:1) to receive repaglinide or metformin monotherapy. Primary endpoint was change in HbA1c from baseline to the end of the trial. Secondary endpoints included changes in glycaemic variability, insulin sensitivity and β -cell function.

Results: Patients in both repaglinide and metformin groups achieved significant reductions in HbA1c (-1.8 ± 1.5 vs $-1.6 \pm 1.5\%$), FPG (fasting blood glucose) (-1.7 ± 1.7 vs -2.1 ± 1.7 mmol/l) and 2-h PPG (post-prandial glucose) (-3.8 ± 3.1 vs -3.8 ± 3.6 mmol/l), with no statistical differences between the groups. Glycaemic variability, glucose infusion rate and β -cell function were all significantly improved from baseline in the two groups (all $P < 0.05$), without any statistical differences in the improvement between the groups.

Conclusions: Repaglinide and metformin achieved comparable efficacy in improving glycaemic control, reducing glycaemic variability, enhancing insulin sensitivity and ameliorating β -cell function. Therefore, repaglinide is an optional agent for initial therapy in Chinese patients with newly diagnosed T2DM.

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Introduction

Diabetes has become a major public health problem and the prevalence of diabetes among Chinese adults was 9.7% in 2008 (1). Many interventional studies have reported that diabetic complication was significantly related to dysglycaemia (2, 3, 4, 5). The UK Prospective Diabetes Study (UKPDS) showed that metformin therapy in overweight and obese patients with type 2 diabetes mellitus (T2DM) could reduce HbA1c and significantly decrease the risk of diabetes-related endpoints (6). Therefore, metformin has been suggested to be the drug of first choice after diet failure in obese patients with T2DM (7).

However, the average BMI of Chinese patients with T2DM was about 25 kg/m², which was relatively lower than that in people from Western countries (1). The Chinese Diabetes Society guideline suggests metformin as the first-line treatment for overweight/obese patients, while insulin secretagogue could also be used alone in newly diagnosed non-obese patients (8). Repaglinide is a short-acting insulin secretagogue with an excellent anti-hyperglycaemic potency and a lower risk of hypoglycaemia. However, whether repaglinide can be used as an initial therapy in Chinese patients with newly

diagnosed T2DM is still unconfirmed. A previous study has demonstrated that repaglinide improved first-phase insulin secretion and played a critical role in the regulation of postprandial blood glucose (9). Several studies have demonstrated that repaglinide was similar to metformin with respect to both glycaemic control and cardiovascular risk profile in patients with T2DM (10, 11).

The aim of this study was to investigate the feasibility of using repaglinide as an initial therapy in Chinese patients with newly diagnosed T2DM naive to oral anti-hyperglycaemic agents, by validating the effects of repaglinide on glycaemic control, glycaemic variability, insulin sensitivity and β -cell function in comparison with metformin monotherapy.

Subjects and methods

Participants

Patients aged 20–90 years, diagnosed with T2DM within 6 months, naive to oral anti-hyperglycaemic drugs, with a BMI of 18.5–30 kg/m² and with an HbA1c level <10.0% were included in this study. Exclusion criteria included T1DM, pregnancy or lactation, impaired hepatic or renal function at screening, decompensated heart failure, unstable angina, alcohol or drug abuse and known or suspected allergy to any trial medications. The study protocol was approved by the Local Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participation.

Study design

This 15-week, open-labelled, parallel-controlled, randomised study was conducted at Chinese PLA General Hospital. Patients were investigated after an overnight fast of at least 10 h. After fasting, blood samples were collected and all patients were served a standard breakfast meal (total energy content 2625 kJ) with 34% fat, 14% protein and 52% carbohydrates. Postprandial blood samples were collected at 2 h after initiation of breakfast. Randomisation was carried out using a computer-generated sequence. The eligible patients were randomised (2:1) to receive thrice-daily monotherapy of repaglinide or metformin. The dose of metformin was 500 mg thrice daily and it remained unchanged through the entire study. Patients receiving repaglinide had an additional 3-week titration period before the dose

maintaining period. The starting dose of repaglinide was 0.5 mg for patients with an HbA1c level <8% or 1 mg for patients with an HbA1c level \geq 8% thrice daily. During the first 3 weeks, repaglinide was uptitrated weekly up to a maximum of 2 mg thrice daily. Repaglinide was titrated by the investigator according to the self-monitored blood glucose of the patient, and the dose could be reduced according to the blood glucose self-monitored by the patients during the following 12 weeks in order to prevent hypoglycaemia based on evaluations from the investigators. Participants were instructed to take repaglinide before meals and metformin with meals. All participants received dietary and exercise advice, and they were asked to follow a recommended controlled-energy diet (25–35 kcal/kg per day) and to undertake aerobic activity for at least 30 min on five occasions per week. There were eight visits in total during the whole 15-week study period.

Study evaluations

The primary efficacy endpoint was change in HbA1c from baseline (week 0) to week 15. The secondary efficacy endpoints included changes in FPG, 2-h PPG, glycaemic variability, insulin sensitivity and β -cell function. Safety and tolerability endpoints included incidences of adverse events (AEs), withdrawals due to AEs, hypoglycaemic events, body weight, physical examination and standard laboratory measures. Pregnancy test was carried out in females of childbearing potential.

Glycaemic variability was evaluated using a 24-h continuous glucose monitoring system (MiniMed, Medtronic, Inc., Northridge, CA, USA) at both baseline and week 15. Data not meeting the manufacturer's standard (correlation of sensor and meter readings not <0.79 and a mean absolute difference not more than 28% (12)) were excluded from the analysis set. A 48-h recording from 0000 h on day 2 to 0000 h on day 4 was performed using the CGM device to quantify the mean amplitude of glycaemic excursions (MAGE) and s.d. of mean blood glucose (SDBG) in each patient (13).

Insulin sensitivity expressed as glucose infusion rate (GIR) was assessed by a hyperinsulinaemic euglycaemic clamp procedure (14). The experiments were conducted in a random double-blind fashion. Briefly, insulin (Novolin R, Novo Nordisk) was infused at a rate of 4 mU/kg per min for 10 min when clamp was started and maintained at 2 mU/kg per min for 180 min. Then, 20% glucose solution was infused (NCA-ST pump, Germany Fresenius Company, Baden-Württemberg, Germany) at a rate

required to maintain a target plasma glucose concentration of 5.0 mmol/l. Glucose concentrations were monitored at 5 min intervals using an automated glucose analyser (BIOSEN5030 Glucose Analyser, EKF Diagnostics, Barleben/Magdeburg, Germany), and the glucose infusion was adjusted accordingly. The GIR was calculated based on the amount of glucose infused during the last 30 min of the clamp during which the GIR was relatively stable.

The function of β -cell (% β) was evaluated using a homeostasis model assessment (HOMA 2) (15), with the use of the HOMA Calculator (www.dtu.ox.ac.uk). Plasma glucose was measured using a glucose-oxidase-based approach, and insulin concentration was determined using a RIA Kit (American Diagnostic Products Corporation, Hauppauge, NY, USA) according to the manufacturer's manual.

Each patient was supplied with a calibrated blood glucose meter (ACCU-CHEK Active, Roche) to record self-monitoring blood glucose profiles (SMBG). The 7-point blood glucose was taken before and 120 min after each meal (breakfast, lunch and dinner), and at bedtime. SMBG was monitored twice a week for the first 3 weeks and once a week for the following 12 weeks in all patients. HbA1c was determined by a chromatography method at baseline and week 15. The inter-assay coefficient of variation (CV) value of HbA1c was 0.5–0.9%, and the intra-assay CV value was 1.6–2.3%.

Statistical analyses

Within-group changes were assessed using the paired *t*-tests when data were normally distributed; otherwise, non-parametric analysis was applied. Between-group differences were analysed using Student's *t*-test. Categorical data were analysed using the χ^2 -test to determine univariate differences between the cohorts. The data are presented as the means \pm s.d. for normally distributed continuous variables, median (5th and 95th percentiles) for non-normal continuous variables. *P* values < 0.05 were considered statistically significant. The safety analyses set included all patients who received at least one dose of study medication. Hypoglycaemic events (hypoglycaemia symptoms and finger glucose ≤ 2.8 mmol/l) were recorded and analysed separately from other AEs.

Results

Characteristics of subjects

A total of 71 subjects were screened and 60 participants were randomly assigned to receive either repaglinide

Table 1 Demographic and baseline clinical characteristics at randomisation (means \pm s.d. or median (5th and 95th percentiles)).

	Repaglinide	Metformin
<i>n</i>	40	20
Age	46.4 \pm 10.6	49.7 \pm 10.0
Gender (M/F)	21/19	16/4
Diabetes duration (months)	0.8 \pm 1.3	0.4 \pm 0.4
BW (kg)	70.5 \pm 12.0	70.7 \pm 11.2
BMI (kg/m ²)	26.2 \pm 3.5	25.1 \pm 3.1
HbA1c (%)	8.0 \pm 1.5	7.9 \pm 1.6
FPG (mmol/l)	8.4 \pm 1.9	9.1 \pm 2.6
2-h PPG (mmol/l)	14.4 \pm 3.6	14.2 \pm 4.3
SBP (mmHg)	129.0 \pm 18.7	124.4 \pm 11.8
DBP (mmHg)	77.8 \pm 10.1	78.6 \pm 7.7
TC (mmol/l)	5.0 (3.7, 6.4)	4.8 (3.5, 5.8)
TG (mmol/l)	1.4 (0.7, 3.9)	1.5 (0.9, 3.5)
LDL-C (mmol/l)	3.1 (2.0, 3.9)	3.1 (1.5, 3.8)
HDL-C (mmol/l)	1.1 (0.8, 1.6)	1.1 (0.9, 1.4)

(*n* = 40) or metformin (*n* = 20). Of them, 59 patients completed the trial and one patient in the repaglinide group withdrew at the last visit. The demographic and clinical characteristics were well balanced between the repaglinide and metformin groups (Table 1).

The dose of repaglinide was initiated at 1.8 \pm 0.9 mg/day at baseline, increased to a maximum of 2.1 \pm 1.7 mg/day by week 3 and decreased to 1.8 \pm 1.5 mg/day on the last day of treatment. The dose of metformin was 1500 mg/day throughout the study.

Glycaemic control

At week 15, mean changes in HbA1c from baseline were $-1.8 \pm 1.5\%$ in the repaglinide group (*P* < 0.01) and $-1.6 \pm 1.5\%$ in the metformin group (*P* < 0.01 , Table 2). No significant difference was found with regard to change in HbA1c level between the two groups (*P* = 0.739). There was no difference in the proportion of patients with an HbA1c level $< 7.0\%$ (87.2 vs 90.0%, *P* = 0.751) and an HbA1c level $< 6.5\%$ (71.8 vs 60.0%, *P* = 0.359) between the repaglinide and metformin groups at week 15.

In patients with an HbA1c level $< 8.0\%$ at baseline, the changes in HbA1c levels from baseline were -0.9 ± 0.7 and $-0.7 \pm 0.6\%$ in the repaglinide (*n* = 25) and metformin groups (*n* = 11) (*P* = 0.456) respectively. In patients with an HbA1c level $\geq 8.0\%$ at baseline, the change in HbA1c from baseline (-3.4 ± 0.9 vs $-2.8 \pm 1.3\%$, *P* = 0.212) was also not significantly different between the repaglinide (*n* = 14) and metformin (*n* = 9) groups (Fig. 1C).

Mean changes in FPG and 2-h PPG from baseline were -1.7 ± 1.7 and -3.8 ± 3.1 mmol/l in the repaglinide

Table 2 Changes in major efficacy endpoints from baseline to the end of the trial.

	Repaglinide	Metformin	Repaglinide–metformin		P value
			Mean \pm S.E.M.	95% CI	
Glycaemic control					
HbA1c (%)	-1.8 ± 1.5	-1.6 ± 1.5	-0.1 ± 0.4	-0.7 to 0.9	0.739
HbA1c <7.0% at end of trial	34 (87.2%)	18 (90.0%)	–	–	0.751
HbA1c <6.5% at end of trial	28 (71.8%)	12 (60.0%)	–	–	0.359
FPG (mmol/l)	-1.7 ± 1.7	-2.1 ± 1.7	0.4 ± 0.5	-1.4 to 0.5	0.362
2-h PPG (mmol/l)	-3.8 ± 3.1	-3.8 ± 3.6	0.0 ± 0.9	-1.8 to 1.9	0.969
Glycaemic variability					
MAGE (mmol/l)	-1.4 ± 2.0	-1.4 ± 1.6	0.0 ± 0.5	-1.1 to 1.0	0.940
SDBG (mmol/l)	-0.4 ± 0.8	-0.5 ± 0.8	0.1 ± 0.2	-0.4 to 0.6	0.675
Insulin sensitivity					
GIR (mg/kg per min)	$+1.2 \pm 3.0$	$+1.2 \pm 2.3$	0.0 ± 0.9	-1.7 to 1.8	0.962
β -cell function					
HOMA2 (% β)	$+20.5 \pm 22.9$	$+17.1 \pm 23.4$	3.3 ± 6.3	-16.1 to 9.4	0.600
FINS (mU/l)	$+1.3 \pm 4.6$	-1.1 ± 6.4	2.4 ± 1.5	-5.4 to 0.5	0.102
2-h INS (insulin levels) (mU/l)	$+9.9 \pm 28.7$	-3.2 ± 29.1	13.1 ± 8.1	-29.3 to 3.0	0.109
Other					
BW (kg)	0.0 ± 3.3	-3.0 ± 2.4	3.1 ± 0.8	-4.7 to -1.4	0.001

group (both $P < 0.01$, Table 2) and -2.1 ± 1.7 and -3.8 ± 3.6 mmol/l in the metformin group (both $P < 0.01$). No significant difference was found in the above glycaemic parameters between the two groups.

The changes in mean blood glucose (MBG) of 7-point blood glucose and mean fasting blood glucose (FBG) based on SMBG data showed similar trends in the two treatment groups through the entire trial period. For both MBG (repaglinide vs metformin: 8.3 ± 1.9 vs 8.3 ± 2.9 mmol/l) and FBG (7.2 ± 1.3 vs 7.2 ± 1.7 mmol/l) at baseline, the values were comparable in the two groups. The values were gradually reduced in the 3-week titration period (with slightly more reduction in the metformin group) and then remained unchanged in the following 12-week dose maintaining period (Fig. 1A and B).

Glycaemic variability

The mean changes in MAGE from baseline of 4.8 ± 2.1 and 4.4 ± 1.3 mmol/l ($n = 37$ in the repaglinide group and $n = 18$ in the metformin group) to week 15 were -1.4 ± 2.0 in the repaglinide group vs -1.4 ± 1.6 mmol/l in the metformin group (both $P < 0.01$). The mean changes in SDBG from baseline of 1.8 ± 0.8 and 1.7 ± 0.6 mmol/l to week 15 were -0.4 ± 0.8 in the repaglinide group vs -0.5 ± 0.8 mmol/l in the metformin group (both $P < 0.01$). For both above glycaemic variability parameters, there was no significant difference between the two treatment groups (Table 2).

Insulin sensitivity

Hyperinsulinaemic euglycaemic clamp was performed on 46 volunteers of the study participants ($n = 31$ in the repaglinide group and $n = 15$ in the metformin group). At week 15, the mean changes in the GIR from baseline of 6.1 ± 2.5 and 6.4 ± 2.0 mg/kg per min were $+1.2 \pm 3.0$ mg/kg per min ($P = 0.035$) in the repaglinide group and $+1.2 \pm 2.3$ mg/kg per min ($P = 0.053$) in the metformin group. No significant difference was found between the two groups in GIR changes (Table 2).

β -cell function

At week 15, the mean changes in HOMA2 (% β) from baseline of 34.0% (13.0, 77.5) and 29.8% (13.8, 85.4) were $+20.5 \pm 22.9\%$ ($P = 0.001$) in the repaglinide group vs $+17.1 \pm 23.4\%$ ($P = 0.020$) in the metformin group. No significant difference was found between the two groups in β -cell function changes (Table 2). HOMA2 (% β) was increased in 89.7% (35/39) of patients in the repaglinide group vs 80.0% (16/20) of patients in the metformin group ($P = 0.527$).

The mean changes in FINS from baseline of 8.1 and 8.8 mU/l were $+1.3 \pm 4.6$ mU/l ($P = 0.083$) in the repaglinide group vs -1.1 ± 6.4 mU/l ($P = 0.407$) in the metformin group. Similarly, at week 15, the mean changes in 2-h INS from baseline of 39.9 and 35.4 mU/l were 9.9 ± 28.7 mU/l ($P = 0.037$) in the repaglinide group vs -3.2 ± 29.1 mU/l ($P = 0.681$) in the metformin group.

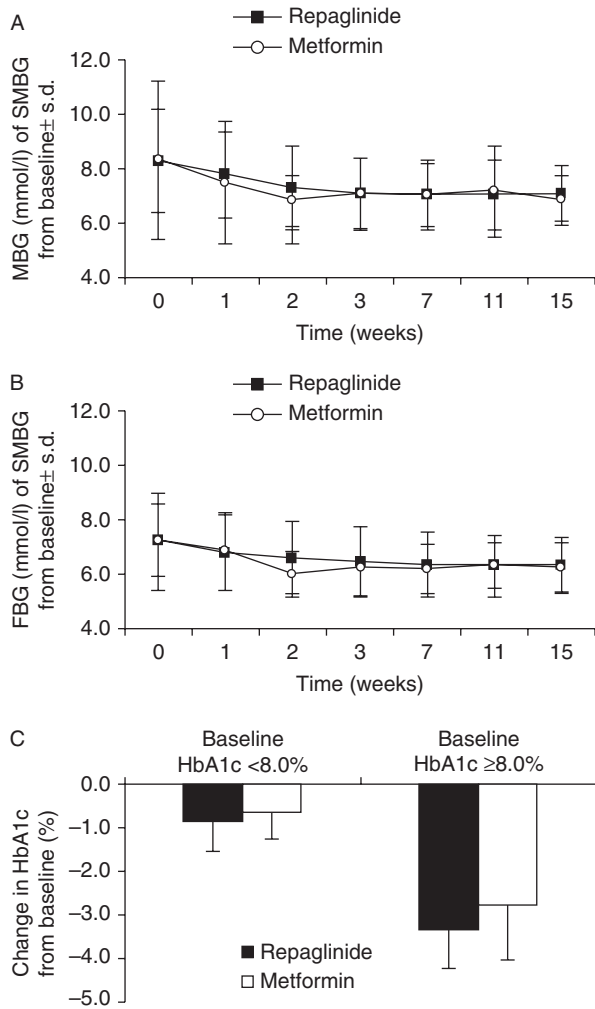


Figure 1
(A, B and C) Glycaemic control from baseline to the end of the trial.

No significant between-group difference was seen for FINS and 2-h INS.

Safety evaluations

A total of ten AEs (three reported in the repaglinide group and seven in the metformin group) were recorded in this study. Five AEs were gastrointestinal tract disorders (repaglinide, one subject and metformin, four subjects) and three AEs were respiratory tract infections (repaglinide, one subject and metformin, two subjects). One subject in the repaglinide group suffered from sunstroke and recovered soon after rest, and one female subject in the metformin group was diagnosed as having uterine fibroids. No major hypoglycaemic event (requiring

assistance or hospital admission) was reported in both treatment groups during the entire period of the study. For minor hypoglycaemic events ($BG \leq 2.8$ mmol/l) or symptomatic hypoglycaemic events, 12 were reported in the repaglinide group (two hypoglycaemic events in two subjects and ten symptomatic hypoglycaemic events in nine subjects) and none in the metformin group. At week 15, the changes in body weight were 0.0 ± 3.3 kg in the repaglinide group ($P > 0.05$) and -3.0 ± 2.4 kg in the metformin group ($P < 0.01$). None of the subjects in either treatment groups reported abnormal findings in physical examination and laboratory measurements.

Discussion

This was a 15-week, open-labelled, parallel-controlled, randomised study to compare the effectiveness of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed T2DM. HbA1c, glycaemic variability, GIR and β -cell function were all significantly improved from baseline by both treatments, without any difference between the groups. Our study provided evidence that repaglinide might have a similar effect on patients with newly diagnosed T2DM in an initial 15-week therapy when compared with metformin.

Risk of developing microvascular complications was intimately related to the glycaemic control of diabetic subjects, which was confirmed by the Diabetes Control and Complications Trial (DCCT) in T1DM and the UKPDS in T2DM (16, 17). Due to robust evidence, current international guidelines recommend metformin as the only first-line oral anti-hyperglycaemic agent for patients with newly diagnosed T2DM (7, 18). As gastrointestinal complications occur in more than 20% of the patients using metformin (19, 20), other anti-hyperglycaemic agents are considered as substitutes for the initial pharmacological therapy for those with contraindications to metformin. In this study, repaglinide and metformin had similar effects on HbA1c, which was in accordance with previous studies (10, 11). At the end of the trial, 87.2% of patients in the repaglinide group and 90.0% of patients in the metformin group achieved HbA1c $< 7.0\%$. Besides its effect on HbA1c, we also found that repaglinide exhibited a similar effect on FPG, 2-h PPG, glycaemic variability, insulin resistance and β -cell function when compared with metformin. Therefore, our study showed that repaglinide could be an optional drug for initial therapy in newly diagnosed T2DM patients, especially for those with contraindications to metformin.

In Chinese patients with T2DM, postprandial glucose was a predominant contributor to excess hyperglycaemia (21). Although repaglinide can markedly improve postprandial glucose control (10), a better effect of repaglinide when compared with metformin in reducing 2-h PPG and glycaemic variability was not found in the study, which was similar to another study reported by Lund *et al.* (22). The failure to detect the superiority of repaglinide could be attributed to the following aspects: first, the study subjects were patients with newly diagnosed T2DM who might have a relatively better pancreatic β -cell function and a more sensitive response to anti-hyperglycaemic agents. Although HbA1c decreased markedly, the dose of repaglinide used in this study was relatively lower when compared with other studies (10, 23). Furthermore, diet control was usually strictly followed by patients with newly diagnosed T2DM (24), which may contribute to glycaemic control. Based on diet control, metformin was associated with balanced improvements in 2-h PPG and glycaemic variability when compared with repaglinide. In addition, neither major nor minor hypoglycaemic events were reported in the metformin group. As glycaemic variability assessed by MAGE was calculated as the variation around MBG by summing the absolute rises or falls encountered in a day, patients treated with metformin might have had relatively lower variability due to no hypoglycaemia. Lund *et al.* (22) compared the effect of metformin vs repaglinide on postprandial metabolism in non-obese T2DM patients, showing significantly higher levels of postprandial insulin and C-peptide with repaglinide vs metformin. There is no statistical difference in 2-h insulin levels between repaglinide and metformin in this study. However, 2-h insulin increased significantly from baseline in the repaglinide group, and changed slightly in the metformin group. The trend is consistent with the study reported by Lund *et al.* (22). The lack of statistical difference in 2-h insulin between the two treatments in this study might be attributed to a high s.d. and a small sample size.

This study suggested that repaglinide and metformin could be used to reduce glycaemic variability in patients with newly diagnosed T2DM. Not only sustained hyperglycaemia but also acute glycaemic variability contributed to diabetic complications (25). Acute glycaemic variability was shown to be more deleterious than sustained high level of glucose to endothelial cells and human kidney proximal tubule cells (26, 27). Glycaemic variability has been a therapeutic target of several clinical studies and several anti-diabetic agents have been confirmed to reduce variability in glycaemia (28, 29, 30). Our data supported

the effectiveness of repaglinide and metformin in glycaemic variability control in patients with T2DM.

Impaired pancreatic β -cell function and insulin resistance were characteristics of T2DM (31). In this study, we found a similar improvement in β -cell function, as measured by HOMA, in the repaglinide and metformin groups. The amelioration of β -cell function was mainly related to the elimination of glucotoxicity after treatment in both groups. Our finding is in accordance with one study reporting that repaglinide improved β -cell function and mimicked the normal postprandial early-phase insulin secretion in patients with T2DM (9) and agrees with other studies showing that repaglinide enhanced β -cell function more effectively than traditional sulphonylureas (11, 32). However, the HOMA model was used under conditions of pharmacologically induced changes in glucose and in particular insulin metabolism such as treatment with an insulin secretagogue. The HOMA model typically pertains to an untreated person and the use of glucose-lowering drugs may violate the basic assumptions in the model. Therefore, we should also note that an apparent increased HOMA (β) after short-term therapy may be due to the pharmacology of repaglinide or improvement in glycaemic control, and this does not mean a 'healthier' β -cell, which had been demonstrated in the study by Kahn *et al.* (33). The reduction in insulin resistance, as evaluated by the GIR (34), was comparable in both groups. It has been reported that certain therapeutic interventions lead to enhanced insulin sensitivity and improved β -cell function (35). Metformin was also shown to be effective in reducing insulin resistance, and similarly, the reduction in insulin resistance by repaglinide could be attributed to its efficacy in glycaemic control.

Open-label design in this study might bias the results. Further limitations include a short study period and a small sample size. Insulin secretagogues may lose efficacy with time and duration of diabetes, so this study is preliminary and a larger sample size and a longer duration are required to further verify the conclusion. In this study, repaglinide was titrated up to a maximum dose of 6 mg/day, while metformin was at a fixed dose of 1500 mg/day. This might have influenced the study results, though the comparative efficacy was observed in this study. However, the mean dose of repaglinide of about 2 mg/day at the end of trial is much lower than the maximum allowed dose of 6 mg/day. In addition, metformin was commonly used up to a dose of 1500 mg/day in real world practice and trials in China (36), rather than being titrated to a dose of 2000 mg/day as recommended by the guidelines. Metformin was initiated

at a dose of 1500 mg/day without titration, which may increase the frequency of gastrointestinal AEs in this study. Lastly, the limited accuracy of the CGM device should be concerned, especially the relatively weak stability in the first day after measurement. Therefore, we quantify glycaemic variability using the intermediate 48-h CGM recording in the study.

In conclusion, in addition to its efficacy in glycaemic control, repaglinide showed comparable effectiveness to metformin in reducing glycaemic variability, enhancing insulin sensitivity and ameliorating β -cell function. This study provided preliminary evidence that repaglinide could be used as an initial therapy in part of Chinese patients with newly diagnosed T2DM who have contraindications to metformin.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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