

# Comparing the effects of twice-daily exenatide and insulin on renal function in patients with type 2 diabetes mellitus: secondary analysis of a randomized controlled trial

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## ABSTRACT

This is a secondary analysis of a randomized controlled trial (RCT) on the effects of the glucagon-like peptide-1 receptor agonists exenatide and insulin aspartate 30 injection on carotid intima-media thickness. Here, we report the renal outcomes of the intervention in patients with type 2 diabetes mellitus (T2DM). Data from the RCT study was used to evaluate the effect of exenatide or insulin given for 52 weeks on estimated glomerular filtration rate (eGFR) in patients with T2DM. The primary end point was the change in the eGFR from baseline between the exenatide and insulin groups in normal versus overweight patients and patients with obesity. The secondary end point was the correlation between change in eGFR and oxidative stress, glycemic control, and dyslipidemia. There was a significant difference in eGFR between the insulin and exenatide groups at 52 weeks ( $p=0.0135$ ). Within the insulin group, the eGFR remained below baseline at 52 weeks in all patients, and there was an increase in body weight in the normal group compared with the overweight patients and patients with obesity. The opposite was observed in the exenatide group. A decrease in body weight was prominent in the exenatide group at 52 weeks ( $p<0.05$ ), the eGFR was below baseline in overweight patients and patients with obesity and significantly above baseline in the normal group ( $p<0.05$ ). The eGFR was positively correlated to 8-oxo-7,8-dihydroguanosine in the insulin group ( $p<0.05$ ) but not the exenatide group. It can be concluded that compared with insulin, exenatide may improve renal function in overweight patients and patients with obesity more than in normal-weight patients with T2DM, but a further RCT is needed to confirm this effect.

## INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective and well-tolerated antihyperglycemic drugs used in the treatment of type 2 diabetes mellitus (T2DM).<sup>1</sup> They can control body weight and blood lipids and reduce the risk of hypoglycemia.<sup>2</sup> GLP-1RAs have also been

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Chronic kidney disease (CKD) is a common complication associated with type 2 diabetes mellitus (T2DM), and diabetic kidney disease (DKD) is a leading cause of morbidity and mortality in diabetics.
- ⇒ Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have renal protective effects in the treatment of T2DM; the underlying mechanism is unclear.
- ⇒ The body weight is closely related to estimated glomerular filtration rate (eGFR).
- ⇒ Obesity is related to high renal plasma flow and elevated GFR, leading to glomerular damage and is associated with nephrotic syndrome and renal failure.
- ⇒ Obesity-related glomerular hyperfiltration improved after weight loss.

## WHAT THIS STUDY ADDS

- ⇒ Exenatide increased eGFR compared with baseline in patients with T2DM in normal weight.
- ⇒ In overweight patients and patients with obesity, eGFR was slightly higher than baseline and gradually decreased after 16 weeks.
- ⇒ The change in eGFR may be related to the weight loss in overweight and obese patients with diabetes after exenatide treatment.
- ⇒ The changes in eGFR were positively correlated with 8-oxo-7,8-dihydroguanosine ( $p<0.05$ ) in the insulin group.

suggested to have renal protective effects. Chronic kidney disease (CKD) is a common complication associated with T2DM, and diabetic kidney disease (DKD) is a leading cause of morbidity and mortality in diabetics. GLP-1RAs have been reported to delay the histological changes of DKD in preclinical models and improve renal biomarkers independent of glucose.<sup>3</sup> Both the LEADER study (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

- ⇒ Exenatide can delay the decrease of eGFR in patients with T2DM without obvious kidney disease.
- ⇒ In overweight patients and patients with obesity with T2DM, exenatide can improve glomerular hemodynamic abnormalities such as hyperfiltration in the early stage of diabetes through weight loss, delay the progression of renal insufficiency in patients with obesity-related glomerular diseases.
- ⇒ The weight loss of overweight patients and patients with obesity indirectly affects the blood glucose, blood lipid, and blood pressure and indirectly improves renal function through the improvement of oxidation stress.

Term Evaluation) with liraglutide and the REWIND study (The Researching Cardiovascular Events with a Weekly INcretin in Diabetes) with dulaglutide showed that GLP-1RAs reduced the incidence of renal complex end-point events (new massive albuminuria, continuous doubling of creatinine, 40% decrease in estimated glomerular filtration rate (eGFR), end-stage renal disease, kidney-induced death) and delayed the progression of diabetic nephropathy.<sup>4,5</sup> The underlying mechanism of glucose-independent renal protection by GLP-1RAs in T2DM is unclear. Possible mechanisms may include direct effects of GLP-1 receptor (GLP-1R) on diabetic kidneys, such as increased natriuresis, improved glomerular hyperfiltration and renal blood flow, and attenuation of renal fibrosis.<sup>6,7</sup> GLP-1RAs have also been reported to reduce the classic risk factors of renal disease like obesity, hypertension, dyslipidemia, and emerging factors like plasma uric acid, oxidative stress, and inflammation.<sup>2</sup>

Inflammation is common in patients with end-stage renal disease.<sup>8</sup> Obesity is a chronic inflammatory disease in which inflammation occurs in the adipose tissue, known as metabolic inflammation.<sup>9</sup> In addition, there is a prevalence of obesity and abdominal obesity in patients with T2DM, which impacts renal function. In addition, a reduction of weight was correlated with slower DKD progression.<sup>10</sup>

Exenatide is a GLP-1RA used for the treatment of people with T2DM. It lowers blood glucose levels by stimulating insulin release, inhibiting glucagon secretion, and delaying gastric emptying. A recent study showed that long-term use of this drug does not affect renal function-decline or onset/progression of albuminuria in patients with T2DM without overt nephropathy compared with titrated insulin glargine.<sup>11</sup> Exenatide was also shown to offer benefits in weight reduction and cardiovascular and renal function compared with insulin.<sup>12,13</sup> However, there are no comparative clinical studies on the effects of exenatide and insulin aspartate 70/30 on renal function in T2DM with atherosclerosis. In this study, we evaluated the effects of exenatide and premixed insulin, after 52 weeks of treatment, on renal function and possible influencing factors, in addition to blood glucose using a secondary analysis of data from randomized controlled trial (RCT) ChiCTR-1800015658.

## MATERIALS AND METHODS

### Study design

This is a secondary analysis of data from the study of carotid intima-media thickness in patients with T2DM. The methods were previously reported.<sup>12,14</sup>

The study enrolled adults (20–75 years of age) with T2DM and inadequate glycemic control with a hemoglobin A1c (HbA1c) between 7.5% and 11.0% despite receiving at least two oral antihyperglycemic drugs at greater than one half of the maximum dose for at least 3 months prior to screening. Patients were randomized to receive exenatide or insulin aspartate 70/30, co-administered with background metformin, for 52 weeks.

### Study outcomes and patient subgroups

The primary end point was a between-group comparison of the change in eGFR from baseline. The secondary objectives included analysis of the correlation between eGFR changes and multiple factors, such as oxidative stress (as measured by high-sensitivity C reactive protein), fibrinogen, and 8-oxo-7,8-dihydroguanosine (8-oxo-Gsn), body weight, diastolic and systolic blood pressure (DBP, SBP), glycemic control (HbA1c and fasting plasma glucose level (FPG)) and dyslipidemia (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C)).

The patients were divided into two groups based on body mass index (BMI), with the overweight and obese group defined as having a BMI  $\geq 24$  kg/m<sup>2</sup>, with the normal weight group defined as having a BMI  $< 24$  kg/m<sup>2</sup>. Fasting serum creatinine was used to calculate eGFR using the CKD Epidemiology Consortium equation. Differences between the groups in the average rate of change in eGFR for two specified periods were quantified: (1) from baseline to week 4 to assess immediate treatment effects; (2) from week 4 to week 52 to assess long-term treatment effects. Exploratory end points included analysis of the correlation between eGFR changes and multiple factors such as HbA1c, FPG, BP, and fasting lipids.

### Statistical analysis

The full analysis set was used for statistical analysis. For the primary end points, the least-squares mean change from baseline to 52 weeks and associated 95% CIs and p values for exenatide versus insulin were derived from a mixed model for repeated measures with age, sex, duration of T2DM, and renal function at baseline as fixed covariates. Normally distributed data are expressed as means and SD, and the t-test was used for comparison. A  $p < 0.05$  indicated a statistically significant difference. All statistical analyses were carried out with IBM SPSS statistical software V.22 for Windows (IBM, Armonk, New York, USA).

## RESULTS

### Change in eGFR

The study included 27 patients treated with exenatide and 32 patients treated with insulin in the analysis. In the exenatide group, 17 patients were of normal weight, while 10 were overweight or had obesity. In the insulin group, 15 patients were of normal weight while 17 were overweight or had obesity. The baseline characteristics of the patients

**Table 1** Demographic and baseline characteristics

	Exenatide group		P value	Insulin group		P value
	Normal N=17	Overweight and obese N=10		Normal N=15	Overweight and obese N=17	
Age, years	60.47±10.88	56.1±15.21	0.391	61.73±9.83	58.76±10.06	0.414
HbA1c, %	8.54±1.03	8.89±1.07	0.412	8.4±0.77	8.26±1.13	0.702
FPG, mmol/L	9.92±2.92	11.17±2.99	0.315	11.34±2.56	10.35±2.47	0.285
eGFR, mL/min/1.73 m <sup>2</sup>	100.9±12.32	105.8±14.18	0.375	101.3±11.02	104.5±11.72	0.442
BMI, kg/m <sup>2</sup>	21.82±1.27	26.75±1.97	<0.0001	22.18±1.44	26.29±1.48	<0.0001
SBP, mm Hg	123.8±17.19	132.5±14.39	0.196	126.7±16.87	124.4±13.68	0.683
DBP, mm Hg	80.29±10.07	80±9.43	0.947	73.33±9	76.76±9.18	0.370
TBIL, mmol/L	12.63±4.75	10.99±4.54	0.393	10.71±2.78	11.8±5.08	0.463
DBIL, mmol/L	3.87±1.59	3.85±1.91	0.983	3.34±0.74	3.66±1.79	0.537
TG, mmol/L	2.27±1.76	2.05±0.99	0.724	2±1.48	2.2±1.55	0.713
TC, mmol/L	4.89±1.49	4.35±1.25	0.342	4.7±0.91	4.56±0.83	0.658
LDL, mmol/L	3.11±1.03	2.87±1.12	0.581	2.8±0.87	2.85±0.65	0.860
HDL, mmol/L	1.07±0.25	1.06±0.41	0.942	1.18±0.22	1.11±0.26	0.412
FIB, g/L	2.89±0.68	2.88±0.64	0.965	2.98±0.25	2.87±0.71	0.543
Irisin, pg/mL	71.04±5.9	73.75±4.66	0.252	71.36±5.09	70.09±5.95	0.551
8-oxo-Gsn, ng/mL	6.58±0.55	6.65±0.42	0.701	6.68±0.71	6.52±0.67	0.574
NT-proBNP, pg/mL	220.2±25.5	202.9±19.18	0.110	218.5±25.17	207.7±23.49	0.250
IMT, mm	1.01±0.216	1.04±0.28	0.784	1.22±0.12	1.04±0.25	0.051

BMI, body mass index; DBIL, direct bilirubin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB, fibrinogen; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IMT, intima media thickness; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; 8-oxo-Gsn, 8-oxo-7,8-dihydroguanosine; SBP, systolic blood pressure; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride.

are shown in [table 1](#). Patients in the two groups were well balanced for most of the baseline characteristics ([table 1](#)).

There was no difference in baseline eGFR between the two groups. The eGFR decreased slightly compared with baseline in both the groups at 4 weeks (exenatide group,  $-0.44$  mL/min/1.73 m<sup>2</sup>; insulin group,  $-3.06$  mL/min/1.73 m<sup>2</sup>). The eGFR gradually recovered after 28 weeks in the exenatide group, while it decreased slowly in the insulin group. From 40 weeks to 52 weeks, there were significant differences in eGFR between the exenatide and insulin groups compared with baseline ( $p=0.0338$ ,  $p=0.0135$ ). At 52 weeks, the changes in eGFR compared with baseline were  $0.56$  mL/min/1.73 m<sup>2</sup> in the exenatide group and  $-4.24$  mL/min/1.73 m<sup>2</sup> in the insulin group, respectively ([table 2](#) and [figure 1](#)).

The eGFR of normal weight patients in the exenatide group increased compared with baseline with treatment. The same was not observed in the insulin group. The eGFR of overweight patients and patients with obesity in the exenatide group was initially higher than baseline (not significant), but gradually decreased after 16 weeks. There was a significant difference in the eGFR between the normal weight patients and overweight patients and patients with obesity of the exenatide group at 52 weeks ( $p<0.05$ ) ([figure 2](#)). The eGFR was significantly higher in the normal weight patients of the exenatide group.

### Body weight changes

In the exenatide-treated group, the body weight of both normal patients and overweight patients and patients with obesity decreased significantly ( $p<0.05$ ). The weight loss was greater in the overweight and obese group compared with the normal weight group. The weight loss was also

faster in the overweight patients and patients with obesity, reaching the lowest point at 32 weeks, while that of the normal patients was at 36 weeks. Thereafter, a slight gain in weight was observed in both groups of patients, although overall weight remained below the baseline. The BMI was significantly lower than baseline in the overweight patients and patients with obesity at 52 weeks ( $p<0.01$ ).

In contrast, body weight increased in the insulin-treated group. Weight gain in the normal weight group was more obvious than in the overweight and obese group, which returned to baseline by 52 weeks ([figure 3](#)). Weight gain in the normal weight insulin group was significantly higher at 52 weeks ( $p<0.05$ ).

### Factors correlated with eGFR changes

A significant positive correlation was observed between changes in eGFR and 8-oxo-Gsn ( $p<0.05$ ) in the insulin group. In contrast, in the exenatide group, a significant negative correlation with FPG, BMI, and HDL was observed ( $p<0.05$ ) ([table 3](#)).

There was no correlation between the changes observed in eGFR and HbA1c during 52 weeks between the two groups. This indicates that changes in renal function are not correlated with improvements in blood glucose levels ([figure 4](#)).

### DISCUSSION

In this study, eGFR decreased gradually in the insulin group over 52 weeks of treatment. However, a decrease in eGFR was not observed in the exenatide group. It has been suggested that GLP-1 may delay the decline of renal function. Following 36 months of liraglutide treatment,

**Table 2** Changes from baseline in exenatide-treated and insulin-treated groups (52 weeks)

	Exenatide group		P value	Insulin group		P value
	Normal N=17	Overweight and obese N=10		Normal N=15	Overweight and obese N=17	
HbA1c, %	-1.25±1.43	-1.42±1.48	0.772	-1.45±1.06	-0.78±1.66	0.194
FPG, mmol/L	-0.68±3.61	-0.798±3.35	0.941	-3.47±2.95	-1.44±3.58	0.097
eGFR, mL/min/1.73 m <sup>2</sup>	2.64±6.72	-2.91±4.99	0.044*	-3.79±6.50	-4.69±7.74	0.741
BMI, kg/m <sup>2</sup>	-0.33±1.93	-1.00±1.05	0.325	1.14±1.00	0.0071±0.83	0.0015*
SBP, mm Hg	-1.18±13.87	-3.00±15.85	0.763	4.67±15.22	0.12±21.63	0.501
DBP, mm Hg	-4.71±11.52	-3.50±12.48	0.802	1.33±10.77	-5.18±9.38	0.083
TBIL, mmol/L	0.21±4.11	2.21±3.43	0.225	-0.50±3.39	-0.15±3.14	0.765
DBIL, mmol/L	0.35±1.49	0.74±1.36	0.527	-0.033±1.04	0.25±1.04	0.460
TG, mmol/L	-0.38±1.76	0.17±0.85	0.293	-0.10±1.42	-0.071±1.71	0.952
TC, mmol/L	-0.47±1.42	0.007±0.67	0.252	-0.025±1.13	-0.089±1.00	0.870
LDL, mmol/L	-0.42±0.93	-0.27±0.67	0.677	-0.04±0.97	-0.26±0.79	0.482
HDL, mmol/L	0.054±0.15	-0.013±0.19	0.321	0.021±0.16	-0.028±0.14	0.387
FIB, g/L	0.34±0.52	0.37±0.31	0.862	0.42±0.42	0.53±0.54	0.544
Irisin, pg/mL	25.88±9.87	26.19±4.03	0.925	25.79±8.31	23.74±9.46	0.601
8-oxo-Gsn, ng/mL	-2.49±0.79	-2.40±0.69	0.799	-1.95±0.88	-2.06±0.59	0.764
NT-proBNP, pg/mL	-109.7±44.38	-91.18±25.67	0.323	-83.27±26.15	-85.21±31.57	0.872
IMT, mm	0.0062±0.25	-0.12±0.22	0.215	0.041±0.15	0.00059±0.27	0.615

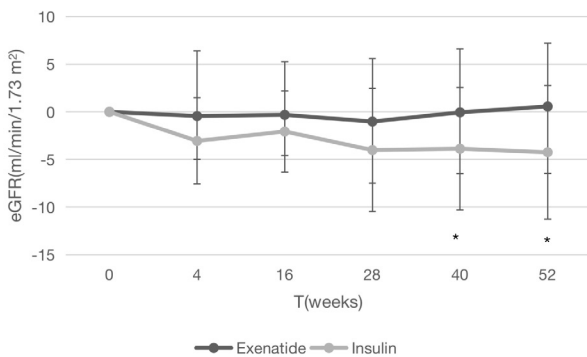
\*P<0.05.  
 BMI, body mass index; DBIL, direct bilirubin; DBIL, direct bilirubin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB, fibrinogen; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; 8-oxo-Gsn, 8-oxo-7,8-dihydroguanosine; TC, total cholesterol; TG, triglyceride.

eGFR decreased by 7.44 mL/min/1.73 m<sup>2</sup> compared with 7.82 mL/min/1.73 m<sup>2</sup> in the placebo group. The decrease of eGFR in the liraglutide group was slower than that in the placebo group, suggesting that GLP-1 has a protective effect on renal function.<sup>14</sup>

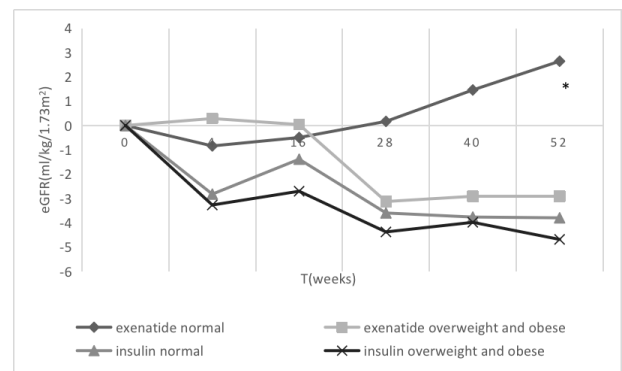
The glycemic control by insulin and exenatide showed no difference in this study. This suggests that the improvement of eGFR by exenatide may be independent of its glucose-lowering effect. Studies have shown that exenatide improves blood glucose control and exerts a protective effect on kidney function by reducing the risk of new microalbuminuria by 14%, and progression to dominant nephropathy by 26%.<sup>15 16</sup> The ADVANCE study (Action in Diabetes and Vascular Disease:Preterax and Diamicon Modified Release Controlled Evaluation) also reported a

21% relative reduction in nephropathy in patients requiring renal replacement therapy after enhanced glycemic control.<sup>17</sup> However, glucose lowering itself had no significant effect on other renal outcomes, like doubling of serum creatinine levels or eGFR reduction rate.<sup>15 16</sup>

Urinary 8-oxo-Gsn is an oxidation product of RNA. The level of 8-oxo-Gsn is used to represent the level of systemic oxidative stress,<sup>18</sup> and is a sensitive marker of oxidative stress.<sup>19</sup> We observed a positive correlation between eGFR and 8-oxo-Gsn (p<0.05) in the insulin group only, suggesting that the decrease of renal function might be related to oxidative stress and inflammation. The interaction

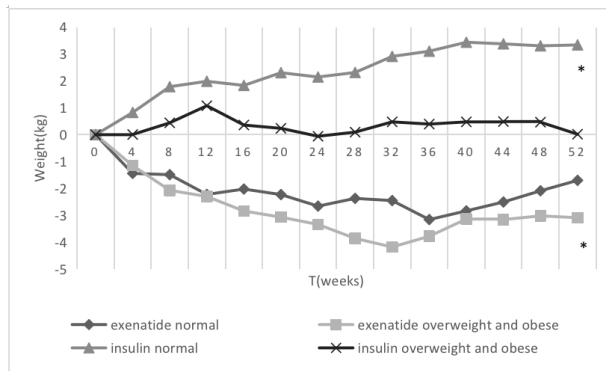


**Figure 1** Changes of renal function in two groups compared with baseline in 52 weeks. \*P<0.05 compared in two groups. eGFR, estimated glomerular filtration rate.



**Figure 2** Changes of renal function in 52 weeks of normal weight patients, overweight patients and patients with obesity with type 2 diabetes mellitus in exenatide group and insulin group. \*P<0.05, in exenatide group normal weight patients compared with overweight patients and patients with obesity. eGFR, estimated glomerular filtration rate.





**Figure 3** Changes of body weight at 52 weeks in body mass index of normal group, overweight group and obese group in exenatide group and insulin group. \* $P < 0.05$ , compared with baseline.

between diabetes, oxidative stress, and inflammation is a much-discussed topic. Chronic inflammation and obesity are suggested to be the principal causes of insulin resistance leading to the development of T2DM. Although the underlying mechanism is not well understood, adipose tissue synthesizes the main pro-inflammatory cytokines, tumor necrosis factor, and the interleukins (IL)-1 and IL-6 linked with body fat mass. These biological factors might play a role in the pathogenesis of diabetes, and complications of T2DM, like diabetic nephropathy.<sup>8</sup> Studies have shown that

**Table 3** Analysis of correlation between eGFR changes and multiple factors

	Exenatide group (n=27)		Insulin group (n=32)	
	Pearson's correlation coefficient	P value	Pearson's correlation coefficient	P value
HbA1c, %	-0.30	0.191	0.04599	0.816
FPG, mmol/L	-0.63	0.002*	-0.08318	0.673
eGFR, mL/min/1.73 m <sup>2</sup>	-0.45	0.045*	-0.05218	0.792
BMI, kg/m <sup>2</sup>	-0.05	0.812	-0.26954	0.165
SBP, mm Hg	0.16	0.496	0.04015	0.839
DBP, mm Hg	0.15	0.511	0.02888	0.886
TBIL, mmol/L	0.19	0.414	0.12	0.541
DBIL, mmol/L	0.08	0.732	-0.20	0.289
TG, mmol/L	0.10	0.665	0.31	0.102
TC, mmol/L	-0.17	0.461	-0.18	0.350
LDL, mmol/L	-0.05	0.823	-0.23	0.219
HDL, mmol/L	-0.43	0.053	-0.17	0.364
FIB, g/L	-0.32	0.169	-0.15	0.421
Irisin, pg/mL	-0.15	0.534	-0.14	0.477
8-oxo-Gsn, ng/mL	-0.06	0.783	0.42	0.035*
NT-proBNP, pg/mL	0.25	0.326	-0.27	0.178

\* $P < 0.05$

BMI, body mass index; DBIL, direct bilirubin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB, fibrinogen; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IMT, intima media thickness; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride.

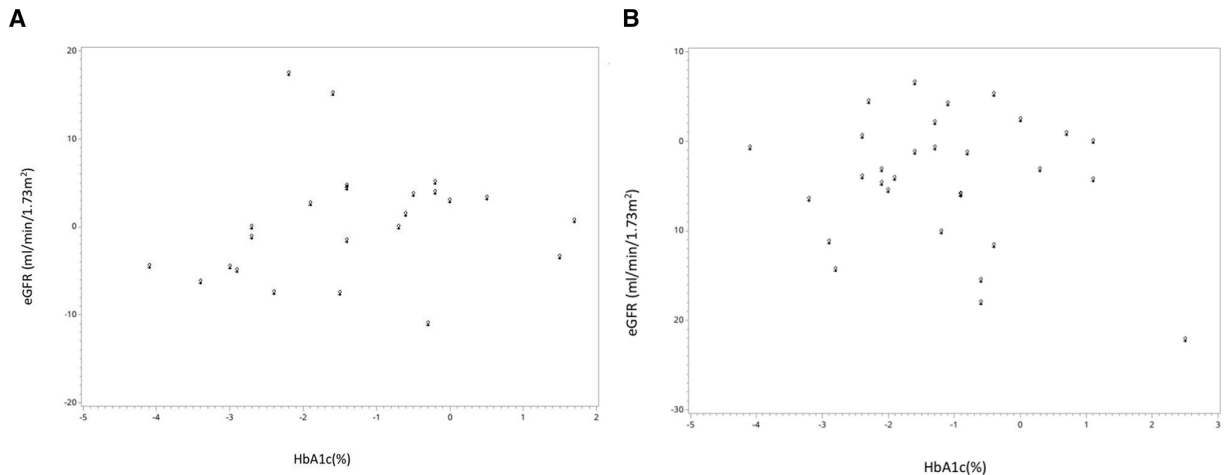
GLP-1 treatment reduces inflammation and oxidative stress levels and delays diabetic nephropathy and acute renal injury.<sup>20,21</sup> However, the protective mechanism of exenatide on renal function is not clearly understood. Its effect may be related to improved oxidative stress,<sup>18,22</sup> atherosclerosis,<sup>12</sup> and vascular endothelial function. Our results on the relationship between eGFR and 8-oxo-Gsn lend support to similar studies,<sup>18,22</sup> suggesting that a decrease in 8-oxo-Gsn in the exenatide group may be due to an improvement in inflammatory responses and thus may delay the decline of renal function.

Chagnac *et al* have shown that eGFR is closely related to body weight.<sup>23</sup> Eight patients with severe obesity with BMI  $48.0 \pm 2.4 \text{ kg/m}^2$  were tested for eGFR,  $145 \pm 14 \text{ mL/min}$  before weight loss, suggesting that obesity can lead to a significant increase in eGFR.<sup>23</sup> After weight loss, BMI decreased to  $32.1 \pm 1.5 \text{ kg/m}^2$  ( $p = 0.001$ ), with a simultaneous eGFR decrease to  $110 \pm 7 \text{ mL/min}$  ( $p = 0.01$ ), suggesting that obesity-related glomerular hyperfiltration improved after weight loss. This may delay the development of obesity-related glomerular diseases. This result is consistent with the findings of our study. In the exenatide group, eGFR increased with treatment compared with baseline in patients with normal weight. In the overweight patients and patients with obesity, eGFR was slightly higher than baseline and gradually decreased after 16 weeks. This change in eGFR may be related to a significant improvement in the weight of overweight patients and patients with obesity with diabetes by exenatide. The weight loss of overweight patients and patients with obesity indirectly affects the blood glucose, blood lipid, and blood pressure and indirectly improves renal function through the improvement of oxidation stress.<sup>24</sup>

Obesity is related to high renal plasma flow and elevated GFR, which can lead to glomerular damage and is associated with nephrotic syndrome and renal failure. Therefore, reducing glomerular hyperfiltration is an important way to prevent or delay the progression of kidney disease in patients with obesity. Exenatide has important theoretical and practical significance for the improvement of renal function in patients with obesity.<sup>25</sup>

The increase in obesity prevalence worldwide poses important questions on assessing kidney function in individuals with obesity. The standard practice of indexing GFR to body surface area (BSA) stems from the observation that GFR increases with larger body size and increased metabolic demands. Therefore, the actual eGFR in patients with obesity is lower than normal patients. With the obesity-related glomerular hyperfiltration improved after weight loss, the eGFR is much more closely related to the real level of the renal function.

Our study found that eGFR decreased transiently during early treatment and recovered normally after long-term treatment in the exenatide group. This observation is supported by Muskiet *et al*,<sup>11</sup> where exenatide also exhibited similar patterns of renal function changes: slight short-term decline (3.5%) followed by eGFR stabilization.<sup>26</sup> The reason for the fluctuation of eGFR may be related to the effect of sodium excretion and diuresis of GLP-1 in healthy people<sup>25</sup> and patients with T2DM.<sup>27-29</sup> GLP-1R is expressed in different parts of the kidney.<sup>30</sup> GLP-1 can block the sodium-hydrogen exchange of proximal tubules,<sup>30</sup> increase



**Figure 4** Scatter plot of changes of estimated glomerular filtration rate (eGFR) and glycated hemoglobin (HbA1c) at 52 weeks in exenatide group (A) and insulin group (B).

the concentration of sodium ions in distal dense plaques, and activate tubuloglomerular feedback to cause preglomerular vasoconstriction, resulting in a sharp decrease in intraglomerular pressure, thus reducing glomerular hyperfiltration.<sup>26</sup> Such renal vascular regulation leads to a sharp decrease in eGFR, followed by a smaller decline in renal function during continued treatment.<sup>26 31 32</sup>

Our study has some limitations; first, the sample size was small, not a multicenter study. In addition, we did not have enough resources to evaluate the influences of exenatide on other inflammatory markers. Finally, the effects of exenatide on other renal outcomes, particularly on urine protein, should be further compared with those of the insulin group.

In summary, exenatide can ameliorate the eGFR in patients with T2DM without obvious kidney disease. The mechanism may be related to improvements in oxidative stress. Especially in overweight patients and patients with obesity with T2DM, exenatide can improve glomerular hemodynamic abnormalities such as hyperfiltration in the early stage of diabetes through weight loss and delay renal insufficiency progression in patients with obesity-related glomerular diseases, and further benefit these patients.

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