Exenatide and renal outcomes in patients with type 2 diabetes and diabetic kidney disease: a multi-center, randomized, parallel study

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Abstract

Background: This trial aimed to assess the effects of exenatide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), on renal outcomes in patients with type 2 diabetes mellitus (T2DM) and diabetic kidney disease (DKD).

Methods: We performed a randomized, parallel study conducted in 4 general hospitals. T2DM patients with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2 and macroalbuminuria, defined as 24-hour urinary albumin excretion rate (UAER) >0.3 g/24-h, were randomized 1:1 to receive exenatide twice daily plus insulin glargine or insulin lispro plus glargine for 24 weeks. The primary outcome was percentage change in UAER after 24 weeks of intervention comparing to baseline measurement. Rates of hypoglycemia, adverse events and change in eGFR during the follow up were set as safety outcomes.

Results: Between March 2016 and April 2019, 92 patients were randomized and took at least one dose of study drug. The mean age of the participants was 56 years. At baseline, the median UAER was 1512.0 mg/24-h, and mean eGFR was 70.4 mL/min/1.73 m^2. After 24 weeks, exenatide reduced 29.7% of the UAER (p = 0.0255). Meanwhile, the body weight declined by 1.3 kg with exenatide (difference between groups was 2.7 kg, p = 0.0001). Comparing to the control group, lower frequency of hypoglycemia as well as more gastrointestinal adverse events were in intervention group.

Conclusions: Exenatide plus insulin glargine for 24 weeks resulted in significant reduction of albuminuria in T2DM patients with DKD.

Trial registration: Clinicaltrials.gov, NCT02690883. Registered 20 February, 2016, https://clinicaltrials.gov/ct2/show/NCT02690883

Background

Diabetic kidney disease (DKD) is one of the common microvascular complication of diabetes. About 40% of patients who are diabetic will develop DKD [1]. Since 2011, the percentage of hospitalized patients with chronic kidney disease related to diabetes mellitus exceeded those related to glomerulonephritis in China [2]. As the leading cause of end stage renal disease (ESRD), DKD could shorten life span by 16 years for patients with early kidney damage [3]. An initiation of hypoglycemic agent which can also protect renal function is of great importance.

Prospective studies showed that proteinuria is an independent predictor of renal insufficiency in type 2 diabetes [4, 5]. Comparing to those with a baseline urinary albumin-to-creatinine ratio (UACR) ≤ 1.0 g/g and estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2, the incidence rate ratio of ESRD or cardiovascular death events was 12.87 for an initial UACR > 2.0 g/g and eGFR ≤ 30 mL/min/1.73 m^2 after a mean follow-up of 2.8 years [6]. As a surrogate end point of DKD progression, regression of albuminuria can reduce the incidence of ESRD irrespective of therapeutic regimen [7]. Therefore, albuminuria is a valid substitute for ESRD in a short-term intervention.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) has emerged as a new class of antihyperglycemic agent that can also lead to weight loss [8]. GLP-1RA control the blood glucose with a low incident of hypoglycemia by stimulating glucose-dependent insulin secretion [9]. Meta-analysis of several cardiovascular (CV) outcome trials showed that GLP-1RA might have beneficial effect on kidney outcomes [10]. As the chemical structures or pharmacokinetics are vary from each GLP-1RA, whether exenatide twice daily (a short-acting exendin-4 structure) has a renal proactive function remains inconclusive. Data form animal experiment suggested that exendin-4 decrease the 24-hour urinary protein obviously in mice within an 8-week treatment [11]. Furthermore, previous pilot study revealed that exenatide decrease the 24-hour urinary protein excretion in patients with type 2 diabetes and microalbuminuria than those on glimepiride treatment after 16 weeks [12]. Systematic review and meta-analysis indicated that combining GLP-1RA and insulin were as effective as insulin alone on hemoglobin A1c (HbA1c), attaching a significant weight loss, lower risk of hypoglycemia and less insulin dosage [13]. However, the relative effect of exenatide plus insulin on renal function in patients with macroalbuminuria remain uncertain.

This study evaluated the effect of exenatide plus insulin glargine on the primary outcome of DKD progression in type 2 diabetes mellitus (T2DM) by defining the percentage change in urinary albumin excretion rate (UAER). the safety and tolerability of exenatide plus insulin glargine were also assessed during 24-week follow-up.

2. Methods

2.1 Study design and participants

A randomized, open-label, parallel study was conducted in 4 general hospitals in China, involving T2DM patients with DKD. All of the 4 sites had received approval from the local ethics committees. Participants ≥ 18 years of age with an eGFR ≥ 30 mL/min/1.73 m^2 and macroalbuminuria (UAER > 0.3 g/24-h) were randomized 1:1 to receive exenatide twice daily plus insulin glargine or insulin lispro plus glargine and followed up for 24 weeks (Table S1 shows the full eligibility criteria). This trial was registered at ClinicalTrials.gov (NCT02690883).

2.2 Interventions

Before randomization, patients had an up to 3-day screening phase and a 2-week run-in phase. At the end of the screening phase, patients fulfilled with all of the eligibility criteria entered the 2-week run-in phase. During the 2 weeks of the run-in phase, basal insulin would be titrated individually twice a week based on the results of the fasting self-monitoring of blood glucose (SMBG). After the run-in period, patients were randomly assigned to one of two groups for anti-hyperglycemic therapies for a total of 24-week: exenatide plus insulin glargine (intervention group) and insulin lispro plus glargine (controlled group). The treatment of exenatide was initiated by 5 μg bid, and up titrated to 10 μg b.i.d. after 4 weeks and then maintained at 10 μg bid until the completion of the study. Insulin lispro was initially treated according to the insulin dosage of previous antihyperglycemic therapies, and further titrated up at 4-week intervals

until to the target fasting plasma glucose (FPG) (Fig. 1). Starting from the run-in period, all the drugs for reducing blood glucose excepted for exenatide or insulin had been excluded. Whereas, other background therapy for hypertension, hyperlipidemia or cardiovascular related risk factors were treated based on the latest guideline during the follow-up [14].

Abbreviations:

T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; UAER, Urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; BMI, body mass index; BP, blood pressure.

2.3 Outcomes

The primary outcome of the study was the percentage change in UAER from baseline at Week 24. Secondary outcomes included: the percentage change in UACR from baseline at week 24, change from baseline in UAER, UACR, HbA1c, FPG, weight and blood pressure (BP). Safety outcomes included: progression of renal function, defined by eGFR, rates of hypoglycemia and adverse event (AE). Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at week 12 and week 24 through face-to-face visit at each site. The telephone or web-based follow-up were scheduled every month in order to gather information about adverse events including hypoglycemic events.

2.4 Sample size

Statistical tests were performed at a significance level of $\alpha = 0.05$ (two-sided). Referenced to previous research results, the percentage change in UAER would be 40% [7, 12] in exenatide group and 20% [15] in control group respectively. The sample size per group was calculated to provide 80% power and the standard deviation would be 30% (hypothesis: superiority). We should enroll at least 90 patients in total (45 per group) to allow a 20% drop out rate.

2.5 Randomization

Based on randomized (1:1), open-label, parallel-group, controlled study design, block randomization method was applied in this study. In order to prevent selection bias, we developed an allocation concealment mechanism that the allocation sequence was kept in a researcher who did not participate in any clinical work. The physician referred the patient who met the eligibility criteria to the research nurse. After getting the informed consent, research nurse assigned the patient to the researcher who have the allocation sequence and get the result of randomization.

2.6 Statistical methods

The full analysis set (FAS) included all randomized subjects who took at least 1 investigational product (IP), and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessments. The FAS was the primary set for efficacy analysis in this study and subjects was analyzed by the group they were randomized to. The per protocol set (PPS) was a subset of the FAS that included patients who finished the final visit and excluded subjects who had significant protocol deviations. The safety analysis

included subjects who took at least 1 dose of IP. Adverse events including hypoglycemia were collected throughout the treatment period.

The primary endpoint was analyzed utilizing mixed model repeated measures (MMRM) on FAS. The MMRM analysis contained terms for treatment group, time, baseline measurement and time by treatment group interaction. For the covariance structure within subject, the unstructured (UN) was used. Within the framework of MMRM, point estimations ± standard errors were presented at each visit for the mean change within each treatment group as well as the differences and 2-sided 95% CI of the mean change between treatment groups. The $p < 0.05$ was considered as significantly. The analysis of primary endpoint on PPS was performed as sensitivity analysis. Secondary endpoints were analyzed utilizing the similar MMRM analysis as described for the primary endpoint. Data were analyzed using SAS 9.4 software.

3. Results

3.1 Recruitment and follow-up

From March 2016 to April 2019, 887 individuals were screened and 92 were randomized (46 in each group). Eleven patients were excluded from effective analysis due to no any follow-up data after randomization. Eight patients discontinued IP: premature intervention discontinuation due to AE (N = 6), withdrawn consent (N = 1) and lost to follow-up (N = 1). These 8 patients were included in the FAS analysis but not in the PPS analysis. Eighty-one (88.0%) patients (43 in intervention group, 38 in control group) in total were included for the FAS analysis and 73 (79.3%) patients (37 in intervention group, 36 in control group) were included in the PPS (Figure 2).

Figure 2 Flowchart of participants through the trial

Abbreviations: FAS, full analysis set; PPS, per protocol set.

3.2 Patient characteristics

Baseline characteristics of study participants were similar in the two groups (details are shown in Table 1). More than half of the patients were male (N = 64, 69.7%). At baseline, the mean (±SD) age of the participants was 56.0±8.4 years and the average time from diagnosis of diabetes was 11.2±6.6 years. The mean body mass index (BMI) was 24.8±3.5 kg/m^2 and the mean HbA1c was 9.0±1.4%. The median [IQR] UACR was 1245.0 [667.1, 2875.2] mg/g, while the median UAER was 1512.0 [782.5, 2818.0] mg/24-h. The mean eGFR was 70.4±23.4 mL/ min/1.73 m^2.

Before run-in period, 35 participants (38.0%) were using metformin, 14 (15.2%) sulphonylurea and 69 (75.0%) insulin. A total of 75 (81.5%) and 70 (76.1%) of those randomized had diagnoses of hypertension

and hyperlipidemia. The majority (N = 80, 87.0%) were using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blocker (ARB) and large numbers of participants (N = 80, 87.0%) were prescribed statin. A total of 25 (27.2%) reported a history of cardiovascular disease.

Table 1 Baseline characteristics of randomized participants

Variable†	Control (n = 46)	Intervention (n = 46)	Total (n = 92)
Age (years)	56.2 (8.0)	55.9 (8.9)	56.0 (8.4)
Male, n (%)	29 (63.0)	35 (76.1)	64 (69.7)
Duration of diabetes (years)	11.4 (7.0)	10.9 (6.2)	11.2 (6.6)
HbA1c (%)	9.0 (1.3)	9.1 (1.4)	9.0 (1.4)
BMI (kg/m²)	23.5 (3.1)	26.1 (3.4)	24.8 (3.5)
Systolic BP (mmHg)	140.3 (14.6)	139.1 (16.7)	139.7 (15.6)
Diastolic BP (mmHg)	79.1 (7.5)	78.3 (8.3)	78.7 (7.9)
Triglycerides (mmol/L)	1.8 (1.1)	1.8 (0.9)	1.8 (1.0)
Total cholesterol (mmol/L)	5.1 (1.4)	5.1 (1.6)	5.1 (1.5)
HDL (mmol/L)	1.2 (0.3)	1.0 (0.4)	1.1 (0.3)
LDL (mmol/L)	3.2 (1.2)	3.0 (1.3)	3.1 (1.2)
eGFR‡ (mL/min/1.73 m²)	69.2 (24.6)	71.5 (22.5)	70.4 (23.4)
UACR (mg/g)	1380.9 [601.8, 2951.5]	1146.2 [709.4, 2488.2]	1245.0 [667.1, 2875.2]
UAER (mg/24-h)	1438.0 [531.0, 2852.0]	1721.0 [982.0, 2816.0]	1512.0 [782.5, 2818.0]
Current smoker, n (%)	18 (39.1)	23 (50.0)	41 (44.6)
Hypertension, n (%)	36 (78.4)	39 (84.8)	75 (81.5)
Hyperlipidemia, n (%)	35 (76.1)	35 (76.1)	70 (76.1)
Cardiovascular disease, n (%)	13 (28.3)	12 (26.1)	25 (27.2)
Sulfonylurea, n (%)	8 (17.4)	6 (13.0)	14 (15.2)
Metformin, n (%)	17 (37.0)	18 (39.1)	35 (38.0)
AG inhibitors, n (%)	11 (23.9)	13 (28.3)	24 (26.1)
Insulin, n (%)	33 (71.7)	36 (78.3)	69 (75.0)
Diuretic, n (%)	7 (15.2)	6 (13.0)	13 (14.1)
Calcium-channel blocker, n (%)	28 (60.9)	28 (60.9)	56 (60.9)
ACEI/ARB	40 (87.0)	40 (87.0)	80 (87.0)

Beta blocker, n (%)	4 (8.7)	9 (19.6)	13 (14.1)
Any anti-hypertensive, n (%)	41 (89.1)	42 (91.3)	83 (90.2)
Statin, n (%)	39 (84.8)	41 (89.1)	80 (87.0)
Any lipid-lowering drug, n (%)	40 (87.0)	42 (91.3)	82 (89.1)
Aspirin, n (%)	10 (21.7)	19 (41.3)	29 (31.5)
Any anti-platelets, n (%)	13 (28.3)	24 (52.2)	37 (40.2)

†. Numeric variables are presented as mean (SD) if normally distributed. Categorical variables are presented as frequency (%). UAER and UACR are presented as median [IQR].

‡. eGFR are calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Abbreviations: HbA1c, hemoglobin A1c; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; UAER, urinary albumin excretion rate; AG, aminoglycosides; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.

3.3 Primary outcome

In the FAS analysis, the percentage change in UAER was significantly lower in the intervention group, leading a difference of -29.71% (95% CI: -55.27% to -4.15%, p = 0.0255) when comparing to the control group (percentage change in UAER: intervention group was 36.69±16.88%, control group was 66.40±17.42%). It was similar in the PPS analysis (percentage change in UAER: intervention group was 30.07±18.03%, control group was 58.89±18.03%, mean difference was -28.81% with a 95% CI of -55.90% to -1.72%, p = 0.0407) (Table 2 and Figure 3A).

Table 2 Changes after 24 weeks of follow-up

†Absolute mean difference between groups. All values expressed in mean ± standard error.

Abbreviations: FAS, full analysis set; PPS, per protocol set; CI, confidence interval; UAER, urinary albumin excretion rate; UACR,urinary albumin-to-creatinine ratio; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BP, blood pressure; eGFR, estimated glomerular filtration rate.

Figure 3 Mean changes from baseline in the albuminuria according to the analysis of MMRM on FAS. (A) Percentage change in UAER (%); (B) Percentage change in ACR (%); (C) Change in UAER (mg/24-h); (D) Change in ACR (mg/g).

* for $p<0.05$. I bars indicate standard error.

Abbreviations: MMRM, mixed model repeated measures; FAS, full analysis set; UAER, urinary albumin excretion rate; ACR, albumin-to-creatinine ratio.

3.4 Secondary outcomes

The percentage change in UACR (intervention group was 80.93±21.13%, control group was 52.53±20.80%) was equivalent to the level of the percentage change in UAER, leading to an absolute mean difference of -28.40% (95% CI: -56.88 to -1.92, $p = 0.0395$). Although there was no significant difference between two groups for the change in UAER at 24 weeks, treatment effect on the change in UACR of exenatide group was greater than the control group (change in UACR: intervention group was 1405.93±276.87 mg/g, control group was 798.12±269.05 mg/g, mean difference was -607.80 mg/g with a 95% CI: of -1112.38 mg/g to -103.22 mg/g, $p = 0.0209$) (Table 2 and Figure 3B-D).

Both of the treatments reduced HbA1c, FPG and systolic BP at 24 weeks, but there were no significant differences between two groups. Among patients receiving exenatide plus insulin glargine, the mean body weight decreased 1.38±0.63 kg, while the mean body weight increased 1.30±0.66 kg among those receiving insulin lispro plus glargine, for a reduction of 2.68 kg ($p = 0.0001$) at week 24 (Table 2).

3.5 Tolerability and safety

The eGFR increased by 0.98±3.59 mL/min/1·73 m² in the control group and by 1.05±3.13 mL/min/1·73 m² in the intervention group at the first visit (week 4), then decreased by 9.19±2.47 mL/min/1·73 m² in the control group and by 4.64±2.34 mL/min/1·73 m² in the intervention group during the whole follow-up, with an absolute difference of 4.55 mL/min/1·73 m² (95% CI: –1.62 to 10.72; $p = 0.1523$).

Twenty-two adverse events in total had been recorded during the follow-up, while 6 patients (13.04%) in the control group and 16 (34.78%) in the intervention group ($p = 0.015$). Adverse events that led to discontinuation of the treatment occurred in 6 patients (13.04%) in the control group and in 5 (10.87%) in the intervention group ($p = 0.726$). Serious adverse events were reported in 4 patients (8.70%) in control group and in 1 (2.17%) patients in intervention group ($p = 0.361$). The majority of adverse events were gastrointestinal events and all of the 15 patients (32.61%) were in the intervention group ($p <0.001$). However, none of the gastrointestinal events had been considered as sever adverse events. Twenty patients (43.5%) in the control group and 10 patients (21.7%) in the intervention group declared to have

been suffering hypoglycemia during the follow-up (p = 0.026). Furthermore, 2 patients in the control group occurred severe hypoglycemia and discontinued their participation (Table S2).

4. Discussion

Through this randomized controlled trial, we found that exenatide plus insulin glargine for 24 weeks could significantly reduce the percentage change in UAER in T2DM patients with macroalbuminuria when comparing to those on the treatment of insulin lispro plus glargine. The difference was robust in the sensitivity analysis within PPS population. Besides, we also found that adding exenatide to insulin glargine leading to weight lost and lower occurrence of hypoglycemia compared with insulin lispro plus glargine. Although gastrointestinal events were common after initiating the treatment of exenatide, most of these events were mild to moderate and none were severe.

During a median follow-up of 6.8 years, 9.6% individuals with DKD occurred ESRD [16]. The kidney benefits of GLP-1RA when comparing to placebo have been reported in several exploratory analysis of cardiovascular outcome studies covering a large number of T2DM patients [17–19]. Second analysis of LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study showed that adding liraglutide, a GLP-1RA, to usual care could reduce the incidence of composite kidney endpoint [17]. Whereas, there has been a small number of randomized controlled trials reported the effect of exenatide on renal outcomes [12, 20]. Results from EXSCEL (The Exenatide Study of Cardiovascular Event Lowering) suggested that once-weekly exenatide had no effect on renal outcomes, as it did not change the eGFR slope nor the changing ratio from microalbuminuria to macroalbuminuria in a further analysis [20]. However, the primary outcome of EXCEL was cardiovascular disease, and most of the participants were in early DKD stage on the baseline. This bias might attenuate the renal effects of exenatide. Though different GLP-1RA has different structure or mechanism of action, the effects of short-acting exenatide on diabetic microvascular complication are not clear.

Our head-to-head design with positive control was superior to placebo control randomized controlled trial as it can identify glucose-independent effects on real outcomes. Similar design was performed in a 16 weeks study comparing the effect of exenatide and glimepiride, resulted in a significant decrease in 24-hour urinary albumin in T2DM patients with microalbuminuria [12]. Considering the poor prognostic outcomes and lack of effective drugs in patients with DKD [6], we put our emphasis on those patients with macroalbuminuria and poor control of blood glucose. Different from glimepiride or other oral antidiabetic drugs, insulin is commonly used in DKD patients as it doesn’t have to be discontinued while eGFR decreasing [21]. Moreover, using injection as control group for exenatide could decrease the medicine difference between usages. To our knowledge, this is the first study to investigate the effect of exenatide plus insulin glargine on UAER in patients with DKD.

Albuminuria is regarded as a surrogate outcome of DKD progression and meta-analysis showed that regression of albuminuria can reduce the incidence of ESRD irrespective of treatment bias [7]. However, most of the trials in this meta-analysis, involving T2DM patients with DKD, focused on anti-hypertensive

drugs [22–26] and none of any GLP-1RA study was included. Various renal risk factors might impact the effect of exenatide on renal outcomes. A systematic review and meta-analysis of randomized controlled trials and observational studies that assessed the benefits of weight loss. The results showed that short-term interventions of nonsurgical weight loss in patients with CKD reduced proteinuria and blood pressure as well [27]. Though the difference between groups of the change in systolic BP was not significant in our study, we can't ignore the impact of weight change or BP change on albuminuria. Thus, future iteration of a larger sample size and a longer follow-up of the incidence of ESRD may in fact demonstrate the effect of exenatide on renal function.

When studying hypoglycemic drugs, we have to take hypoglycemia events into account. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study have shown that intensive blood glucose control led to increases in mortality or cardiovascular events and hypoglycemia was the main reason [28, 29]. Several risk factors, including age, duration of diabetes and insulin therapy, polypharmacy, previous history of hypoglycemia and presence of macroalbuminuria, were found to be associated with hypoglycemia [30–32]. In this study, the incidence of hypoglycemia was significantly lower in patients treated with exenatide plus insulin glargine than in those treated with insulin lispro plus glargine. Therefore, the decrease in hypoglycemia may reduce the incidence of cardiovascular events, which have been validated in previous studies [10, 33, 34].

The study protocol has certain limitation that we did not perform a blinding procedure during the follow-up and it might lead to bias during the intervention. In order to avoid the selection bias, the physicians or the nurses would not know the treatment assignment until the randomization had been done [35]. Also, we did not collect all the information we've planed due to discontinuation of follow-up. Even so, the MMRM on FAS which included at least 2 points of follow-up was robust enough to detect the difference of percentage change in UAER between groups.

5. Conclusions

In conclusion, this multi-center, randomized, parallel study indicated that exenatide plus insulin glargine for 24 weeks resulted in significant reduction of albuminuria in T2DM patients with DKD. Results from this study will provide fresh evidence on the short-acting exenatide adding to insulin on the progression of kidney function in patients with macroalbuminuria.

Abbreviations

DKD: Diabetic kidney disease; ESRD: End stage renal disease; UACR: Urinary albumin-to-creatinine ratio; eGFR: Estimated glomerular filtration rate; GLP-1RA: Glucagon-like peptide-1 receptor agonists; CV: Cardiovascular; HbA1c: Hemoglobin A1c; T2DM: Type 2 diabetes mellitus; UAER: Urinary albumin excretion rate; SMBG: Self-monitoring of blood glucose; FPG: Fasting plasma glucose; BP: Blood pressure; AE: Adverse event; FAS: Full analysis set; IP: Investigational product; PPS: Per protocol set;

MMRM: Mixed model repeated measures; UN: Unstructured; BMI: Body mass index; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blocker.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional research ethics committee of Nanfang Hospital, Guangdong Second Traditional Chinese Medicine Hospital, Guangdong Provincial Hospital of Chinese Medicine, Guangdong second provincial general hospital and was registered on ClinicalTrials.gov. Informed written consents were obtained from all patients enrolled in this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

There were no conflicts of interest between each author.

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Authors' contributions

X-YW, QZ and H-JZ performed data analysis, interpreted the results, and wrote the manuscript. Y-MX and M-PG contributed to the design of the study, reviewed and

edited the manuscript. S-YS, WM, M-CZ, J-ML, J-LB, X-YT, J-LH, G-GX and PL conducted the enrolment and follow-up of the study. All authors read and approved the final manuscript.

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Table 2

Due to technical limitations, Table 2 is only available as a download in the supplemental files section.

Figures

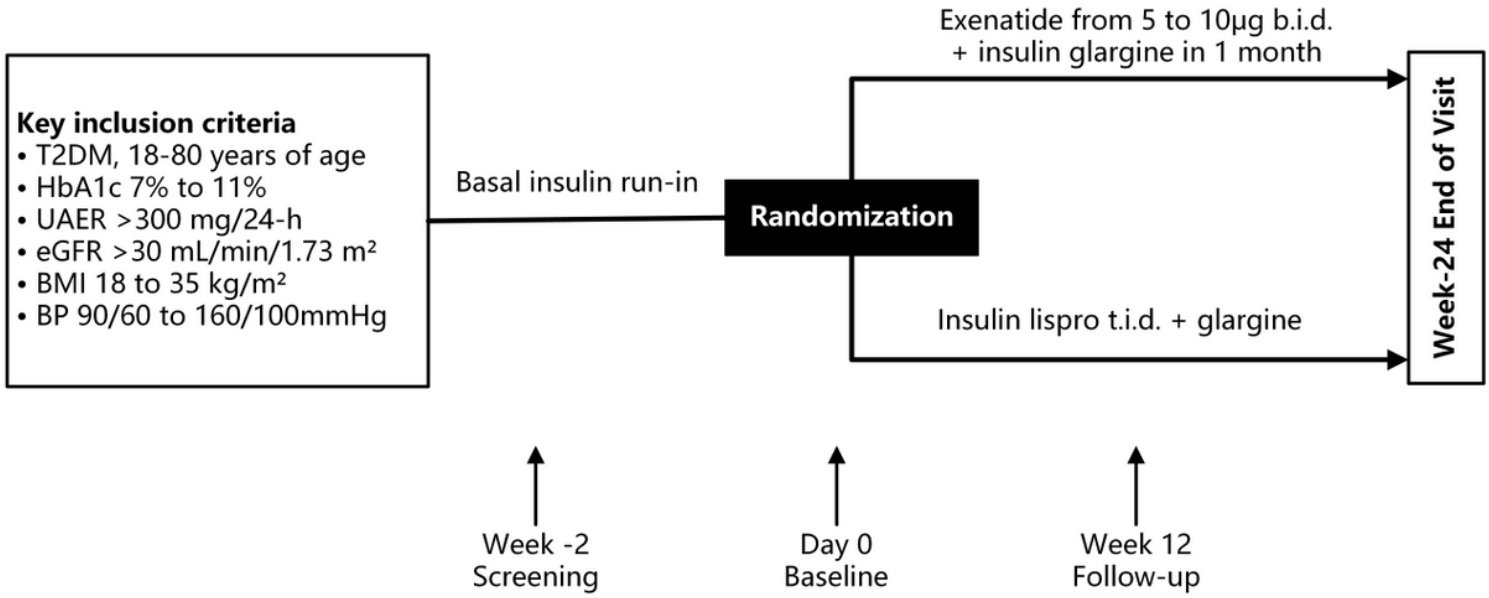

Figure 1

Trial design Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; UAER, Urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; BMI, body mass index; BP, blood pressure.

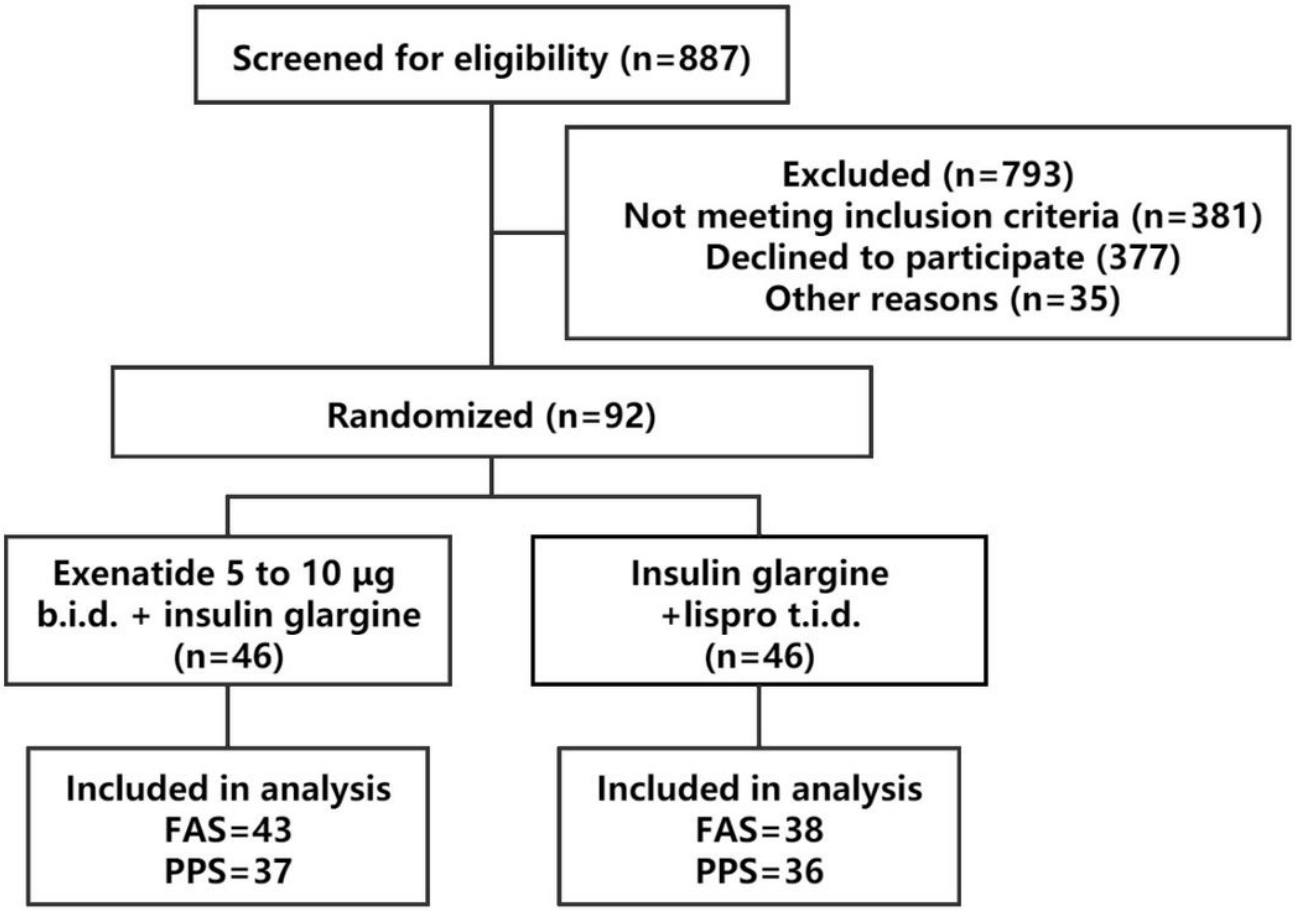

Figure 3

Flowchart of participants through the trial Abbreviations: FAS, full analysis set; PPS, per protocol set.

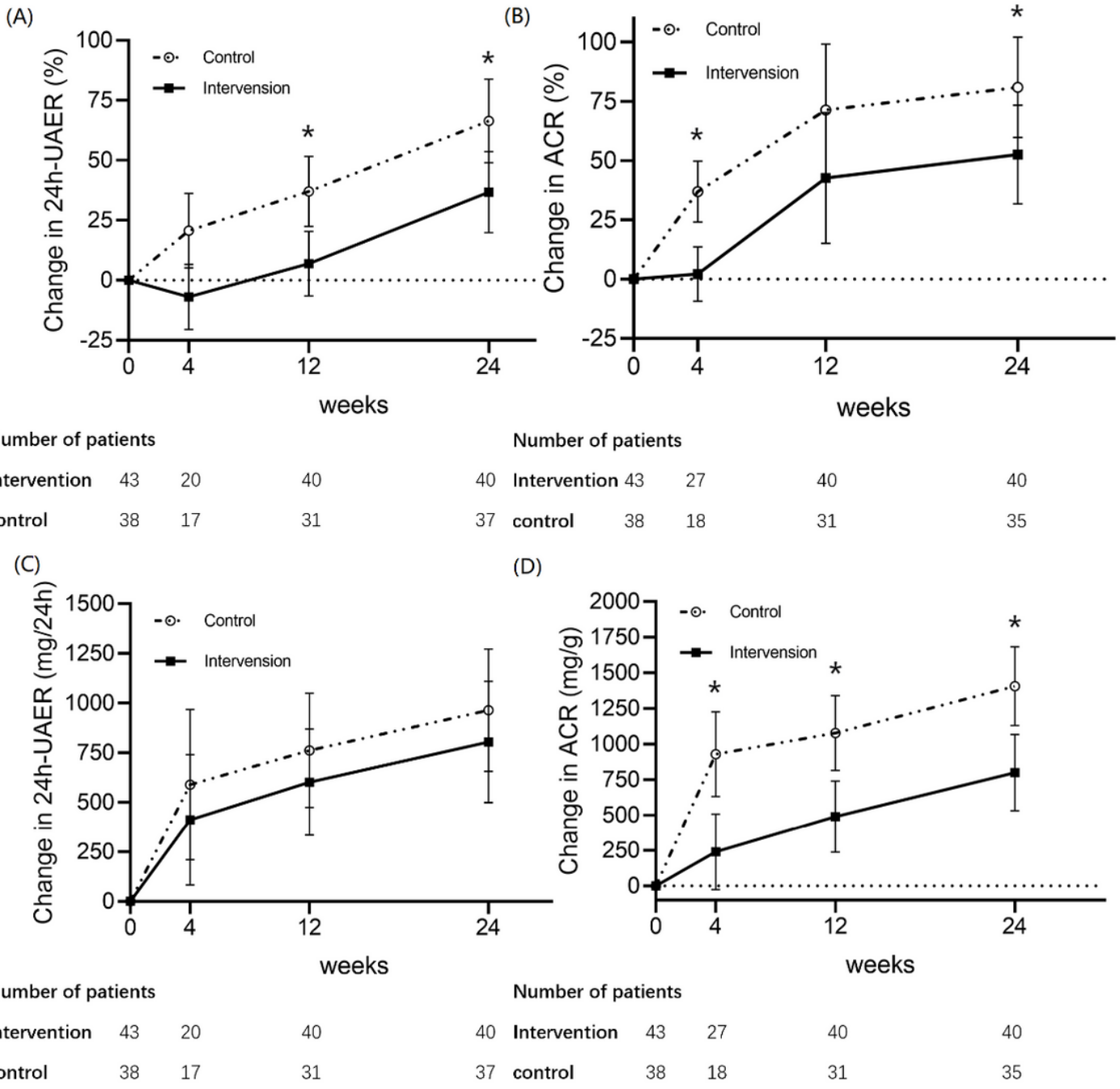

Figure 5

Mean changes from baseline in the albuminuria according to the analysis of MMRM on FAS. (A) Percentage change in UAER (%); (B) Percentage change in ACR (%); (C) Change in UAER (mg/24-h); (D) Change in ACR (mg/g). * for $p<0.05$. I bars indicate standard error. Abbreviations: MMRM, mixed model repeated measures; FAS, full analysis set; UAER, urinary albumin excretion rate; ACR, albumin-to-creatinine ratio.

Supplementary Files

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