Kruppel-like factor 4 improves obesity-related nephropathy through increasing mitochondrial biogenesis and activities

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Abstract

Obesity is positively linked to multiple metabolic complications including renal diseases. Several studies have demonstrated Kruppel-like factor 4 (KLF4) participated in renal dysfunction and structural disorders in acute kidney injuries, but whether it affected the process of chronic kidney diseases was unknown. Therefore, present study was to disclose the role of renal KLF4 in dietary-induced renal injuries and underlying mechanisms in obesity. Through utilizing high-fat diet-fed mice and human renal biopsies, we provided the physiological roles of KLF4 in protecting against obesity-related nephropathy. Decreased levels of renal KLF4 were positively correlated with dietary-induced renal dysfunction, including increased levels of creatinine and blood urea nitrogen. Overexpression of renal KLF4 suppressed inflammatory response in palmitic acid-treated mouse endothelial cells. Furthermore, overexpressed KLF4 also attenuated dietary-induced renal functional disorders, abnormal structural remodelling and inflammation. Mechanistically, KLF4 maintained renal mitochondrial biogenesis and activities to combat obesity-induced mitochondrial dysfunction. In clinical renal biopsies and plasma, the renal Klf4 level was negatively associated with circulating levels of creatinine but positively associated with renal creatinine clearance. In conclusions, the present findings firstly supported that renal KLF4 played an important role in combating obesity-related nephropathy, and KLF4/mitochondrial function partially determined the energy homeostasis in chronic kidney diseases.

Keywords: chronic kidney disease, inflammation, Kruppel-like factor 4, mitochondria, obesity

1 | INTRODUCTION

Obesity brings numerous risks and unhealthy consequences for global health. Obesity-induced metabolic disorders contribute to an increased incidence of renal complications, including chronic kidney diseases (CKDs). Renal lipotoxicity, characterized by excess lipid deposits, is one of main proposed pathological mechanisms, which further initiates increased pro-inflammatory response, excess production of reactive oxygen species (ROS) and abnormal structure. In details, there are variety of obesity-linked renal changes, including glomerular hypertrophy, fibrosis and up-regulation of glomerular filtration rate. Therefore, it is necessary to explore novel therapeutic approaches to eliminate the renal lipotoxicity.
Increased energy uptake, especially excess circulating free fatty acid, shows a positively associated with susceptibility to renal injury.\textsuperscript{3,4} Upon fatty acid accumulation and increased oxidation, renal cells, including endothelial cells, tubular cells and mesangial cells, can be severely damaged. Mechanistically, one of proposed mechanisms is mitochondrial dysfunction in obesity-associated renal injuries but is incompletely understood. Renal mitochondrial dysfunction often exhibits as an induction of pro-inflammatory cytokines resulting in inflammatory damage and accumulation of lipid deposit leading to renal lipotoxicity.\textsuperscript{5} Peroxisome proliferator-activated receptor (PPAR) \(\gamma\) coactivator 1\(\alpha\) (PGC1\(\alpha\)), 5\' AMP-activated protein kinase (AMPK) and sirtuin (SIRT) pathways are potential molecular signalling mediating the pathophysiological changes in obesity-induced renal diseases.\textsuperscript{6-8} However, it is still need to further explore more valuable therapeutic targets to combat renal lipotoxicity and dysfunction.

Kruppel-like factors (KLFs) are a subfamily of the zinc finger class, determining various critical development, such as differentiation, proliferation and inflammation.\textsuperscript{9} There are multiple studies have showed KLFs participate in the process of renal pathophysiology. For examples, Mallipattu et al\textsuperscript{10} found KLF6 was critical for maintaining renal mitochondrial function and decreasing podocyte death. KLF15 mediated the differentiation of podocytes and protected against renal injuries.\textsuperscript{11} Another widely studied member of KLFs is KLF4, which transcriptionally activating or repressing the expression of multiple genes.\textsuperscript{12-14} Xiao et al and Chen et al found KLF4 functioned as a suppressor of renal fibrogenesis.\textsuperscript{15,16} KLF4 also determined the pharmacological benefits in renin-angiotensin blockade-mediated reduction in proteinuria.\textsuperscript{17} Besides, endothelial KLF4 improved renal function and determined the benefits of statin in ischaemic acute kidney injury by decreasing inflammatory response.\textsuperscript{18} However, the role and molecular regulating signalling of KLF4 in obesity-related nephropathy are unknown.

To this end, the current study was to explore the dynamic links of KLF4 and renal dysfunction in dietary-induced obese mouse models. Then, we further explored the potential molecular mechanisms of mitochondrial biogenesis and activities. These findings provided solid evidence that renal KLF4/mitochondrial function was a crucial molecular mechanism underlying the pathophysiological changes of obesity-induced renal diseases.

2 | MATERIALS AND METHODS

2.1 | Reagents

The biochemical kits for measuring blood urea nitrogen (#EIABUN) and creatinine (#EIAUCN) were purchased from Thermo (Thermo Fisher). The haematoxylin (#H9627), eosin solution (#HT110216) and Masson trichrome staining kit (#HT15) were purchased from Sigma chemicals (Sigma). Anti-F4/80 (ab6640) and anti-KLF4 (ab106629) antibodies were purchased from Abcam. Anti-phospho-I\(\kappa\)B (#9246), anti-I\(\kappa\)B (#9242) and anti-Tubulin (#2128) antibodies were purchased from Cell Signaling.

2.2 | Animal experiment

The animal experimental protocol was approved by the Institutional Animal Use and Care Committee at the Wenzhou Medical University. Fourteen male C57BL/6J mice, aged 6 weeks, were fed with 60% high-fat diet (HFD, Cat#D12492, Research diets). For virus transfection, \(1 \times 10^{12}\) adeno-associated virus (AAV) particles encoding Klf4 or control were locally administrated to mice by ultrasound microbubble. Briefly, the virus particles were mixed with Optison (Mallinckrodt) in 50% v/v ratios and injected into the renal artery. Ultrasound transducer (Sonitron 2000, NEPA GENE, Co.) exposed directly onto one side of the kidney with a continuous wave output of 1 MHz ultrasound for 1 minute. The infusion cannula is then removed, and the wound closed. A total of 12 mice were assigned to standard chow (STC). After the mice were killed, the serum and kidneys were collected for further analysis.

2.3 | Renal histological analysis

Kidneys were fixed in 4% paraformaldehyde and embedded in paraffin. The paraffin sections (5 \(\mu\)m) were dehydrated and stained using haematoxylin and eosin solution or Masson Trichrome staining kit. For immunohistological analysis of macrophages, 5-\(\mu\)m renal sections were processed with antigen retrieval, 5% \(\text{H}_2\text{O}_2\) and 3% BSA. Slides were incubated with anti-F4/80 antibody and then stained with secondary antibody and DAB HRP substrate. Then, the images were viewed by a light microscope (400\(\times\) amplification, Nikon).

2.4 | Total RNA extraction, cDNA synthesis, reverse transcription and real-time PCR

Kidney tissues or endothelial cells were homogenized in TRizol (Invitrogen) for RNA extraction. Reverse transcription was carried out using the Superscript III Reverse Transcription kit (Invitrogen), and quantitative PCR analysis was performed using SYBR Green quantitative kit (Applied Biosystems, CA). The primer sequence of detected mRNA was listed as following: Klf4: F-5\' ‐ GTCAAGTTCCTCCAGCAAGTACAGC−3\'; R-5\' ‐ CATCCAGTATCGACCCATC−3\'; TNF-\(\alpha\): F-5\' ‐ AGGCATGATGTC TAAAGAC−3\'; R-5\' ‐ AGATGCAAATGGCGCTGAC−3\'; IL-6: F-5\' ‐ GTCTTTCCTACCCAAATTCCA−3\'; R-5\' ‐ TAAAGCACTAGTGGTTGCC GA−3\'; COX-2: F-5\' ‐ CCAAGGCCCTCCTACACCTTCC−3\'; R-5\' ‐ CTCTGGAGG CTGAGACAAAGG−3\'; Cox-2: F-5\' ‐ AACCCTGGGGGGTGTATGAG−3\'; R-5\' ‐ GACAGGAAGGGATGGTTGTGT; GAPDH: F-5\' ‐ AGGAGCGAGACCC CATCAAC−3\'; R-5\' ‐ GATGAACCTTTGGTGCAC−3\'. Relative gene levels were normalized to GAPDH level.

2.5 | Immunoblot analysis

Kidney tissues or endothelial cells were lysated, and 50 \(\mu\)g protein extracts was separated by 10% SDS-PAGE electrophoresis. The protein was electrotransferred to a 0.22 \(\mu\)m
polyvinylidene difluoride membrane (Amersham Biosciences). After blocked in 10% BSA containing non-fat milk, the membranes were incubated with different primary antibodies and secondary antibodies. Immunoreactive bands were visualized by using enhanced chemiluminescence reagents (Bio-Rad). The relative band density was calculated using Image J analysis software.

2.6 | Adenosine triphosphate (ATP) and oxygen consumption measurement

Mitochondrial ATP and endogenous basal oxygen consumption was measured as previous report. In briefly, mitochondria were extracted from kidney tissues and measured by an ATP measurement kit for mitochondrial ATP or a clark electrode for oxygen consumption.

2.7 | Study on human subjects

From October 2015 to December 2017, a total of 27 individuals under renal biopsies were recruited. The renal biopsies were collected and stored in liquid nitrogen until further measurement. The basic clinical parameters of these subjects were also collected. All participants have been informed clinical consent, and related analysis protocol was approved by human ethics committee of Wenzhou Medical University.

2.8 | Statistical analysis

Data were collected and presented as mean ± SD. Student’s t test was used for comparing 2 groups, and ANOVA was used for multiple groups (GraphPad, San Diego, CA). Differences were considered to be significant at \( P < .05 \).

3 | RESULTS

3.1 | Decreased levels of KLF4 were positively associated with renal dysfunction in obese mice

Previous study has demonstrated renal endothelial KLF4 was involved in the process of acute kidney injury, but no report determined the possible role of KLF4 in chronic renal diseases. To this end, present study firstly measured the levels of KLF4 in mouse kidneys fed with high-fat diet (HFD). Compared with lean mice, the mRNA of Klf4 was time dependently decreased in HFD-fed mice (Figure 1A). Consistently, there was significant down-regulation of KLF4 protein in mice fed with HFD for 8 or 16 weeks (Figure 1B-1C). Circulating creatinine and blood urea nitrogen (BUN) are crucial parameters for defining renal dysfunction. As showed in Figure 1D-1E, renal Klf4 levels were negatively correlated with the up-regulated levels of serum creatinine (\( r = −0.7439, P < .001 \)) and BUN (\( r = −0.6459, P < .01 \)). These results indicated renal KLF4 might participate in the process of renal dysfunction in obese mice.

3.2 | Overexpression of Klf4 attenuates inflammatory accumulation in palmitic acid-treated mouse renal endothelial cells

Similarly, palmitic acid (PA) obviously decreased the levels of KLF4 gene (Figure 2A) and protein (Figure 2B-2C) in mouse renal endothelial cells. To disclose the effects of KLF4 on renal function, we firstly overexpressed Klf4 levels to identify the consequences in vitro. Figure S1 showed that adeno-associated virus (AAV) encoding Klf4 successfully overexpressed KLF4 mRNA (Figure S1A) and protein levels (Figure S1B-1C) in endothelial

![Figure 1](image-url)

**Figure 1** Renal KLF4 level is closely associated with renal dysfunction in obese mice. Six-week male C57BL/6J mice were fed with standard chow (STC) or high-fat diet (HFD) for 0, 8 or 16 wk. A, Real-time PCR analysis of renal Klf4 levels. B-C, Western blot analysis of KLF4 (B) and quantitative analysis of relative density (C). D-E, Correlation between renal Klf4 levels and serum creatinine (D) and blood urea nitrogen (BUN, E). Correlation was assessed by non-parametric Spearman’s test. Data are shown as mean ± SEM (* \( P < .05 \), ** \( P < .01 \) and *** \( P < .001 \), n = 5-6 mice/group).
cells. PA is a well-established stimulator for inflammatory response. Treatment of PA significantly increased the expression of inflammatory factors, including TNF-α, IL-6, Cox-2, and iNOS (Figure 2D-2E). However, overexpression of Klf4 effectively suppressed these gene levels (Figure 2D-2E). NF-κB signalling, as a crucial transcriptional factor in regulating inflammatory response, is widely studied in metabolic diseases. As showed in Figure 2F-2G, PA obviously increased the phosphorylated levels of IκB and IκB degradation, whereas overexpression of Klf4 decreased the activation of NF-κB (P < .01). Furthermore, consistent with a previous finding in the mouse model with acute kidney injury, overexpression of Klf4 also inhibited adhesion cytokines, including VCAM-1 and ICAM-1 (Figure 2H, P < .05).

3.3 | Overexpression of Klf4 improves high-fat diet-induced renal injuries through modulating mitochondrial function

Several studies have shown KLF4 is critical mediator of obesity-related complications, including cardiomyopathy, systemic inflammation and metabolic syndromes. Therefore, present study further explored the effects of renal KLF4 in obesity-related nephropathy. Adeno-associated virus (AAV) encoding Klf4 efficiently increased renal KLF4 levels, as compared with obese mice (Figure 2A-2C). After HFD treatment for 16 weeks, overexpression of renal Klf4 could not affect the body weight (Figure 2D), but significantly decreased kidney weight (Figure 2E), as compared with Ctrl-treated obese mice. Furthermore, obese mice exhibited increased levels of serum creatinine and BUN (P < .001), whereas overexpression of Klf4 significantly decreased these up-regulation (P < .01). HE staining also indicated overexpression of Klf4 improved renal abnormal structural remodelling, such as attenuation of enlarged glomerular size (Figure 3C-3D). Overexpression of Klf4 also decreased HFD-induced renal fibrosis, as indicated in Masson trichrome staining (Figure 3E). Macrophage infiltration is one important character of obesity-related nephropathy. As showed in Figure 3G, HFD obviously initiated F4/80+ macrophage infiltration into kidneys (P < .001), but overexpression of Klf4 decreased the macrophage accumulation (P < .01). Furthermore, overexpression of Klf4 effectively suppressed gene levels of inflammatory cytokines, as compared with obese mice (Figure 3H).

Mechanistically, KLF4 determines mitochondrial function in several diseases with metabolic disorders. To this end, present study further investigates whether KLF4 participated in obesity-induced renal mitochondrial dysfunction. Obese mice treated with AAV-Klf4 significantly decreased HFD-induced triglyceride deposits and free fatty acid levels in kidneys (Figure 4A-4B, P < .05). Mitochondrial quantity and biochemical activities control mitochondrial function. Western blot analysis showed HFD dramatically decreased mitochondrial quantity, as indicated by α-porin, whereas overexpression of Klf4 up-regulated its protein level in kidneys (Figure 4C-4D, P < .05). Consistently, overexpression of Klf4 also increased mitochondrial (mt) DNA levels in both lean and obese mice (Figure 4E). Next, present study measured the mitochondrial...
activities in kidneys. As showed in Figure 4F, the citrate synthase activity of extracted renal mitochondria was decreased in obese mice, but overexpression of Klf4 significantly recovered its level in HFD-fed mice (P < .05). HFD also significantly decreased mitochondrial ATP production by 58.3%, whereas the relative ATP levels were obviously up-regulated in AAV-Klf4-treated obese mice (Figure 4G, P < .05). Furthermore, we measured the mitochondrial endogenous respiration activity with the presence of oligomycin A, an ATP synthase inhibitor. As Figure 4H showed, without coupling activity, HFD treatment significantly decreased the oxygen consumption, but AAV-Klf4-treated mice could improve the endogenous respiration activity (P < .01). Furthermore, overexpression of Klf4 also decreased renal superoxide product (Figure S4A, P < .01), but increased anti-oxidative factor SOD production (Figure S4B, P < .01). All these findings supported KLF4-affected renal function by regulating mitochondrial biogenesis and activities in obese mice.

### 3.4 Renal expression of KLF4 is potential prognostic marker for renal dysfunction in clinical analysis

Plasma creatinine levels and creatinine clearance (Ccr) are clinical diagnostic parameters of renal injuries.26 Then, present study collected 27 renal biopsy samples and plasma for further analysis. The detail clinical parameters of these subjects included age (54.34 ± 13.23 years), BMI (27.40 ± 6.03 kg/m²), fasting glucose (5.04 ± 0.78 mmol/L), insulin (6.24 ± 4.05 μU/mL), triglyceride (1.11 ± 0.49 mmol/L) and cholesterol (5.41 ± 1.34 mmol/L). As showed in Figure 5A, relative mRNA levels of Klf4 were negatively associated with plasma creatinine value (P < .01, r = −0.5381), but positively correlated with Ccr (P < .001, r = 0.6809). These close clinical correlation indicated renal KLF4 level was a potential prognostic biomarker of renal injuries.

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The current study supported the concept that KLF4 played a major role in dietary-induced renal injuries and identified that KLF4 determined renal mitochondrial function in this pathogenesis. We demonstrated that renal KLF4 reduction was closely related to increased levels of circulating creatinine and blood urea nitrogen. Overexpression of KLF4 protected against inflammatory response, structural disorders and dysfunction in obese mice. Importantly, we also demonstrated that KLF4 improved renal mitochondrial function by increasing mitochondrial biogenesis and activities in obese mice.

Mitochondrial dysfunction is one of potential mechanisms involved in multiple metabolic complications including the obesity-associated nephropathy but is not fully understood. Renal mitochondrial dysfunction often exhibits as an induction of pro-inflammatory cytokines resulting in inflammatory damage and accumulation of lipid deposit leading to renal lipotoxicity. Increased energy uptake, especially excess circulating free fatty acid, showed a positively associated with susceptibility to renal injury. The increased fatty acid accumulation and oxidative stress damaged renal cells, including endothelial cells, mesangial cells and tubular cells. Mechanistically, several crucial signalling were involved in lipid-induced renal mitochondrial dysfunction. PGC1α/PPARγ signalling was linked to cellular metabolic flexibility through stimulating mitochondrial biogenesis. Guo et al showed that PGC1α attenuated obesity-induced rat renal mesangial hypertrophy. Podocyte PGC1α protein levels in human biopsy samples were decreased in patients with diabetic kidney disease. Besides, the improved activities of AMPK and SIRT protected mitochondrial function and renal biology. As co-factor for mitochondrial functional, KLF4 promoted mitochondrial biogenesis in heart through cooperating with PGC1α/
Inflammation initiates the progress of renal abnormal homeostasis leading to acute and chronic renal damages. Obesity triggers the production of multiple factors in the renal inflammation, including transcriptional pathways, pro-inflammatory cytokines and adhesion molecules. Previous findings have supported that pro-inflammatory cytokines, such as TNF-α, IL-6 and iNOS, obviously increased in obese mouse proximal tubule and glomerular cells. Besides, there is obvious secretion of adhesion molecules, such as VCAM-1 and ICAM-1, which further recruit immune cell infiltration. Macrophage infiltration is one of major contributors to the development of chronic kidney disease. Macrophage infiltration was significantly correlated with the extent of glomerulosclerosis, interstitial fibrosis and glomerular hypertrophy in human renal injuries. Mechanistically, NF-κB, as a key transcriptional factor, determines the renal inflammatory response in patients with CKD. Abnormal activation of NF-κB is also a crucial feature in mouse renal inflammation. In present study, our findings supported the abnormal induction of renal inflammation in dietary-induced nephropathy. More importantly, we initially demonstrated that KLF4 also participated in the process of obesity-related renal inflammation via down-regulating NF-κB activity.

KLF4, as a member of zinc finger transcription factors, activates or represses the transcriptional activity of multiple genes. Cardiac KLF4 controlled mitochondrial homeostasis and functional changes. Macrophage KLF4 determined the plasticity of adipose tissue resident macrophages and systemic inflammation in obese mice. More importantly, studies also found KLF4 functioned as a suppressor of renal fibrogenesis. Endothelial KLF4 exhibited protection against ischaemic acute kidney injury. Interestingly, current study also found the crucial role of KLF4 in obesity-related renal injuries. Overexpression of KLF4 obviously improved renal function and inhibited inflammatory response partially by up-regulation of mitochondrial biogenesis and activities in obese mice. More importantly, clinical renal biopsies further confirmed the close correlation between renal KLF4 levels and renal function, which supported the prognostic ability of KLF4 in kidney diseases.

In conclusions, decreased renal KLF4 level was important indicator for obesity-related nephropathy, whereas genetic over-expression of KLF4 effectively improved renal function partially through up-regulation of mitochondrial biogenesis and activities. Therefore, renal KLF4/mitochondrial regulation pathway could explain the pathophysiological changes in obesity-related nephropathy and was a potential therapeutic target for chronic kidney diseases.

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**CONFLICT OF INTEREST**

All authors declare there are no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

LW Jin, HY Ye and M Pan conducted the animal experiments and data analysis; Y Chen and BR Ye conducted the cell experiments; Y Zheng, WW Huang, SF Pan and Z Shi conducted the clinical analysis; LW Jin and J Zhang designed and monitored the whole project and write the manuscript.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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