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ORIGINAL ARTICLE

Effects of dapagliflozin combined with short-term intensive insulin therapy on β-cell function in patients with newly diagnosed type 2 diabetes mellitus—a randomized controlled study

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Abstract

Purpose This study was aimed to evaluate the effect of dapagliflozin as add-on medication to short-term intensive insulin therapy on β-cell function in newly diagnosed type 2 diabetes mellitus (T2DM) patients.

Methods Sixty participants were recruited and randomized to receive either multiple daily insulin injections alone (MDI group), receiving pre-meal insulin aspart and insulin glargine at bedtime, or in combination with dapagliflozin 10 mg per day (MDI+DAPA group). Data was collected at baseline (d0), 14 days after reaching euglycemia (D14), and at the 12-week visit (W12). Fasting C-peptide concentration, areas under the curve (AUC) for C-peptide (CP) and insulin (INS), homeostasis model assessment (HOMA) indices, early insulin secretion index (EISI), and glycemic control were compared before and after treatment.

Results The two groups achieved euglycemia in similar time. Daily average insulin dosage in the MDI+DAPA group (0.27 ± 0.12 U/kg·day, $n = 28$) was lower than that in the MDI group (0.36 ± 0.22 U/kg·day, $n = 29$) ($p = 0.050$). HbA1c and plasma glucose were significantly decreased after treatment but of no significant difference between the two groups. Proportions of patients who achieved HbA1c ≤ 6.5% were similar (58.6% in the MDI group vs. 53.6% in the MDI+DAPA group, $p = 0.701$). Fasting C-peptide elevated after treatment but were comparable in the two groups. Both groups obtained similar improvements of AUC-CP, AUC-INS, HOMA-β, EISI, and HOMA-IR.

Conclusion Dapagliflozin as add-on could reduce daily insulin dosage, but bring no additive effect in improving β-cell function for newly diagnosed T2DM patients receiving intensive insulin therapy.

Trial registration The study was approved by the Chinese Clinical Trial Registry (ChiCTR.org.cn: ChiCTR1800015822).

Keywords Dapagliflozin · Intensive insulin therapy · β-cell function · Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, fundamental pathophysiological mechanism of which is deterioration of β-cell function and insulin resistance [1]. Researches manifested that at least 50% of β-cell function has been impaired when T2DM was diagnosed and the defect would progress over time [2–5].

Intensive insulin therapy has been proven to induce euglycemia without medication for over 1 year in some of the newly diagnosed T2DM patients [6–8]. The underlying mechanism might be elimination or alleviation of glucotoxicity and lipotoxicity [9].

Dapagliflozin, a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT-2), has shown favorable effects on both glycemic control and reduction of renal and cardiovascular outcomes [10, 11]. There were also reports on β-cell function improvement and insulin resistance reduction of dapagliflozin [12, 13].

Short-term intensive insulin therapy is recommended for newly diagnosed T2DM patients in clinical practice guidelines in China [14]. And in most medical centers, such patients were admitted in hospital to receive the treatment. Therefore, maximizing the efficacy of treatment during hospitalization is always crucial for endocrinologists. We wondered whether

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dapagliflozin as add-on medication could have extra effect on β-cell function and insulin resistance for newly diagnosed T2DM patients receiving intensive insulin therapy. Hence, the present trial, a randomized controlled study, was conducted.

Materials and methods

Study subjects

The trial started in March 2018 and the last patient was enrolled in August 2020. A total of 60 newly diagnosed T2DM patients, men and women aged between 18 and 75, without any usage of antidiabetic medication before, were enrolled. T2DM was diagnosed on the basis of the 1999 World Health Organization diagnostic criteria. Patients were excluded if they had: (1) severe acute diabetic complications including diabetic ketoacidosis and hyperosmolar nonketotic coma, (2) serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels > 3 times the upper limit of normal (ULN), or severe hepatic insufficiency, (3) eGFR < 60 mL/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease (MDRD) equation, (4) positive autoimmune antibodies against islets, (5) a recent history of being treated with corticosteroid, immunosuppressing drugs, or cytotoxic drugs, (6) known Cushing's syndrome, thyrotoxicosis, acromegaly, or other diseases that could have effects on blood glucose level, (7) known currently unstable or serious oncologic, infectious, malnutritious diseases, (8) allergies to contents of medications applied in the trial, and (9) been assessed by the investigators as being unsuitable for the study for other reasons including but not limited to psychiatric or psychosocial conditions.

Study design

All patients were hospitalized in the Department of Endocrinology of Dongguan Tungwah Hospital. A computer-generated randomization assigned participants into two equally sized groups. During hospitalization, all participants received diabetic education, including diet control, exercise, and glucose monitoring. Patients in the multiple daily insulin injection (MDI) group received pre-meal insulin aspart (NovoRapid®, Novo Nordisk) and insulin glargine (Lantus®, Sanofi) at bedtime. In the MDI plus dapagliflozin (MDI+ DAPA) group, patients were treated with dapagliflozin 10 mg per day in addition to the aforementioned MDI regimen. Initial insulin dosage was 0.4–0.6 IU/kg·day and total daily dosage was divided into 60% of prandial (20% for each meal) and 40% of basal. Capillary blood glucose were monitored at least 7 times per day, according to which daily insulin doses were titrated. Euglycemia was defined as fasting blood glucose ≤ 7.0 mmol/L and 2-h postprandial blood glucose ≤ 10.0 mmol/L. Once euglycemia was achieved (D1), the above treatments were maintained for 14 days. On the final day of treatment, the last insulin dose was insulin aspart before dinner (no bedtime insulin glargine). After suspension of medications, all patients were followed up for 12 weeks and required to maintain only diet and physical exercise control but no antidiabetic agents during this 12-week period.

Baseline data of all participants such as gender, age, blood pressure, height, weight, waist circumference, HbA1c, and lipid profiles were collected. All patients underwent a 75g-OGTT and serum glucose, insulin, and C-peptide were measured at 0, 30, 60, 120, and 180 min. These data were measured before treatment (d0), 14 days after reaching euglycemia (D14), and at the 12-week follow-up (W12).

Daily insulin dosages and adverse events including hypoglycemia, urinary infection, and DKA were also recorded.

The study protocol and informed consent document were approved by the Institutional Review Board and Medical Ethics Committee of Dongguan Tungwah Hospital (IRB Number: 2017DHLL018). All recruited patients provided written informed consent for participation. This study was registered at ChiCTR.org.cn with registration number of ChiCTR1800015822.

Study endpoints

In this study, the primary objective was to evaluate whether dapagliflozin as add-on medication to intensive insulin therapy could have extra effect on fasting C-peptide changes, in turn reflecting insulin secretory function. The primary endpoint was the fasting plasma C-peptide concentration, at D14 and W12. Secondary endpoint was areas under curve (AUC) for C-peptide. Other indices including AUC for insulin, homeostasis model assessment of insulin resistance (HOMA-IR), HOMA-β, and early insulin secretion index (EISI) were analyzed as exploratory endpoints.

Calculations

The above indices were calculated as follows:

(1) AUC for C-peptide and insulin were calculated using trapezoidal rule, e.g., $AUC\text{-}CP$ (ng/mL × h) = $(CP_{0min} + CP_{30min}) \times 0.5 / 2 + (CP_{30min} + CP_{60min}) \times 0.5 / 2 + (CP_{60min} + CP_{120min}) \times 1 / 2 + (CP_{120min} + CP_{180min}) \times 1 / 2$

(2) $HOMA\text{-}IR = FPG$ (mmol/L) × *fasting insulin (FINS)* (μIU/mL) / 22.5;

(3) $HOMA\text{-}\beta = 20 \times FINS$ (μIU/mL) / [FPG (mmol/L) − 3.5];

(4) $EISI = \Delta I30 / \Delta G30 = [INS_{30min}$ (μIU/mL) − $FINS$ (μIU/mL)] / [GLU_{30min} (mmol/L) − FPG (mmol/L)].

Statistical analysis

Sample size calculation was based on the data of Fang et al. [15], which reported the fasting C-peptide at 12 weeks of T2DM patients receiving intensive insulin therapy with or without dapagliflozin. Based on their work, the difference of fasting C-peptide between the two groups is 0.2 ng/L (SD = 0.2 ng/L). Thus, the sample size required for analysis of the primary endpoint was 54 subjects, to ensure a two-sided significance level of 0.05 and statistical power of 0.90 with a drop-out rate of 15%.

Data were analyzed with IBM® SPSS® Statistics Version 22. Normally distributed data were presented as mean ± SD, and non-normally distributed variables (triglyceride, AUC-CP, AUC-INS, EISI, HOMA-IR, and HOMA-β) were expressed as median (interquartile range). Independent-sample *t*-test or Mann-Whitney *U* test was used to compare differences between two groups of normally or non-normally distributed data, respectively. Paired *t*-test or Wilcoxon signed rank test was performed to estimate the changes between each time point within the group. The χ^2 test or Fisher's exact test was applied to analyze the differences of proportions. A two-sided value of $p < 0.05$ was defined statistically significant.

Results

Baseline characteristics

The enrolled patients were 40.6 ± 8.6 years in age, and HbA1c of 11.8 ± 2.1% (Table 1). They were randomly assigned to the MDI group ($n = 30$) or the MDI+DAPA group ($n = 30$). One patient in the MDI+DAPA group did not finish therapy during hospitalization due to withdrawal of consent. At the subsequent 12 weeks visit, 2 patients (1 in the MDI group, 1 in the MDI+DAPA group) were lost to follow-up. Table 1 illustrates the baseline clinical characteristics of patients in the two groups. Most of them were comparable, except for family history and triglyceride. The positive rate of family history was significantly higher in the MDI+DAPA group (43.3%) than that in the MDI group (13.3%) ($p = 0.010$). Triglyceride also showed statistical difference, with 2.27(1.81) mmol/L in the MDI+DAPA group and 1.69(1.36) mmol/L in the MDI group ($p = 0.015$). Other indices including plasma glucose, C-peptide and insulin profiles, and β-cell function markers had no significant differences between the two groups.

Table 1 Baseline characteristics of study population

	MDI group ($n = 30$)	MDI+DAPA group ($n = 30$)	*p* value
Gender (male/female)	24(80.0) / 6(20.0)	24(80.0) / 6(20.0)	1.000
Age (years)	39.3 ± 7.9	41.9 ± 9.1	0.231
Family history (with/without)	4(13.3) / 26(86.7)	13(43.3) / 17(56.7)	0.010
Systolic pressure (mmHg)	121 ± 16	120 ± 17	0.841
Diastolic pressure (mmHg)	84 ± 13	80 ± 13	0.191
Weight (kg)	67.3 ± 10.0	71.0 ± 10.1	0.162
Body mass index (kg/m^2)	24.19 ± 3.47	24.83 ± 2.61	0.423
Waist circumference (cm)	88.6 ± 10.1	90.9 ± 6.5	0.302
HbA1c (%)	11.9 ± 2.2	11.6 ± 2.0	0.637
Fasting plasma glucose (mmol/L)	13.25 ± 3.69	14.92 ± 4.53	0.124
Fasting plasma insulin (mU/L)	9.00 ± 5.58	12.65 ± 14.89	0.213
Fasting plasma C-peptide (ng/mL)	1.74 ± 1.08	1.95 ± 1.05	0.456
Total cholesterol (mmol/L)	5.27 ± 1.02	5.30 ± 1.38	0.927
Triglyceride (mmol/L)	1.69(1.36)	2.27(1.81)	0.015
HDL-cholesterol (mmol/L)	0.98 ± 0.22	0.98 ± 0.25	0.960
LDL-cholesterol (mmol/L)	3.68 ± 0.98	3.30 ± 0.96	0.139
HOMA-β	22.34(23.60)	16.44(21.04)	0.701
EISI	0.316(0.86)	0.305(1.75)	0.595
AUC-INS (μIU/mL × h)	46.95(54.14)	42.34(55.31)	0.988
AUC-CP (ng/mL × h)	9.11(7.75)	8.71(8.30)	0.802
HOMA-IR	4.53(4.84)	5.03(5.82)	0.344

Data are presented as mean ± SD, median (interquartile range), or number (percentage) according to the type of data as appropriate. *HOMA* homeostatic model assessment, *EISI* early insulin secretion index, *AUC* area under the curve, *CP* C-peptide

Glycemic control and insulin dosage

All patients achieved euglycemia in the first week of therapy. The median time to reach euglycemia was 4.0(3.0) days in the MDI group, while the number was 3.5(2.0) in the MDI+DAPA group. There was no significant difference (p = 0.763). After achieving euglycemia, daily insulin dosages decreased gradually. There were no significant differences in average capillary FBG and 2hBG after achieving euglycemia between the two groups (Fig. 1). However, daily average insulin dosage in the MDI+DAPA group was lower than that in the MDI group (0.27 ± 0.12 versus 0.36 ± 0.22 U/kg·day, p = 0.050) (Fig. 1). After treatment, both at D14 and W12, HbA1c, FPG, and plasma glucose after a 75g-OGTT were all significantly decreased, but no difference was observed between the two groups (Figs. 2 and 3). Proportions of patients who achieved HbA1c ≤ 6.5% at W12 were similar in both groups (58.6% in the MDI group versus 53.6% in the MDI+DAPA group, p = 0.701).

Beta cell function and insulin resistance

Figure 3 illustrates the OGTT plasma glucose, C-peptide, and insulin profiles. They were generally comparable between the two groups at d0, D14, and W12, respectively. There was no significant difference of fasting C-peptide concentrations between the two groups, either at D14 or W12. In both groups, AUC-CP, AUC-INS, EISI, and HOMA-β were ameliorated significantly after treatment compared with baseline (Fig. 4). AUC-CP improved more significantly in the MDI+DAPA group than in the MDI group, at both D14 and W12. For EISI in the MDI+DAPA group, the improvement also sustained at 12-week visit (p = 0.004, D14 vs. W12), while no similar amelioration could be found in the MDI group. In addition, AUC-INS increased after treatment, but the improvements in the two groups were similar. However, there was no such improvement in HOMA-β at W12 compared with that at D14. HOMA-IR reduced significantly after treatment at D14 compared with baseline in both groups. At the 12-week visit, HOMA-IR in both groups elevated, but only in the MDI group showed significant difference compared with D14 (p = 0.035).

Adverse events

During the hospitalization, the incidence of hypoglycemia which was defined as capillary blood glucose level < 3.9 mmol/L was similar in both groups (29 times in the MDI group, 28 times in the MDI+DAPA group, p = 0.666). There were 3 cases of urinary infection in the MDI group, while 1 was observed in the MDI+DAPA group. Rate of incidence showed no significant differences (p = 0.611). Not any case of DKA was observed.

Discussion

The current study assessed the effect of dapagliflozin as add-on agent to MDI treatment on β-cell function and insulin resistance in newly diagnosed T2DM patients. By using a 75g-OGTT, we found that dapagliflozin combined with short-term intensive insulin therapy did not bring extra benefit in amelioration of pancreatic β-cell function.

Progressive β-cell dysfunction is the basic mechanism of the development or deterioration of hyperglycemia [1]. For newly diagnosed type 2 diabetic patients, preserving their β-cell function to the largest extent is essential. Intensive insulin therapy, by fast correction of glucotoxicity and lipotoxicity, is able to induce durable amelioration in insulin sensitivity, leading to long-term glycemic remission [6–8]. Thus, short-term

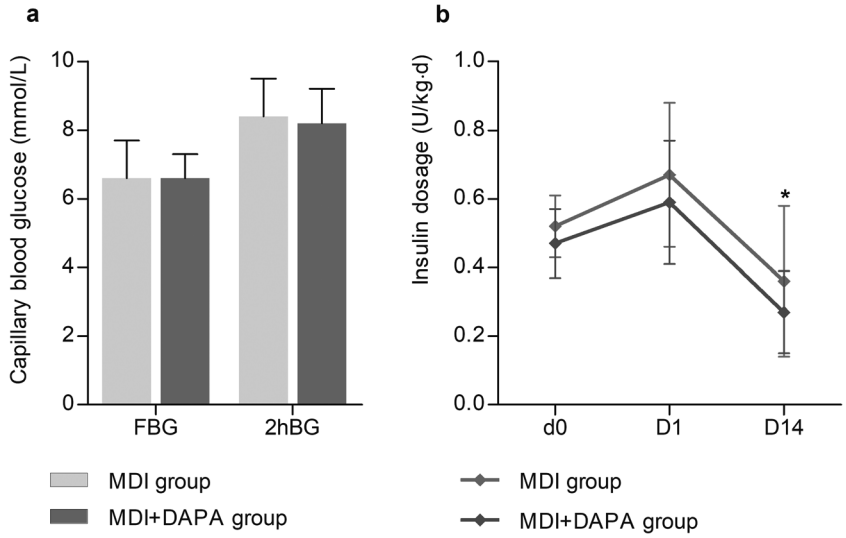

Fig. 1 **a** Mean capillary blood glucose after reaching euglycemia and **b** daily insulin dosage of the two treatment groups. *p < 0.05 for comparison between the two treatment groups. FBG, fasting capillary blood glucose; 2hBG, 2-h postprandial capillary blood glucose; d0, baseline; D1, the day when achieved euglycemia; D14, the 14th day after achieving euglycemia

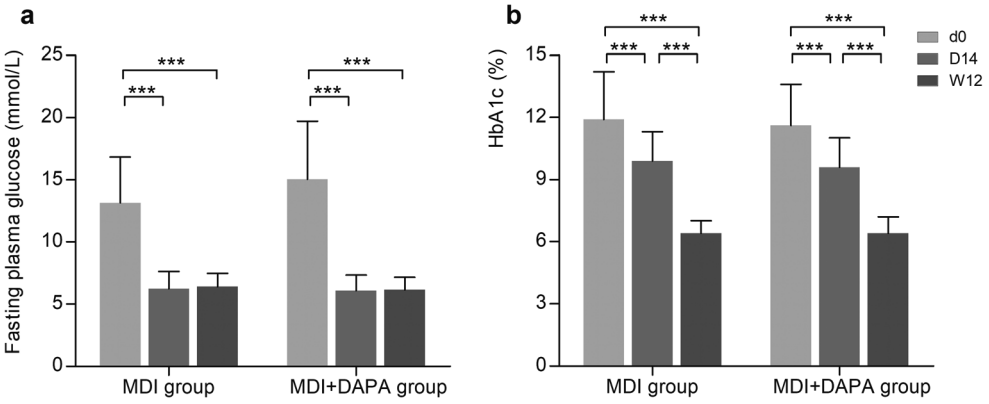

Fig. 2 Glycemic control of the two groups, **a** fasting plasma glucose, and **b** HbA1c. ***$p < 0.001$. d0, baseline; D14, the 14th day after achieving euglycemia; W12, the 12-week visit

intensive insulin therapy is recommended for newly diagnosed T2DM patients in clinical practice guidelines in China [14]. Recent clinical researches revealed that dapagliflozin, or other SGLT-2 inhibitors, improved β-cell function and insulin resistance, which might be due to mitigation of glucotoxicity [12, 13, 16, 17]. Ferrannini et al. [18] even reported an immediate improvement after just one single-dose of empagliflozin.

To our knowledge, no previous study has evaluated β-cell function of dapagliflozin as add-on to short-term intensive insulin therapy for newly diagnosed T2DM patients. In the current study, OGTT-derived C-peptide and insulin profiles after treatment at D14 and W12 were significantly increased in both groups. All the other β-cell function indices also improved, thereby confirming the efficacy of the intervention in this

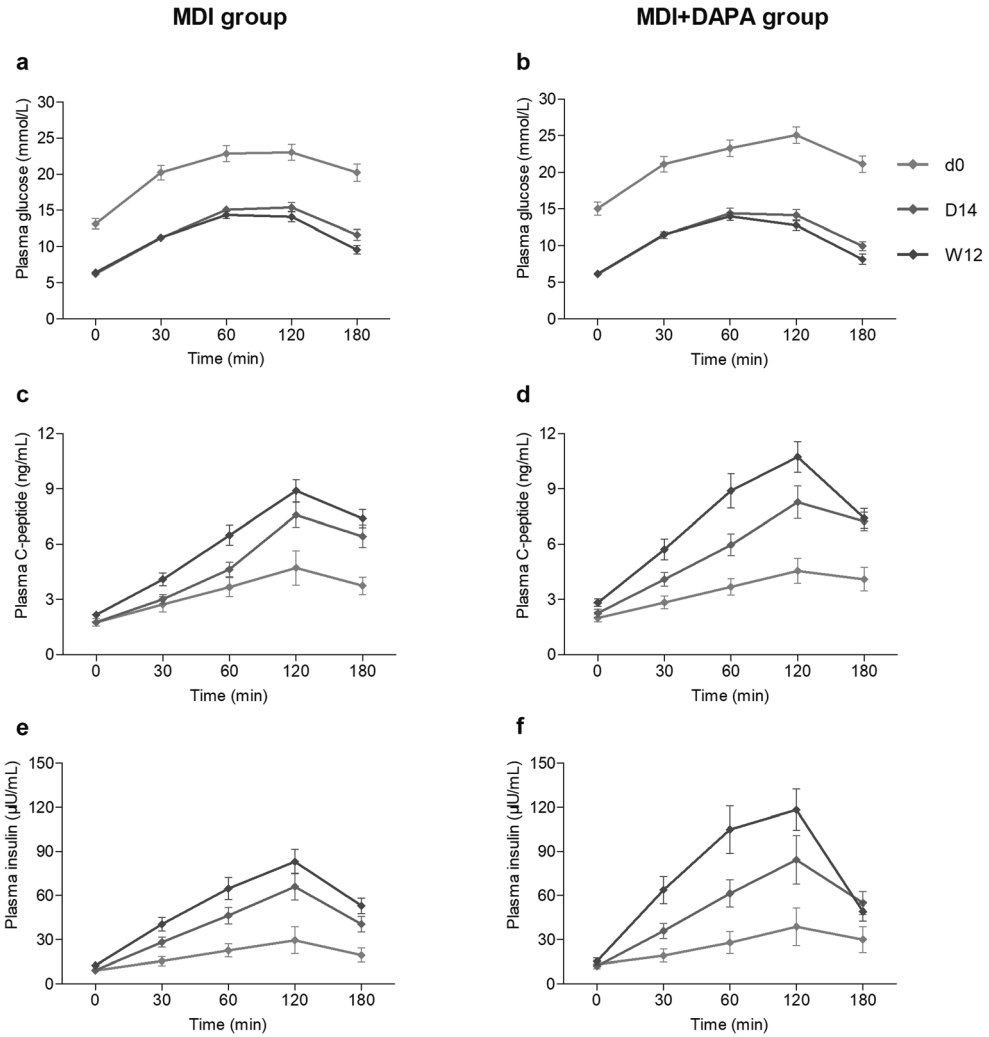

Fig. 3 Plasma (**a**, **b**) glucose, (**c**, **d**) C-peptide, and (**e**, **f**) insulin concentrations after a 75g-OGTT of the two groups. Plots represent mean ± SEM. d0, baseline; D14, the 14th day after achieving euglycemia; W12, the 12-week visit

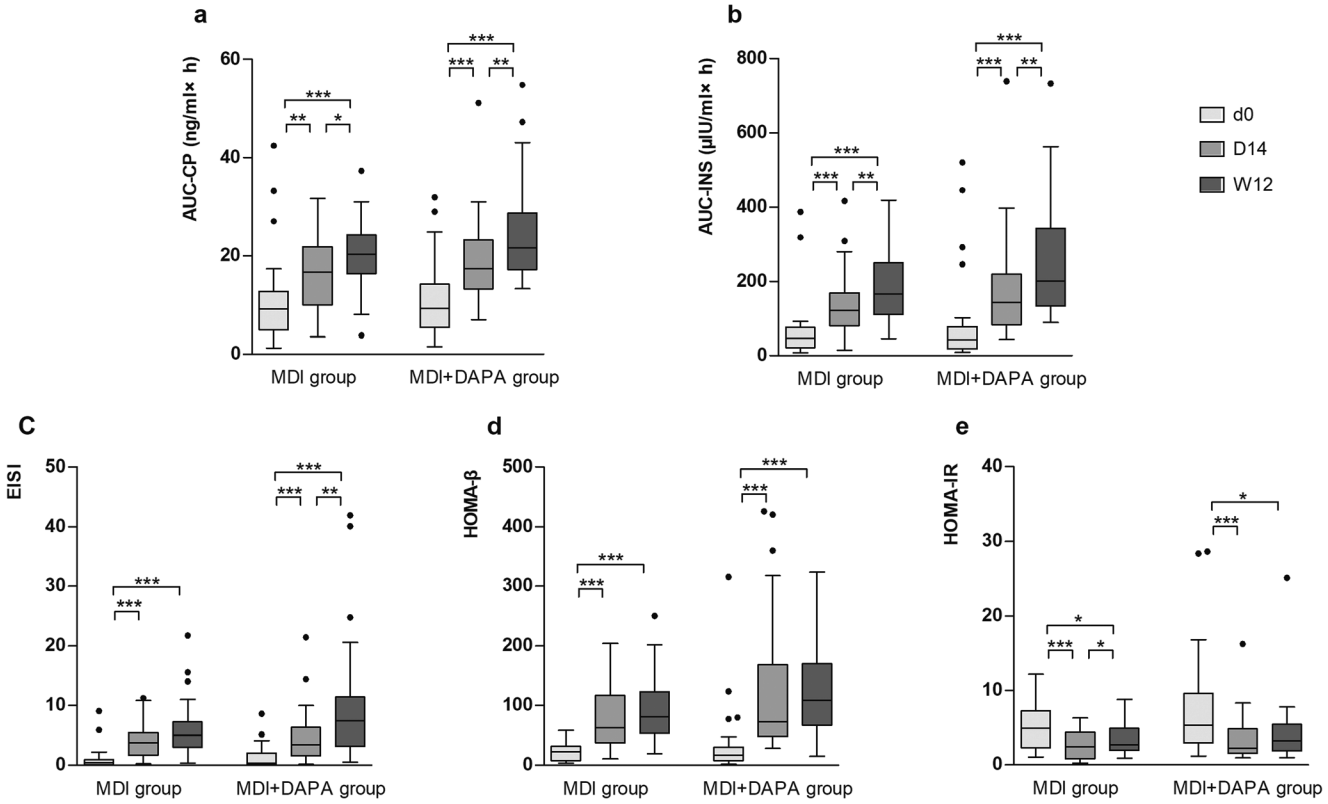

Fig. 4 Box plots of β-cell function indices, **a** AUC-CP, **b** AUC-INS, **c** EISI, **d** HOMA-β, and **e** HOMA-IR. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. AUC-CP, area under the curve for plasma C-peptide; AUC-INS, area under the curve for plasma insulin; EISI, early insulin secretion index; HOMA, homeostasis model assessment; d0, baseline; D14, the 14th day after achieving euglycemia; W12, the 12-week visit

patient population. However, there were no significant differences between the two treatment groups, indicating that dapagliflozin does not further enhance the effect of short-term intensive insulin therapy on β-cell function. As mentioned above, there were researches revealing that SGLT-2 inhibitors could improve β-cell function [12, 13, 16, 17], but they were applied as mono-therapy and compared with other antidiabetic agents or placebo in those studies. Their improvements were closely correlated with decrement of plasma glucose, implying that β-cell function amelioration was mainly resulted from elimination of glucotoxicity. In our study, all patients in both groups achieved euglycemia in 1 week and maintained similar glycemic control even after cessation of treatment. Thus, it was not surprising that their improvements of β-cell function indices were similar.

However, when comparing with themselves at different time points, we found that AUC-CP improvement was more significant in the MDI+DAPA group. Remarkably, after suspension of treatment, dapagliflozin provided a sustained significant improvement of EISI at D14 while no such change was observed in the MDI group. As EISI takes into account the 30-min response upon glucose stimulation, it is more sensitive for evaluation of the early phase of insulin release than other indices used in the study. It is also reported that SGLT-2 inhibitors mitigate insulin resistance [12]. In the current study, we observed a decrease of HOMA-IR after treatment, but elevation after suspension of medication. Interestingly, with the use of dapagliflozin, the elevation was not significant. Taken together, we suggest that the prolonged improvement of EISI is most likely due to amelioration of insulin resistance. But as these were explorative indices, further researches designated EISI as primary endpoints were needed to confirm our findings.

The present study also demonstrated a significant reduction in plasma glucose levels after treatment at D14 and even after cessation of medication at W12. This acknowledged the role of dapagliflozin plus MDI therapy in glycemic control for newly diagnosed T2DM patients. Furthermore, dapagliflozin reduces daily insulin requirement as expected, reaching the same level of blood glucose with those accepting MDI alone. However, there was no difference of HbA1c, fasting plasma glucose, or number of patients who achieved euglycemia after treatment suspension between the two groups, indicating the short-term use of dapagliflozin does not bring additive effects on glycemic control for patients receiving MDI therapy.

As SGLT-2 inhibitors lower plasma glucose by enhancing urinary glucose excretion, urinary infections are known adverse effects. However, the current study did not observe a difference between the two treatment groups. Plus, due to its insulin-independent antidiabetic mechanism, dapagliflozin did not cause apparent increase in hypoglycemia. Therefore, dapagliflozin is sufficiently safe.

There were some limitations in this study. First, the primary endpoint of the study, fasting C-peptide concentration, was one of the easiest but apparently not the best index to measure pancreatic β-cell function. Hyperglycemic clamp is by far the gold standard to evaluate β-cell function, but it is costly, time-consuming, and difficult to implement. Researches revealed that chronic hyperglycemia may deteriorate meal- and glucose-induced endogenous insulin secretion, somewhat confounding C-peptide and insulin response [19, 20]. On the contrary, fasting serum C-peptide is not associated with baseline glycemic control [20, 21] and is simple for assessment of basal endogenous insulin secretion in daily clinical practice. As participants recruited in this study were drug-naive, glucotoxicity probably existed. In this case, the lack of influence of baseline HbA1c on fasting C-peptide might be helpful to evaluate the residual beta-cell function. Second, the sample size estimation was based on the primary endpoint, so when analyzing the other indices, it might be relatively small and reduce the statistical power. Future studies with a large enough sample size setting other indices such as EISI as primary endpoint will be needed to further explore the question. Third, the study population might not be a good representative for general T2DM patients. Dapagliflozin was approved for only 1 year in China when the study began. Most patients were reluctant to participate in a study on a somewhat new drug.

In conclusion, dapagliflozin as add-on medication was effective and safe in glycemic control and could reduce daily insulin requirement, but it did not bring additive effects on improvement of β-cell function for newly diagnosed T2DM patients receiving short-term intensive insulin therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-022-01089-w.

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Availability of data and material Data sharing will be considered only on a collaborative basis with the principal investigators, after evaluation of the proposed study protocol and statistical analysis plan.
Code availability Not applicable.

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Declarations

Ethics approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol and informed consent document were approved by the Institutional Review Board and Medical Ethics Committee of Dongguan Tungwah Hospital (IRB Number: 2017DHLL018) and the Chinese Clinical Trial Registry (ChiCTR.org.cn: ChiCTR1800015822).

Consent to participate All recruited patients provided written informed consent for participation.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Kahn SE. Clinical review 135: the importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab. 2001;86(9):4047–58.
2. Sakuraba H, Mizukami H, Yagihashi N, Wada R, Hanyu C, Yagihashi S. Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese type II diabetic patients. Diabetologia. 2002;45(1):85–96.
3. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003;52(1):102–10.
4. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH, Yoo SJ, Kang MI, Cha BY, Lee KW, Son HY, Kang SK, Kim HS, Lee IK, Bonner-Weir S. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab. 2003;88(5):2300–8.
5. Wajchenberg BL. Beta-cell failure in diabetes and preservation by clinical treatment. Endocr Rev. 2007;28(2):187–218.
6. Ilkova H, Glaser B, Tunçkale A, Bagriaçik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. Diabetes Care. 1997;20(9):1353–6.
7. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng JP. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. Diabetes Care. 2004;27(11):2597–602.
8. Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, Hu Y, Zhou Z, Yan X, Tian H, Ran X, Luo Z, Xian J, Yan L, Li F, Zeng L, Chen Y, Yang L, Yan S, 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(9626):1753–60.
9. Hu Y, Li L, Xu Y, Yu T, Tong G, Huang H, Bi Y, Weng J, Zhu D. Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and β-cell function in subjects with long-term remission. Diabetes Care. 2011;34(8):1848–53.
10. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. Cardiovasc Diabetol. 2015;14:142.
11. Scheen AJ. Sodium-glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2020;16(10):556–77.
12. Kaneto H, Obata A, Kimura T, Shimoda M, Okauchi S, Shimo N, Matsuoka TA, Kaku K. Beneficial effects of sodium-glucose cotransporter 2 inhibitors for preservation of pancreatic β-cell function and reduction of insulin resistance. J Diabetes. 2017;9(3):219–25.
13. van Raalte DH, Verchere CB. Improving glycaemic control in type 2 diabetes: stimulate insulin secretion or provide beta-cell rest? Diabetes Obes Metab. 2017;19(9):1205–13.
14. Jia W, Weng J, Zhu D, Ji L, Lu J, Zhou Z, Zou D, Guo L, Ji Q, Chen L, Chen L, Dou J, Guo X, Kuang H, Li L, Li Q, Li X, Liu J, Ran X, et al. Standards of medical care for type 2 diabetes in China 2019. Diabetes Metab Res Rev. 2019;35(6):e3158.

15. Fang WJ, Li XY, Feng QW, et al. Effects of dapagliflozin on type 2 diabetes mellitus with inadequate glycemic control after insulin treatment. J Intern Med Concepts Pract. 2018;13(03):153–7.
16. Kurosaki E, Ogasawara H. Ipragliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors in the treatment of type 2 diabetes: preclinical and clinical data. Pharmacol Ther. 2013;139(1):51–9.
17. Merovci A, Mari A, Solis-Herrera C, Xiong J, Daniele G, Chavez-Velazquez A, et al. Dapagliflozin lowers plasma glucose concentration and improves β-cell function. J Clin Endocrinol Metab. 2015;100(5):1927–32.
18. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, Broedl UC, Woerle HJ. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest. 2014;124(2):499–508.
19. Funakoshi S, Fujimoto S, Hamasaki A, Fujiwara H, Fujita Y, Ikeda K, Takahara S, Seino Y, Inagaki N. Analysis of factors influencing postprandial C-peptide levels in Japanese patients with type 2 diabetes: comparison with C-peptide levels after glucagon load. J Diabetes Investig. 2011;2(6):429–34.
20. Yoshiji S, Hasebe M, Iwasaki Y, Shibue K, Keidai Y, Seno Y, Iwasaki K, Honjo S, Fujikawa J, Hamasaki A. Exploring a suitable marker of glycemic response to dulaglutide in patients with type 2 diabetes: a retrospective study. Diabetes Ther. 2022;13:733–46.
21. Højberg PV, Vilsbøll T, Zander M, Knop FK, Krarup T, Vølund A, Holst JJ, Madsbad S. Four weeks of near-normalization of blood glucose has no effect on postprandial GLP-1 and GIP secretion, but augments pancreatic B-cell responsiveness to a meal in patients with type 2 diabetes. Diabet Med. 2008;25(11):1268–75.