Original Article

Protective effects of liraglutide on glomerular podocytes in obese mice by inhibiting the inflammatory factor TNF-α-mediated NF-κB and MAPK pathway

Yongjian Ye [a,1], Xing Zhong [a,1], Na Li [b], Tianrong Pan [a,*]

[a] Department of Endocrinology, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, China
[b] Department of Endocrinology, Chaohu Hospital of Anhui Medical University, Hefei 238000, China

A B S T R A C T

Objective: To evaluate the protective effects of Glucagon-like peptide-1(GLP-1) receptor agonist (liraglutide) on glomerular podocytes of obese mice, and explore the possible underlying mechanism.
Methods: Twelve of the thirty-four healthy and clean male mice were randomly selected as the normal control group. The remaining twenty-two mice were included in the high-fat diet (HFD) feeding group. After twelve weeks of high-fat diet and normal diet, two mice each from the HFD feeding group and the normal control group were randomly selected and sacrificed to suggested that the modeling was successful in the HFD feeding group. Then, twenty mice were randomly divided into HFD + liraglutide group (liraglutide group, n = 10) and HFD group (n = 10). The morphology and the structure of glomerular podocytes were observed using electron microscopy. Podocyte foot process diameter, glomerular basement membrane thickness were measured. ELISA was performed to determine the serum tumor necrosis factor α (TNF-α) level. The expression levels of TNF-α protein and nuclear factor-kappa B (NF-κB) in kidney tissues, extracellularsignal regulating kinase(ERK), c-Jun N-terminal kinase (JNK) and p38MAPK in the mitogenactivated protein kinases(MAPK) pathway were detected by western blotting.
Results: HFD-feeding caused significant renal injury, podocyte pathological changes, podocyte foot process diameter and glomerular basement membrane thickness were significantly increased compared with the control group. Liraglutide injection significantly alleviated HFD-induced effects on renal functions and podocyte morphology, as 24 h urine protein, urinary albumin and podocyte histomorphology. Moreover, HFD-induced Inflammatory reaction were obviously attenuated by Liraglutide administration, so did the HFD-induced activation of TNF-α-mediated NF-κB and MAPK pathways.
Conclusion: Liraglutide reduced urinary albumin excretion in obesity-related glomerulopathy model mice, and improved podocyte morphology and structural damage. The mechanism may be partly related to the inhibition of TNF-α-mediated NF-κB and MAPK pathways.

Introduction

Obesity is gradually becoming a hot issue worldwide. Several studies have revealed the serious effects of obesity on human health [1–4]. Obesity has been on the rise over the past few decades. According to the World Health Organization statistics, the proportion of obese people has been tripled since 1975 and about 13% of adults worldwide are affected by obesity [5]. At the same time, over-weight people accounted for 39% of the total population [5]. With the rapid increase in the number of obese people, the prevalence of obesity-related glomerulopathy (ORG) is significantly increasing. ORG is characterised by kidney damage due to insulin resistance and chronic inflammation caused by obesity and metabolic syndrome [6]. In animal experiments, the prevention of obesity can significantly improve renal function injury and changes in tissue structure [7]. Now, there are few studies on drug intervention in ORG. Therefore, more researches are needed on drugs therapy for ORG.

The morphological manifestations of ORG mainly include focal glomerular sclerosis and glomerular hypertrophy accompanied by podocyte hypertrophy and decreased density, increased width of foot processes as well as destruction of podocyte microstructure [8–10]. Podocyte injury is associated with the severity of protein-

uria and renal function damage, and it can be used as a marker of ORG, playing an important role in the onset and progression of ORG [11]. The pathogenesis of ORG is still unclear, and related studies have shown that inflammation plays a very important role [12]. TNF-α, as an important inflammatory factor, its production is related to low density lipoprotein stimulation and causing a series of damage to the kidney [13]. NF-κB and MAPK are important pathways for mediating inflammatory. Studies have shown that NF-κB and MAPK pathways can be activated in obese organisms, leading to kidney damage [14].

Glucagon-like peptide-1(GLP-1) receptor is not only found in the pancreas, but also in various other tissues such as heart, blood vessels, nerves, gastrointestinal tissue, fat, liver and kidney [15,16]. Liraglutide, a novel GLP-1 receptor agonist, not only reduces blood glucose effectively, but also plays a certain protective role in various tissues of the human body. Recently, few studies have shown that GLP-1 receptor agonists have certain therapeutic effects in ORG. GUO reported that GLP-1 significantly reduce glomerular damage caused by high fat diet, and decrease renal function damage, thereby slowing down the development of ORG effectively [17]. However, the effects of GLP-1 receptor agonists on glomerular podocytes are not well understood in ORG.

Hence, this study aimed to investigate the effects of GLP-1 receptor agonist (liraglutide) on podocytes of HFD induced obese mice as well as the underlying possible mechanisms.

Materials and methods

Materials

A total of 34 C57BL/6J male mice (SPF grade) weighing (19.04 ± 0.37) g were enrolled. Liraglutide was purchased from Novo Nordisk (Denmark). ELISA assay kits were purchased from Shanghai Yuanye Biotechnology Co., Ltd. Western blot kits were purchased from Beyotime Biotechnology Co., Ltd. (Shanghai). The serum triacylglycerol (TG), total cholesterol (CHO), low density lipoprotein (LDL) and fasting blood glucose (FBG) kits were purchased from BHKT Clinical Reagent Co., Ltd. (Beijing). Automatic microplate reader were purchased from BioTek Co., Ltd. (USA).

Experimental method

Establishment of the experimental model

Thirty-four mice were adaptively fed for 10 d. After that, 12 mice were randomly selected to be included in the normal control group, and were fed with normal feeding stuff. The remaining 22 mice were included in the HFD feeding group, and were given high-fat feeding stuff (formulation: cholesterol 2%, lard 6%, egg yolk powder 10%, bile salt 0.2% and basic feeding stuff 81.1%). After 12 weeks of high-fat diet and normal diet, 2 mice each from the HFD feeding group and the normal control group were randomly selected and sacrificed. Renal pathology suggested that the modeling was successful in the HFD feeding group. Mice in the HFD feeding group were randomly divided into liraglutide group (10 mice) and HFD group (10 mice), and were then fed with high-fat food. Among them, mice in the liraglutide group were subcutaneously injected with liraglutide 0.6 mg/ (Kg d), while mice in the HFD group was subcutaneously injected with normal saline 0.6 mg/(kg d). The weights of the mice were measured regularly each week at a fixed time point. The dose of the drugs was adjusted accordingly based on the changes in the weight of the mice, and the intervention was performed for 12 weeks. Throughout the experiment, the mice in each group were housed in standard cages with 4–5 mice per cage. The mice had free access to water, the temperature of the cage was controlled at 20–25 °C, and were maintained in a 12/12 h light-dark cycle (lighting time 7:00–19:00).

Sample collection

The 24-h urine of mice was collected via the metabolic cage, and the statistics of each mouse were performed for the total urine volume. The supernatant was extracted after centrifugation to measure the total amount of 24-h urinary albumin in mice. The intervention was performed till the end of week 24. The body weight of mice was calculated, and the blood was drawn from the inner canthus. The supernatant was extracted after centrifugation, and then the mice were sacrificed by decapitation to obtain the bilateral kidneys. The wet weight of the right kidney was weighed, and some renal tissues were obtained to prepare pathological sections, while the remaining renal tissues were placed in a refrigerator at −80 °C.

Electron microscopic observation

A portion of marginal renal cortex from mice in each group was rapidly cut into small (1-mm^3) pieces and fixed in 2.5% glutaraldehyde for 30 min at room temperature to prepare ultrathin sections and dyed with uranium lead dyeing. Ultrathin sections were observed by electron microscopy at a magnification of ×2000. Collected 10 fields of view and randomly measure 8 podocyte diameters and glomerular basement membrane thickness, taking the average. The ultrastructure of the renal tissue in the different groups was observed under a transmission electron microscope (JEM-1230; Jeol, Tokyo, Japan).

Biochemical detections

The supernatant was preserved at minus 80 °C after centrifugation. The serum TC, TG, LDL and FBG were detected by automatic microplate reader, and follow the kit instructions for a series of steps.

ELISA analysis

Random blood samples collected in experimentation were centrifuged ubder the condition of 3000 RPM for 5 min, washed with PBS and gather supernatant. Serum tumor necrosis factor-α (TNF-α) and urinary albumin indicators were detected using ELISA kits, and follow the kit instructions for a series of steps.

Western blot analysis

Cell lysate was added into about 1000 mg of renal cortical tissue, and then the supernatant was extracted after grinding. Electrophoresis for the protein samples was performed on sodium dodecyl sulfate-polyacrylamide gel, and then the samples were transferred onto a polyvinylidene fluoride (PVDF) membrane for sealing for 2 h. The samples were incubated using nuclear factor-kappa B(NF-κB) (1:1000), extracellularsignal regulating kinase (ERK) (1:1000), c-Jun N-terminal kinase (JNK) (1:1000), p38 (1:1000), as well as phosphorylated ERK (1:1000), JNK (1:1000) and p38 (1:1000) antibodies at 4 °C overnight. The PVDF membrane was then removed, and the membrane was washed with PBST for 5 times (10 min at each time). After that, the samples were incubated using the secondary antibody on a shaker at room temperature for 2 h. Proteins were quantitatively expressed by ECL method, and the gray value of the bands was analyzed using ImageJ software.

Data analysis and processing

Data processing was performed using SPSS 16.0 statistical software. Continuous data that met the normal distribution were expressed as $\bar{x} \pm s$. Differences among the groups were analyzed by one-way analysis of variance and Spearman analysis was used to

Table 1
Changes of 24 h urinary albumin, body weight, wet weight of the right kidney, blood lipids, blood glucose and serum TNF-α in each group of mice ($\bar{x} \pm s$).

Item	Normal control group ($n = 10$)	HFD group ($n = 10$)	Liraglutide group ($n = 10$)	F value	P value
Albumin (μg/L)	52.09 ± 6.82	137.38 ± 15.18[*]	82.21 ± 8.29[**]	162.329	<0.001
Body weight (g)	24.44 ± 1.27	50.47 ± 5.59[*]	31.91 ± 2.89[**]	882.628	<0.001
Wet weight of the right kidney (g)	0.17 ± 0.04	0.22 ± 0.12[*]	0.18 ± 0.04[**]	160.499	<0.001
TG (mmol/L)	0.47 ± 0.42	1.79 ± 0.16[*]	1.25 ± 0.23[**]	57.591	<0.001
TC (mmol/L)	2.45 ± 0.21	12.09 ± 0.48[*]	5.76 ± 0.53[**]	1439.94	<0.001
LDL (mmol/L)	0.56 ± 0.17	1.14 ± 0.46[*]	0.78 ± 0.31[**]	7.412	0.003
FBG (mmol/L)	4.73 ± 0.48	5.05 ± 0.47	4.84 ± 0.51	1.039	0.368
TNF-α (pg/mL)	123.91 ± 6.14	180.98 ± 12.39[*]	153.01 ± 5.93[**]	107.891	<0.001

Compared with the normal control group: [*]$P < 0.05$. Compared with the HFD group: [**]$P < 0.05$.

evaluate the data correlation at the end of the 24-week intervention period. $P < 0.05$ was considered to be statistically significant.

Results

Changes of body weight, wet weight of the right kidney, blood lipids, blood glucose and urinary albumin of mice

In the HFD group, the body weight, wet weight of the right kidney and blood lipids in mice were increased significantly compared to those in the normal control group (P < 0.05). The above indicators were significantly decreased compared to those in the HFD group after intervention with liraglutide (P < 0.05). There was no significant difference in fasting blood glucose level among the three groups. Compared with the normal control group, ELISA demonstrated that the urinary albumin excretion was increased significantly in the HFD group (P < 0.05). However, after intervention with liraglutide, the urinary albumin excretion of mice was declined significantly, compared to those in the HFD group (P < 0.05). Compared with the normal control group, the serum TNF-α was increased significantly in the HFD group, while the levels of serum TNF-α in the liraglutide group were significantly lowered than that in the HFD group according to ELISA. The difference between the groups was statistically significant (P < 0.05) (Table 1).

Pathological changes of renal tissues in each group of mice

Based on the results of electron microscope, the structure of glomerular podocytes in the normal control group remained clear, and the foot processes showed no fusion. In the HFD group, the margination occurred in the nuclear chromatin, the nuclear membrane gap was wider than that of the normal control group, the mitochondria showed vacuolar degeneration, and the foot processes were swollen and fused, while the structure remained ambiguous. The podocyte foot process diameter and glomerular basement membrane thickness increased significantly (P < 0.05). In the liraglutide group, the margination of nuclear chromatin of the podocytes was improved and the gap width of the nuclear membrane was shortened, while the mitochondrial degeneration and the foot process fusion were improved significantly. In addition, the podocyte foot process diameter and glomerular basement membrane thickness decreased significantly compared to those in the HFD group (P < 0.05) (Fig.1).

Expressions of TNF-α, NF-κB and mitogen activated mrotein kinases (MAPK) protein in renal tissues of mice

In HFD group, the expressions of TNF-α, NF-κB, as well as phosphorylated JNK, ERK and p38 proteins in the renal tissues were
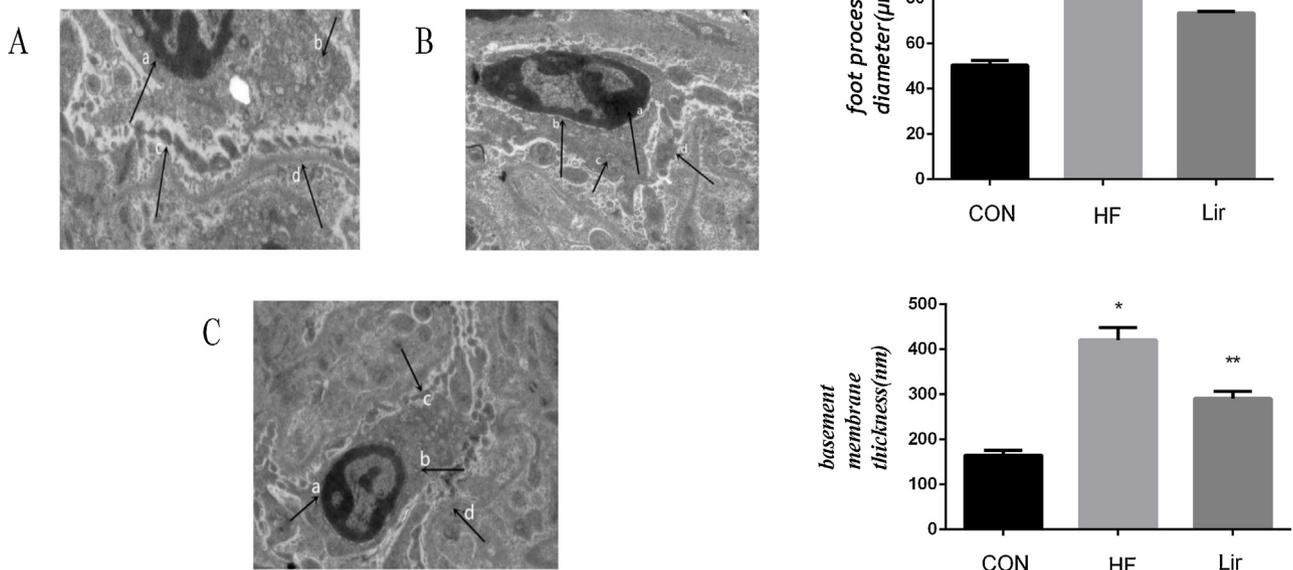
Fig. 1. Pathological changes of podocytes of renal tissues in each group ×2000.
(A) Normal control group: the morphology and microstructure of normal podocytes (B) HFD group: there was margination of nuclear chromatin in podocytes, widening of nuclear membrane gap, mitochondrial vacuolar degeneration, foot process fusion, thickening of basement membrane. (C) Liraglutide group: compared to the HFD group, the margination of the nuclear chromatin in podocytes was improved, width of the nuclear membrane gap was shortened, the mitochondrial vacuolar degeneration was alleviated, the foot process fusion was improved and the thickness of the basement membrane was reduced.
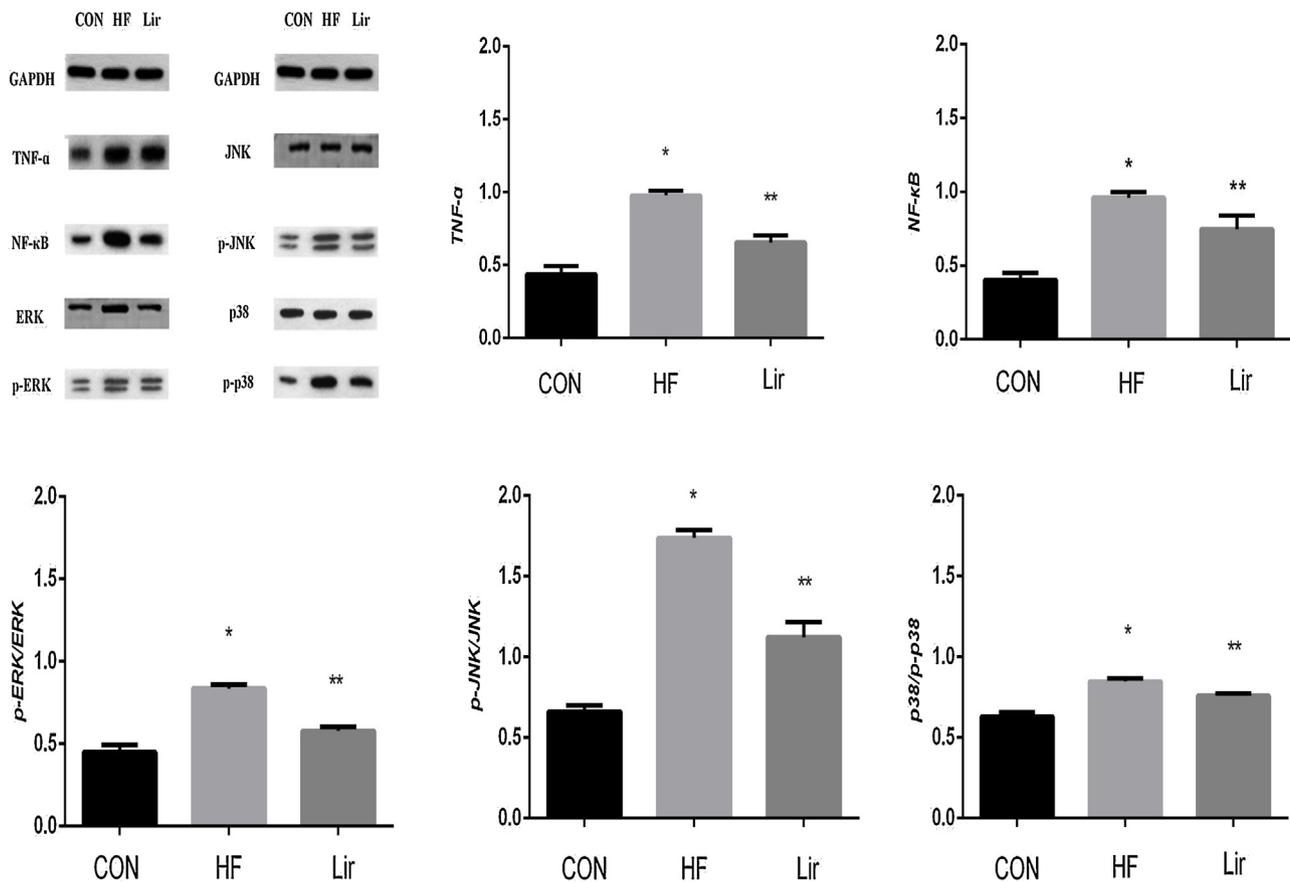
Fig. 2. Changes of TNF-α, NF-κB as well as phosphorylated JNK, ERK and p38 proteins in the renal tissues of mice.

elevated significantly compared to those in the normal control group ($P < 0.05$). After intervention in the liraglutide group, the expressions of TNF-α, NF-κB as well as phosphorylated JNK, ERK and p38 proteins in the renal tissue were decreased significantly compared to those in the HFD group, showing significant differences between the groups ($P < 0.05$) (Fig. 2).

The correlation of the reduction between serum TNF-α and renal TNF-α protein expression in liraglutide group

Spaerman analysis showed that the reduction in serum TNF-α had positive significantly relationship with the reduction in renal TNF-α protein expression in liraglutide group (r = 0.939, $P < 0.05$).

Liraglutide significantly inhibited TNF-α-mediated NF-κB and MAPK pathways. Compared with normal control group, the expressions of TNF-α, NF-κB and phosphorylated JNK, ERK and p38 proteins in the HFD group were significantly higher, [*]$P < 0.05$. Compared with HFD group, the expressions of TNF-α, NF-κB as well as phosphorylated JNK, ERK and p38 proteins in the renal tissues of mice of liraglutide group were decreased significantly,[**]$P < 0.05$.

Discussion

The results of this study demonstrated increased body weight, abnormal lipid metabolism, urinary albumin excretion increased and podocyte injury in obese mice with 24-week of HFD, increasing the expressions of TNF-α, NF-κB and phosphorylated MAPK. After 12 weeks of intervention with liraglutide, the body weight, blood lipids and the urinary albumin were significantly lowered than those of obese mice in high-fat diet group, the pathological damage of podocytes was significantly improved, while the expressions of TNF-α, NF-κB and phosphorylated MAPK were inhibited.

There was a positive correlation between the reduction in serum TNF-α and renal tissue TNF-α, expression in linalutide group, which suggesting that linalutide could not only reduce systemic inflammation in the body, but also inhibit the expression of local TNF in the kidney, both of which may provide protection or have a synergistic effect on the kidney.

Previous studies have shown that obese mice have a range of kidney damage, including glomerular hypertrophy, podocyte foot process diameter and glomerular basement membrane thickness increased [14,17,18], as confirmed by our findings. Inflammatory reaction plays an important role in the injury of ORG podocytes. In obese patients, the secretion of inflammatory factors such as TNF-α, IL-6, monocyte chemotactic protein-1 (MCP-1), leptin were significantly increased, which resulted in a significant increase in the levels of inflammatory responses. In addition, secretion of anti-inflammatory factors was reduced such as interleukin-10 (IL-10), adiponectin, and the dynamic balance of inflammation in the body was shattered, resulting in the formation of a persistent micro-inflammatory state of multiple organ injuries such as the kidney [19]. Among them, TNF-α has been confirmed to be involved in podocyte injury and apoptosis [20]. In our study, the serum TNF-α levels and TNF-α in renal tissue were increased in HFD group. A basic study showed that TNF-α could activate cAMP-rar and p38MAPK pathways, improving podocyte injury [21]. Ikezumi et al. have found that TNF-α secreted by macrophages can inhibit the activity of podocyte-specific proteins (nephrin and podocin) by activating p38 MAPK and JNK signaling pathways to induce podocyte injury, increase urinary protein excretion and aggravate renal injury [22]. Besides, numerous studies have demonstrated that NF-κb and MAPK pathways are activated in obese mice induced by high-fat diet, causing inflammation in the kidneys [14,23–25]. Our study have similar results to those of the previous study, NF-

κB protein, as well as phosphorylation of JNK, ERK, and p38 in the MAPK pathway were increased in obese mice induced by HFD. These results confirmed the potential role of TNF-α-mediated NF-κB and MAPK pathways in ORG podocyte injury.

The protective effects of GLP-1 receptor agonists on ORG are multi-faceted, protecting the kidney by improving glomerular hemodynamics, anti-inflammatory, anti-oxidative stress, insulin resistance. A big data study has shown that GLP-1 receptor agonists can significantly reduce the risk of new-onset persistent macroalbuminuria in patients with chronic kidney disease, improve renal function such as creatinine and uric acid, thus play a protective role in the kidneys [26]. GLP-1 receptor agonists can also significantly improve renal tissue pathological damage, such as glomerular hypertrophy, glomerulosclerosis, basement membrane thickening, podocyte foot process fusion [27,28]. Our study has similar results. In addition, literature have reported that the inflammatory factors in obese mice such as TNF-α, IL-6, MCP-1 were significantly decreased after treatment with liraglutide, suggesting effective improvement in the inflammatory state of the body [29]. Same as that study, the serum TNF-α content, TNF-α in renal tissue were decreased significantly in liraglutide group in our study. DAI et al. study have found that liraglutide significantly inhibited the expression of TNF-α in glomerular mesangial cells induced by high glucose, thereby reducing inflammation and improving the renal disease [30]. In addition, another study have shown that liraglutide can significantly improve the renal disease in diabetic rats, and its possible mechanism of action on ERK and JNK/NF-κB pathways, thus inhibiting the inflammatory responses [31]. Results of this study showed that NF-κB protein as well as phosphorylation of JNK, ERK and p38 in MAPK pathway were significantly reduced in obese mice after 12 weeks of intervention with liraglutide. Previous studies and our findings suggested that liraglutide may protect podocytes of obese mice by inhibiting TNF-α-mediated NF-κB and MAPK pathways to produce anti-inflammatory effects.

However, there are certain limitations in our study. Liraglutide itself has the effect of reducing lipid indices and body weight, but our study did not set up a diet intervention group. Therefore, it cannot fully explain whether the changes in podocytes were due to lipid indices and weight lossing or improvement of podocyte disease caused by the direct action of liraglutide. Besides, blood pressure was not measured, and the protective effect of blood pressure on the kidney has not been ruled out. There were some studies shown that 0.9% NaCl has adverse renal consequences, so administration of 0.9% NaCl to these mice may have reduced the difference between the groups.

In conclusion, liraglutide significantly alleviated proteinuria and renal podocyte lesions in obese mice induced by high fat, which may be due to inhibition of inflammatory factor TNF-α-mediated NF-κB and MAPK pathways. However, the exact mechanism should be further elucidated.

Ethical statement

All animal experiments comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors clearly indicate in the manuscript that such guidelines have been followed.

Conflict of interest

All authors have no conflict of interest. All authors have disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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