Dapagliflozin plus calorie restriction for remission of type 2 diabetes: multicentre, double blind, randomised, placebo controlled trial

Yuejun Liu,[1] Ying Chen,[1] Jianhua Ma,[2] Jiayang Lin,[3] Changqin Liu,[4] Xuejun Li,[4] Yong Xu,[5] Hongyu Kuang,[6] Lixin Shi,[7] Yaoming Xue,[3] Bo Feng,[8] Dalong Zhu,[9] Guang Wang,[10] Jinkui Yang,[11] Xinhua Xiao,[12] Xuefeng Yu,[13] Jiaqiang Zhou,[14] Yuqian Bao,[15] Qing Su,[16] Minzhi Lyu,[17] Xiaomu Li,[1] Huijie Zhang,[3] Xiaoying Li[1,18]

For numbered affiliations see end of the article

Correspondence to: X Li
li.xiaoying@zs-hospital.sh.cn
(ORCID 0000-0002-9383-5757)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;388:e081820
http://dx.doi.org/10.1136/bmj-2024-081820

Accepted: 19 November 2024

ABSTRACT

OBJECTIVE
To assess the effect of dapagliflozin plus calorie restriction on remission of type 2 diabetes.

DESIGN
Multicentre, double blind, randomised, placebo controlled trial.

SETTING
16 centres in mainland China from 12 June 2020 to 31 January 2023.

PARTICIPANTS
328 patients with type 2 diabetes aged 20-70 years, with body mass index >25 and diabetes duration of <6 years.

INTERVENTIONS
Calorie restriction with dapagliflozin 10 mg/day or placebo.

MAIN OUTCOME MEASURES
Primary outcome: incidence of diabetes remission (defined as glycated haemoglobin <6.5% and fasting plasma glucose <126 mg/dL in the absence of all antidiabetic drugs for at least 2 months); secondary outcomes: changes in body weight, waist circumference, body fat, blood pressure, glucose homoeostasis parameters, and serum lipids over 12 months.

RESULTS
Remission of diabetes was achieved in 44% (73/165) of patients in the dapagliflozin group and 28% (46/163) of patients in the placebo group (risk ratio 1.56, 95% confidence interval (CI) 1.17 to 2.09; P=0.002) over 12 months, meeting the predefined primary endpoint. Changes in body weight (difference −1.3 (95% CI −1.9 to −0.7) kg) and homoeostasis model assessment of insulin resistance (difference −0.8, −1.1 to −0.4) were significantly greater in the dapagliflozin group than in the placebo group. Likewise, body fat, systolic blood pressure, and metabolic risk factors were significantly more improved in the dapagliflozin group than in the placebo group. In addition, no significant differences were seen between the two groups in the occurrence of adverse events.

CONCLUSION
The regimen of dapagliflozin plus regular calorie restriction achieved a much higher rate of remission of diabetes compared with calorie restriction alone in overweight or obese patients with type 2 diabetes.

TRIAL REGISTRATION
ClinicalTrials.gov NCT04004793.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Very low energy intake and bariatric surgery induce remission of diabetes via systemic and cellular energy deficit, but they are not easy to implement

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors induce energy deficit, which is attenuated by compensatory hyperphagia

The effect of SGLT-2 inhibitors and calorie restriction on diabetes remission has not been investigated in a randomised controlled trial

WHAT THIS STUDY ADDS

The combined regimen of dapagliflozin and regular calorie restriction can lead to remission of diabetes in overweight or obese patients with type 2 diabetes

This study provides a practical strategy to achieve remission for patients with type 2 diabetes

Introduction

Type 2 diabetes is a global public heath challenge and affects 422 million adults worldwide.[1] Several studies show that early type 2 diabetes is not necessarily a permanent condition and can be reversed by an intensive weight management programme. In the DiRECT trial, participants who had had diabetes for up to six years underwent an intensive dietary intervention. Diabetes remission (defined as glycated haemoglobin (HbA_{1c}) <6.5% after at least two months off all antidiabetic drugs) was achieved in 46% of the intervention group, with a mean body weight reduction of 10%.[2] However, the strategy of a very low energy diet in routine care settings remains a challenge. Bariatric surgery is the most effective method of weight loss and can achieve 60-70% remission of diabetes in obese patients.[3 4] However, this option is not widely accepted owing to a high financial cost and the short term and long term risks of adverse events.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (oral glucose lowering drugs) lead to an energy deficit and reduce hyperglycaemia in patients with type 2 diabetes by inhibiting renal glucose re-absorption and increasing urinary glucose excretion.[5] Dapagliflozin promotes approximately 70-80 g of urinary glucose excretion with an associated caloric loss of 280-320 kcal per day and produces a mean weight loss of 2-3 kg in patients with type 2 diabetes.[6] The weight loss effect of SGLT-2 inhibitor therapy is attenuated owing to the metabolic adaption of compensatory hyperphagia,

which, however, could be overcome by calorie restriction. Dietary intervention and metabolic surgery improve insulin sensitivity by inducing a systemic and cellular energy deficit. Energy deficit induced by antidiabetic drugs potentially provides the third line of evidence. Thus, we hypothesised that dapagliflozin plus calorie restriction could achieve greater energy deficit and greater reduction of hyperglycaemia than calorie restriction alone and could lead to remission of diabetes in a generally acceptable way.

Methods

Study design and participants

This study was a multicentre, double blind, randomised, placebo controlled clinical trial conducted in 16 centres in China. Eligible participants were aged 20 to 70 years, had a body mass index greater than 25, had a diagnosis of type 2 diabetes made within the previous six years, and had HbA_{1c} between 6.5% and 10% in patients who had no use of any antidiabetic agents or less than 10% in those taking metformin at screening. We excluded patients with serious cardiovascular or cerebrovascular diseases within three months before randomisation, acute diabetic complications within 30 days, current use of any antidiabetic agents other than metformin, weight loss of more than 5 kg within six months, use of weight loss drugs within 30 days, current treatment with systemic steroids or change in dosage of thyroid hormones within six weeks, participation in another trial of an investigational drug or weight loss programme within three months, a history of bariatric surgery or other gastrointestinal surgeries within two years, cancer, pregnancy or current planned pregnancy, serious liver dysfunction, or chronic kidney disease.

Randomisation and masking

Eligible participants were randomly assigned in a one-to-one ratio to receive 10 mg of dapagliflozin or placebo per day for 12 months, stratified by whether they were treated with metformin at baseline. The statistician who generated the randomisation sequence was not involved in the determination of eligibility or the entry of patients. Randomisation was achieved by an independent third party (Trial Data Pharmaceutical Technology; Shanghai, China) using a centralised interactive web based randomisation system (Trial Data IWRS) with block size of four and stratification according to metformin treatment at screening (yes or no). Dapagliflozin and placebo tablets were identical in size, shape, colour, and appearance, were packaged in identical bottles, and were administered in the same dosage and route. The investigators, clinical staff, dietitian, and patients were masked to treatment throughout the study.

Procedure

All participants were instructed to follow a calorie restriction diet with an energy deficit of 500~750 kcal per day, with fat <35% and protein >15%, based on an actual daily calorie intake at baseline of no less than 1200 kcal per day for men and 1000 kcal per day for women. Participants were provided with protein shakes (Nutriease, Zhejiang Nutriease, China) twice a day for the first three months to improve adherence to the targeted energy intake, and all participants received dietary counselling throughout the trial as previously described.[7] Participants met with the dietitian every month and received messages or telephone calls every two weeks for the first six months and monthly thereafter. Participants were requested to record a dietary log and food picture on a custom mobile study application and to accomplish a three day dietary record (two weekdays and one weekend day) at each visit. Moreover, all participants were encouraged to increase their physical activity and maintain their individual sustainable exercise intensity (for example, 150 minutes of brisk walking every week or more than 10 000 steps per day). We used the international physical activity questionnaire short form to assess physical activity and then calculated the metabolic equivalent of task value.

Participants with metformin treatment at screening were requested to take dapagliflozin or placebo for at least four months and maintained their initial daily dosage of metformin. For participants who achieved normoglycaemia (defined as fasting plasma glucose <110 mg/dL and HbA_{1c} <6.5%) for two months, metformin was stopped first. Participants then stopped taking dapagliflozin or placebo when normoglycaemia was maintained for another two months. Participants without metformin treatment at screening were requested to take dapagliflozin/placebo for at least four months and stop taking it when normoglycaemia was achieved for two months. We considered participants who had HbA_{1c} <6.5% and fasting plasma glucose <126 mg/dL in the absence of all antidiabetic drugs for at least two months as having achieving remission of diabetes. HbA_{1c} was measured at screening, at baseline, each month for the first four months, and every two months thereafter. Fasting plasma glucose was measured monthly at each visit. Participants were asked to self-monitor blood glucose two to four times a week after the intervention was started. We regarded participants with poorly controlled glycaemia (defined as self-measured fasting capillary blood glucose >180 mg/dL and repeated laboratory measured fasting plasma glucose >180 mg/dL within five days) as needing additional antidiabetic medication and withdrew them from the study. Withdrawal from the study due to poor glycaemic control was considered to be a failure to achieve remission of diabetes. The intervention of dapagliflozin or placebo was discontinued at 12 months for all participants. The trial duration included 12 months of dapagliflozin or placebo intervention and two months of follow-up for the assessment of incidence of diabetes remission.

Outcomes

The primary outcome was the incidence of remission of diabetes (defined as HbA_{1c} <6.5% and fasting plasma glucose <126 mg/dL in the absence of all antidiabetic

drugs for at least two months) over the 12 month intervention. Secondary outcomes included changes in body weight, waist circumference, body fat, blood pressure, glucose homoeostasis parameters, and serum lipids during the 12 month intervention. We defined changes in these parameters in each group as the values measured when remission of diabetes was determined (that is, two months after either dapagliflozin or placebo was stopped) minus those measured at baseline. In participants who discontinued the trial in advance or did not meet drug stopping criteria, we report changes as parameters measured at the final visit minus those measured at baseline. We report differences between the groups as estimated mean differences—that is, effect of dapagliflozin minus effect of placebo. Adherence to the medication, dietary programme, and physical activity was evaluated monthly. HbA_{1c} was measured in the central laboratory (Guangzhou Kingmed Center for Clinical Laboratory, Guangzhou, China) using high performance liquid chromatography with a Bio-Rad Variant Haemoglobin A_{1c} assay. We used homoeostasis model assessment to evaluate insulin resistance (HOMA-IR) and β cell function (HOMA-β).[8] The body fat mass and lean mass were quantified using dual energy x ray absorptiometry in centres where it was available. We used the 12 item Short-Form Health Survey Questionnaire (SF-12) to evaluate quality of life.

Statistical analysis

The sample size calculation suggested that 328 participants (164 per group) would provide 80% power to detect a significant difference (12.3%) in the remission rate between the dapagliflozin group and the placebo group at a significance level of 0.05 using a two tailed test, assuming an anticipated dropout rate of less than 20%.

We did all analyses according to the intention-to-treat principle unless stated otherwise. For the primary outcome, we used a Cochran-Mantel-Haenszel test, stratified according to whether participants were treated with metformin at baseline, to estimate the risk ratio and corresponding 95% confidence interval (CI). For the secondary outcomes, we used a mixed effect model with an autoregressive correlation matrix to correct for the correlations of repeated measurements to assess the effects of treatments on changes in the trial outcomes, with metformin treatment as a stratification factor, study centre as a random effect, and baseline value, treatment group, time, and their interaction as fixed effects. We handled missing data with multiple imputations using the Markov Chain Monte Carlo method. An independent data monitoring committee reviewed safety and efficacy data. We present categorical variables as numbers and percentages and continuous variables as mean (standard deviation (SD)) or median (interquartile range (IQR)). We considered a two sided P value <0.05 to indicate statistical significance. We used SAS version 9.4 for all statistical analyses.

Patient and public involvement

No funding was allocated for involvement of patients or the public in the design, conduct, reporting, or dissemination plans of our research. Nevertheless, we consulted with doctors, physician scientists, and statisticians for the study intervention and protocol. We spoke to the patients about the study and the concept of remission of diabetes and asked a member of the public to read our manuscript after submission. Once this study is published, we will disseminate the results to the public through social media and write blogs to explain the results.

Results

Characteristics of participants

Between 12 June 2020 and 31 January 2023, 328 participants were enrolled and randomly assigned to receive calorie restriction with 10 mg of dapagliflozin (165 participants) or placebo (163 participants) and comprised the intention-to-treat population (fig 1). Baseline characteristics of the participants were similar between the two groups (table 1). The mean age of the participants was 46.7 years, 66% (218/328) were men, and the mean body mass index was 28.2. The mean HbA_{1c} was 7.3%, and 45% (148/328) of participants were treated with metformin at baseline. The energy intake and the percentages of energy intake from carbohydrates, protein, and fats were similar in two groups during the trial (supplementary table A). Likewise, physical activity and scores on the SF-12 physical and mental components were similar in the two groups (table 1; supplementary table A).

Remission of diabetes

The median duration of the intervention was 9 (IQR 4-12) months in the dapagliflozin group and 12 (4-12) months in the placebo group. During the trial, 44% (73/165) of participants in the dapagliflozin group achieved remission of diabetes compared with 28% (46/163) in the placebo group. The risk ratio for diabetes remission stratified by whether participants were treated with metformin at baseline was 1.56 (95% CI 1.17 to 2.09) (table 2). Results were similar after further adjustment for intervention time (supplementary table B) and in the per protocol analysis set (supplementary table C). In additional analyses of long term remission of diabetes, the risk ratio for three months' diabetes remission was 1.64 (95% CI 1.14 to 2.37) and that for four months' diabetes remission was 1.74 (1.18 to 2.56) (supplementary table D).

Clinical outcomes associated with 12 month intervention

The mean weight loss from baseline to the final visit was greater in the dapagliflozin group than in the placebo group (5.0 (SD 4.5) *v* 3.2 (3.8) kg). We found a significant difference between the two groups in weight change (−1.3 (95% CI −1.9 to −0.7) kg). Metabolic risk factors were also significantly improved in the dapagliflozin group compared with the control group,

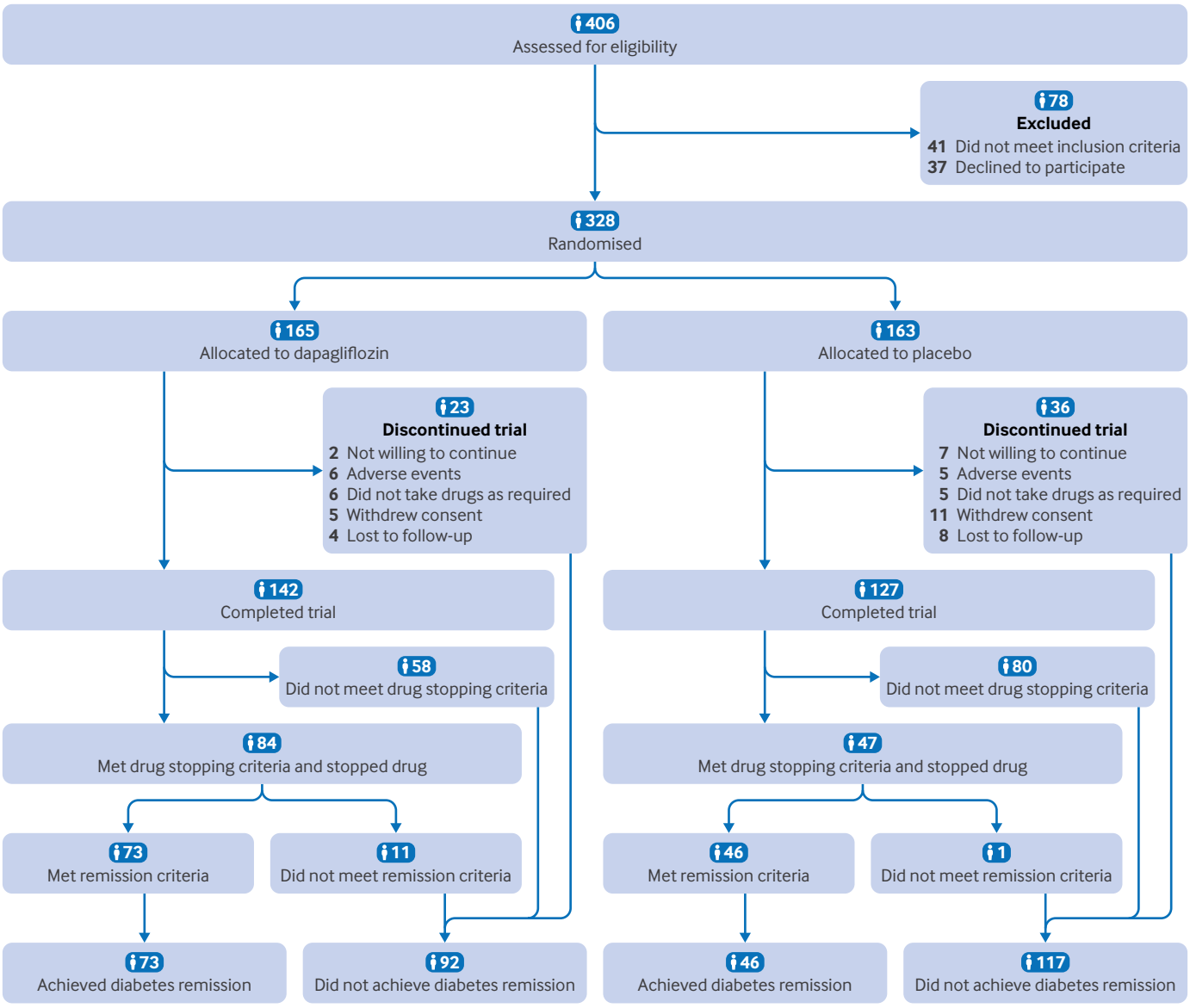

Fig 1 | Flowchart of participants through study. Randomisation was stratified according to whether metformin was used at baseline. Withdrawal from study due to poor glycaemic control was considered as failure of diabetes remission. Drug stopping criteria refers to achievement of normoglycaemia (defined as fasting plasma glucose <110 mg/dL and glycated haemoglobin <6.5%) for two months. Participants stopped taking dapagliflozin or placebo on achievement of drug stopping criteria

including body fat mass, systolic blood pressure, fasting plasma glucose, HbA_{1c}, HOMA-IR, high density lipoprotein cholesterol, and triglycerides (table 2). Furthermore, both the dapagliflozin group and the placebo group were associated with improvement in waist circumference, diastolic blood pressure, HOMA-β, total cholesterol, low density lipoprotein cholesterol, and lean mass, with no differences between the groups (table 2). Results were similar in a sensitivity analysis using multiple imputed data (supplementary table E).

Adherence

We evaluated participants' adherence in several ways. The mean percentage of days that participants adhered to the prescribed medication was 91.5% in the dapagliflozin group and 88.1% in the placebo group. Compliance with the daily energy intake target and with prescribed diets and physical activity was similar in the two groups (supplementary figure).

Safety outcomes

During the trial, two serious adverse events (hospital admission for urinary tract infections) were reported in the dapagliflozin group, representing 1.2% of 165 participants. No deaths occurred during the trial. The rates of occurrence of mild and moderate adverse events were similar in the two groups (table 3).

Discussion

In this randomised, double blinded and placebo controlled trial, we found that a regimen of dapagliflozin plus moderate calorie restriction

doi: 10.1136/bmj-2024-081820 | *BMJ* 2025;388:e081820 | the bmj

Table 1 | Baseline characteristics of study participants

Characteristics	Dapagliflozin (n=165)	Placebo (n=163)
Mean (SD) age, years	46.4 (10.4)	47.1 (11.4)
No (%) male sex	112 (68)	106 (65)
Mean (SD) weight, kg	81.2 (14.7)	83.0 (15.2)
Mean (SD) body mass index	28.9 (3.5)	29.6 (4.3)
Mean (SD) waist circumference, cm	98.0 (10.1)	99.5 (10.4)
Mean (SD) blood pressure, mm Hg:		
Systolic	125.4 (13.4)	128.1 (14.1)
Diastolic	81.8 (9.4)	82.9 (8.7)
No (%) hypertension	90 (55)	93 (57)
Median (IQR) diabetes duration, years	0.3 (0.0-2.2)	0.2 (0.0-2.1)
Mean (SD) fasting plasma glucose, mg/dL	138.9 (28.7)	141.4 (30.8)
Mean (SD) HbA_{1c}, %	7.2 (0.9)	7.4 (1.0)
Median (IQR) HOMA-IR	4.8 (3.1-7.2)	4.1 (2.7-6.5)
Median (IQR) HOMA-β, %	65.7 (47.3-105.1)	61.1 (38.2-97.5)
Mean (SD) total cholesterol, mg/dL	183.7 (40.8)	186.2 (40.9)
Mean (SD) low density lipoprotein cholesterol, mg/dL	111.2 (36.4)	112.7 (37.3)
Mean (SD) high density lipoprotein cholesterol, mg/dL	43.3 (8.9)	44.8 (10.6)
Median (IQR) triglycerides, mg/dL	152.3 (105.4-212.5)	142.6 (102.7-206.3)
Mean (SD) serum creatinine, μmol/L	68.9 (16.4)	67.0 (13.1)
Median (IQR) eGFR, mL/min/1.73 m^2	101.0 (82.6-137.3)	103.2 (83.1-139.7)
Mean (SD) daily energy intake, kcal/day	2356.8 (883.0)	2256.3 (775.0)
Median (IQR) physical activity, MET h/w	11.6 (4.4-19.6)	11.6 (3.3-17.9)
Mean (SD) body fat mass, %	34.0 (6.2)	34.1 (6.9)
Mean (SD) body lean mass, %	63.9 (6.1)	63.5 (7.2)
No (%) metformin treatment	74 (45)	74 (45)
Median (IQR) SF-12 score:		
Physical component summary	50.4 (44.8-53.8)	49.9 (45.8-53.5)
Mental component summary	56.0 (50.0-58.9)	56.0 (49.9-58.6)

eGFR=estimated glomerular filtration rate; HbA_{1c}=glycated haemoglobin; HOMA-IR=homoeostasis model assessment of insulin resistance; HOMA-β=homoeostasis model assessment of β cell function; IQR=interquartile range; MET=metabolic equivalents; SD=standard deviation; SF12=12 item Short-Form Health Survey Questionnaire.

remarkably increased the rate of remission of diabetes (44%) compared with calorie restriction alone (28%) in overweight or obese patients with type 2 diabetes. We also found significantly greater reduction in body weight (difference −1.3 kg) and HOMA-IR (difference −0.8) in the dapagliflozin group. In addition, dapagliflozin plus calorie restriction achieved greater improvement in systolic blood pressure, body fat, serum triglycerides and high density lipoprotein cholesterol concentrations. Our findings show that a regimen of dapagliflozin plus regular calorie restriction was effective and practicable in leading to remission of early type 2 diabetes.

Comparison with other studies

Several clinical studies have assessed the effects of a weight management programme on remission of diabetes.[9] The DiRECT study reported that intensive weight management leading to a mean 10% reduction in body weight achieved a remission rate of 46% in patients with type 2 diabetes during a 12 month intervention.[2] The weight management programme comprised intensive calorie restriction (825-853 kcal/day formula diet for three to five months) that is difficult for patients with diabetes and obesity to comply with. In the DiRECT study, participants were aware of their planned allocation to the control or intervention group because the unit of randomisation was the primary care centre. The Look AHEAD study showed that intensive lifestyle intervention with a calorie intake goal of 1200-1800 kcal per day leading to a mean 8.6% body weight reduction achieved a diabetes remission rate of 11.5% during the first year.[10] Thus, the regimen with prescribed calorie restriction was a more practicable and feasible intervention, but the effect of calorie restriction on remission of diabetes was modest.

In our regimen of calorie restriction, we adopted an energy deficit of 500~750 kcal per day, which is practicable and is suggested in the American Diabetes Association's diabetes guideline.[11] Our intervention comprised feasible calorie restriction and dapagliflozin, which resulted in extra excretion of approximately 70-80 g of glucose in the urine and an additional 280-320 kcal of energy loss per day.[12] Our study showed that the combined regimen of dapagliflozin plus calorie restriction produced greater weight loss (6%) and a relatively higher diabetes remission rate (44%) that is close to the remission rate of 46% in the DiRECT study.[2] In our study, either body weight reduction or dapagliflozin alone could not achieve such a higher rate of diabetes remission. Previous studies showed that an energy deficit led to reduction of excess fat accumulation in the liver and pancreas, as well as improvement of insulin resistance and first phase insulin response.[13] Some other studies showed that early intensive insulin therapy in patients with newly diagnosed type 2 diabetes might improve β cell function and result in extended diabetes remission.[14 15] Our finding of improvement in HOMA-IR rather than in HOMA-β with the combination

Table 2 | Effects of dapagliflozin compared with placebo on diabetes remission and metabolic risk factors. Values are means (SD) unless stated otherwise

	Dapagliflozin (n=165)	Placebo (n=163)	Intervention effect (95% CI)*	P value
Primary outcome				
No (%) in diabetes remission	73 (44)	46 (28)	1.56 (1.17 to 2.09)	0.002
Secondary outcomes				
Change in body weight, kg	−5.0 (4.5)	−3.2 (3.8)	−1.3 (−1.9 to −0.7)	<0.001
Change in waist circumference, cm	−5.6 (5.7)	−4.9 (5.9)	−0.5 (−1.2 to 0.1)	0.11
Change in fat mass, %	−2.1 (2.8)	−1.4 (3.4)	−0.5 (−0.9 to 0)	0.05
Change in lean mass, %	2.1 (3.2)	1.2 (4.2)	0.2 (−0.3 to 0.8)	0.42
Change in systolic blood pressure, mm Hg	−4.0 (12.3)	−3.6 (13.1)	−1.9 (−3.0 to −0.7)	0.002
Change in diastolic blood pressure, mm Hg	−1.4 (8.7)	−1.3 (8.8)	−0.3 (−1.2 to 0.6)	0.47
Change in fasting plasma glucose, mg/dL	−23.4 (25.0)	−13.8 (29.1)	−9.2 (−11.8 to −6.7)	<0.001
Change in HbA_{1c}, %	−1.0 (1.0)	−0.8 (0.9)	−0.2 (−0.3 to −0.1)	0.003
Median (IQR) change in HOMA-IR	−1.8 (−3.7-0.2)	−0.6 (−2.0-0.6)	−0.8 (−1.1 to −0.4)	<0.001
Median (IQR) change in HOMA-β, %	4.0 (−16.8-25.0)	2.8 (−12.7-20.8)	−0.7 (−6.3 to 5.0)	0.82
Change in total cholesterol, mg/dL	5.1 (35.4)	−1.0 (34.1)	2.1 (−1.5 to 5.6)	0.26
Change in low density lipoprotein cholesterol, mg/dL	0.9 (29.4)	−2.7 (31.7)	2.1 (−1.0 to 5.2)	0.19
Change in high density lipoprotein cholesterol, mg/dL	4.8 (6.9)	2.3 (6.2)	1.3 (0.4 to 2.2)	0.003
Change in triglycerides, mg/dL	−17.3 (−62.0-7.1)	−4.4 (−35.4-20.4)	−16.4 (−31.3 to −1.6)	0.03

CI=confidence interval; HbA_{1c}=glycated haemoglobin; HOMA-IR=homoeostasis model assessment of insulin resistance; HOMA-β=homoeostasis model assessment of β cell function; IQR=interquartile range; SD=standard deviation.
*Risk ratio (95% CI) for primary outcome. Estimated mean difference (95% CI) for secondary outcomes; that is, effect of dapagliflozin minus that of placebo, from mixed effects linear regression model with metformin treatment as stratification factor, study centre as random effect, and baseline value, treatment group, time, and their interaction as fixed effects. Changes in each group are defined as values measured when diabetes remission was determined (2 months after either dapagliflozin or placebo was stopped) minus those measured at baseline; in participants who discontinued trial in advance or did not meet drug stopping criteria, changes are reported as values measured at final visit minus those measured at baseline.

of dapagliflozin and calorie restriction is consistent with studies of bariatric surgeries.[16] Of note, our data showed that dapagliflozin plus calorie restriction significantly reduced body fat compared with calorie restriction alone.

In summary, our results support the strategy of dapagliflozin plus regular calorie restriction (prescribed according to current dietary guidelines) as an effective and sustainable approach for remission of diabetes in patients with early type 2 diabetes. Initial combination therapy is recommended by guidelines from the American Diabetes Association/European Association for the Study of Diabetes for attainment and maintenance of glycaemic targets. Our study suggests that the combination therapy including dapagliflozin for patients with potential for remission of diabetes (for example, overweight or obese, diabetes duration less than six years) provides a potential pharmacological approach to achieve remission of diabetes.

Table 3 | Serious adverse events and adverse events. Values are numbers (percentages)

	Dapagliflozin (n=165)	Placebo (n=163)
Serious adverse events		
Urinary tract infection	2 (1.2)	0
Adverse events		
Nausea	1 (0.6)	0
Vomiting	1 (0.6)	0
Diarrhoea	1 (0.6)	1 (0.6)
Gastro-oesophageal reflux disease	1 (0.6)	0
Gastrointestinal discomfort	0	2 (1.2)
Dizziness	0	1 (0.6)
Somnolence	0	1 (0.6)
Urinary tract infection	7 (4.2)	3 (1.8)
Vaginitis	2 (1.2)	0
Hypoglycaemia	10 (6.1)	7 (4.3)
Haematuria	1 (0.6)	2 (1.2)
Renal calculi	0	1 (0.6)

Number of participants with at least one treatment related adverse event that occurred during trial. Participants may have had adverse event at more than one time point.

Strengths and limitations of study

Our study was a multicentre, placebo controlled and randomised trial. The structured dietary programme was practicable and feasible in a clinical setting. Participants in our study had good adherence to the combined regimen of SGLT-2 inhibitor and moderate calorie restriction.

The study had some limitations. Firstly, our findings cannot be generalised to patients with a duration of type 2 diabetes of more than six years or to populations of other races or ethnic groups. Secondly, we defined remission of diabetes as maintaining normoglycaemia for two months after discontinuation of antidiabetic drugs, which was consistent with the DiRECT study, whereas an international expert group recently proposed a definition of maintenance of normoglycaemia after cessation of antidiabetic drugs for three months.[2] Thirdly, body composition measurement by dual energy x ray absorptiometry was not done in all centres. Fourthly, total energy expenditure was not assessed in this trial.

Conclusions

Our multicenter, double blind and randomised trial showed that the combined regimen of dapagliflozin and regular calorie restriction was effective in achieving remission of diabetes, lowering body weight, and improving metabolic risk factors among overweight or obese patients with type 2 diabetes. Our findings provide an alternative and more practical strategy than intensive weight management to achieve remission for patients with early type 2 diabetes.

AUTHOR AFFILIATIONS

[1]Ministry of Education Key Laboratory of Metabolism and Molecular Medicine, Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai, China

[2]Department of Endocrinology, Nanjing First Hospital, Nanjing, China

[3]Department of Endocrinology and Metabolism, Nanfang Hospital, Southern Medical University, Guangzhou, China

[4]Department of Endocrinology and Diabetes, The First Affiliated Hospital of Xiamen University, Xiamen, China

[5]Department of Diabetes and Endocrinology, Affiliated Hospital of Southwest Medical University, Luzhou, China

[6]Department of Endocrinology, The First Affiliated Hospital of Harbin Medical University, Harbin, China

[7]Department of Endocrinology and Metabolism, Affiliated Hospital of Guizhou Medical University, Guizhou, China

[8]Department of Endocrinology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

[9]Department of Endocrinology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China

[10]Department of Endocrinology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

[11]Department of Endocrinology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

[12]Department of Endocrinology, Peking Union Medical College Hospital, Beijing, China

[13]Department of Endocrinology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[14]Department of Endocrinology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

[15]Department of Endocrinology and Metabolism, Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai, China

[16]Department of Endocrinology, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China

[17]Department of Biostatistics, Zhongshan Hospital of Fudan University, Center of Evidence-based Medicine, Fudan University, Shanghai, China

[18]Shanghai Key Laboratory of Metabolic Remodeling and Health, Institute of Metabolism and Integrative Biology, Fudan University, Shanghai, China

We are grateful to the participants, doctors, and nurses in this trial.

Contributors: YL, YC, JM and JL contributed equally to this study. XL, XL, and HZ conceived and designed the trial. YL, JM, CL, XL, YX, HK, LS, YX, MD, BF, DZ, GW, JY, XX, XY, JZ, YB, QS, XL, HZ, and XL collected the data. YL, YC, JL, ML, and HZ analysed the data. YL, YC, JM, JL, HZ, and XL wrote the manuscript. JM, HZ, and XL revised the manuscript. All authors critically revised the results, reviewed the manuscript, and approved the final version. XL, HZ, and XL contributed equally to this work and should be considered as co-corresponding authors; they had full access to the data and had primary responsibility for the final publication. XL is the guarantor. The corresponding author (XL) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by grants from the National Nature Science Foundation of China (32241011, 82330024, 92357306) and National Nature Science Foundation of China for Distinguished Young Scholars (82325011), and partially by a grant from AstraZeneca (ESR-18-13952). The funders had no role in considering the study design or in the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest and declare: support from National Nature Science Foundation of China, National Nature Science Foundation of China for Distinguished Young Scholars, and AstraZeneca for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol and amendments were reviewed and approved by the ethics committees at each centre. All the participants provided written informed consent.

Data sharing: Data from this study can be requested from the corresponding author. Submission of a proposal with a valuable research question and data access agreement will be required.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The findings of the study will be disseminated to the public through social media and blogs. Once this study is published, we plan to present the study outcomes at congresses in China and worldwide.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 International Diabetes Federation. *IDF Diabetes Atlas.* 10th ed. International Diabetes Federation, 2021.
2 Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541-51. doi:10.1016/S0140-6736(17)33102-1
3 Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577-85. doi:10.1056/NEJMoa1200111
4 Adams TD, Davidson LE, Litwin SE, et al. Weight and Metabolic Outcomes 12 Years after Gastric Bypass. *N Engl J Med* 2017;377:1143-55. doi:10.1056/NEJMoa1700459
5 Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC Med* 2013;11:43. doi:10.1186/1741-7015-11-43
6 List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009;32:650-7. doi:10.2337/dc08-1863
7 Liu D, Huang Y, Huang C, et al. Calorie Restriction with or without Time-Restricted Eating in Weight Loss. *N Engl J Med* 2022;386:1495-504. doi:10.1056/NEJMoa2114833
8 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-9. doi:10.1007/BF00280883
9 Churuangsuk C, Hall J, Reynolds A, Griffin SJ, Combet E, Lean MEJ. Diets for weight management in adults with type 2 diabetes: an umbrella review of published meta-analyses and systematic review of trials of diets for diabetes remission. *Diabetologia* 2022;65:14-36. doi:10.1007/s00125-021-05577-2
10 Gregg EW, Chen H, Wagenknecht LE, et al, Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;308:2489-96. doi:10.1001/jama.2012.67929
11 ElSayed NA, Aleppo G, Aroda VR, et al, on behalf of the American Diabetes Association. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care* 2023;46(Suppl 1):S128-39. doi:10.2337/dc23-S008
12 Tang W, Leil TA, Johnsson E, Boulton DW, LaCreta F. Comparison of the pharmacokinetics and pharmacodynamics of dapagliflozin in patients with type 1 versus type 2 diabetes mellitus. *Diabetes Obes Metab* 2016;18:236-40. doi:10.1111/dom.12594
13 Taylor R, Al-Mrabeh A, Sattar N. Understanding the mechanisms of reversal of type 2 diabetes. *Lancet Diabetes Endocrinol* 2019;7:726-36. doi:10.1016/S2213-8587(19)30076-2
14 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;20:1353-6. doi:10.2337/diacare.20.9.1353
15 Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2013;1:28-34. doi:10.1016/S2213-8587(13)70006-8
16 Sandoval DA, Patti ME. Glucose metabolism after bariatric surgery: implications for T2DM remission and hypoglycaemia. *Nat Rev Endocrinol* 2023;19:164-76. doi:10.1038/s41574-022-00757-5

Web appendix: Supplementary materials