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Study on the Mechanism of Kidney Damage Caused by Obesity Based on Downregulation of AQPs Expression in Rats

Estudio Sobre el Mecanismo de Daño Renal Causado por la Obesidad Basado en la Regulación Negativa de la Expresión de AQP en Ratas

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SUMMARY: Obesity is a significant risk factor for chronic kidney disease (CKD) development. Essentially, dissolved materials in the liquid fraction of blood are formed into a filtrate by the action of glomerulus. In this way, the kidney remove waste and recycle filtered nutrients (including water) via uriniferous tubules (namely renal tubules and collecting ducts), which can reabsorb and secrete some components in urine. When long-term fat accumulation occurs in the kidney, it accelerates a series of kidney damage, e.g. inflammation and fibrosis. It has been suggested that excess lipid accumulation led to lipotoxicity and may be the major driver of water reabsorption dysfunction. Moreover, long-term fat accumulation further leads to tubular diseases. However, the direct mechanism by which obesity contributes to kidney damage based on downregulation of AQPs expression remains elusive. Here, our data showed that 90-day HFD feeding induced obesity in rats that exhibited multiple pathological damage in kidney, especially, downregulation of AQPs protein level, including AQP2, AQP3 and AQP4, high expression of TGFβ1, Smad2, ADRP and CD36. Accordingly, we further emphasized on the mechanism between the tubulointerstitial inflammation and fibrosis and AQPs caused by lipotoxicity, revealing a potential intervention strategy for the clinical treatment in future.

KEY WORDS: Obesity; Kidney damage; Uriniferous tubules; AQPs; Lipotoxicity.

INTRODUCTION

A growing and disturbing global public health crisis caused by obesity is prevalent all over the world, while the rapid growth of obesity in developing countries, where probably due to the wide availability and accessibility of deeply processed foods which are high in calories but lack nutritional value, has had a significant impact on the chronic kidney disease (CKD) (James, 2008; Zukiewicz-Sobczak *et al*., 2014; Chawla *et al*., 2014). A vast amount of data has reported a strong relationship between obesity and CKD, and obesity can serve as an independent risk factor for kidney damage. Epidemiological investigations have found that the prevalence of adult CKD is about 10.8%, and the body mass index (BMI) of CKD patients is significantly higher than that of people without kidney injury (Zhang *et al*., 2012). Moreover, compared with normal-weight subjects, being overweight or having high body fat can increase sharply the risk of CKD, especially in obese individuals, regardless of their metabolic status, even in the absence of remarkable metabolic abnormalities (Kovesdy *et al*., 2017; Alizadeh *et al*., 2019; Jhee *et al*., 2020).

Kidney endothelial function has been impaired in obesity at the insulin resistance stage before the increase of blood sugar and blood pressure, like the upregulation of Kim-1, a urinary tract biomarker of renal tubule injury, which suggests that there may be other inductors to cause kidney damage or other potential mechanisms to cause kidney microvascular injury (Han *et al*., 2002; Park, *et al*., 2015). Importantly, obesity simultaneously accompanied by many clinical manifestations, such as decreased renal blood flow, increased intrarenal pressure and urinary protein. In short, the disturbance of body water and electrolyte balance

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is closely related to these clinical manifestations, especially similar to diabetes insipidus. Uriniferous tubules (namely renal tubules and collecting ducts), as single epithelial duct, are mainly responsible for nutrient transport and water reabsorption in the original urine, while the obstruction of water reabsorption is one of the main causes of polydipsia and polyuria. Therefore, the organic lesions of uriniferous tubules may be one of the new ideas and new research linking obesity and potential kidney damage in the future.

Aquaporins (AQPs) are a family of integral membrane proteins that act as water channels. In terms of individual organisms, AQPs are located throughout the body in multiple parenchymal organs, including the brain, retina, heart, blood vessels, liver, spleen, intestines and kidneys (Ishibashi *et al*., 2009). Kidney expresses at least nine AQPs, including AQP1~8 and AQP11, six of which have been proved to play a role in body water balance. AQP1, AQP2, AQP3, AQP4, AQP7 and AQP8 are distributed differentially and strategically along the nephron to facilitate water reabsorption and urine concentration (Kortenoeven & Fenton, 2014; Moeller *et al*., 2016; Michalek, 2016). Collecting tubules are very important portion of final water reabsorption in body through AQP2, AQP3 and AQP4 (Terris *et al*., 1995, 1996; Kortenoeven & Fenton, 2014). AQP2 is expressed at the principal cells of collecting duct, which localized from the connecting tubule through the papillary duct. In detail, AQP2 traffics between the intracellular vesicular compartment and the apical plasma membrane of principal cell. It has been reported that AQP2 is regulated both in trafficking (short-term regulation) and in abundance (long-term regulation) via renal V2 Vasopressin Receptor (V2R) and arginine vasopressin (AVP) (Terris *et al*., 1996; Christensen *et al*., 1998). AQP3 is expressed at the basolateral membrane of collecting duct epithelium in cortex and outer medulla (He & Yang, 2019). AQP4 is expressed at the basolateral membrane of epithelial cell and is localized in the epithelium of inner medullary collecting duct and the S3 region of proximal tubule (Van Hoek *et al*., 2000; Kim *et al*., 2001; Kortenoeven & Fenton, 2014). Interestingly, both AQP3 and AQP4 are regulated in abundance by AVP in long-term (Poulsen *et al*., 2013; Kortenoeven & Fenton, 2014). Driven by the transcellular osmotic gradient formed by sodium ions and urea (medulla), water molecules enter principal cells via AQP2 expressed on the apical plasma membrane and exit principal cells via AQP3 and AQP4 expressed on the basement membrane. Put it all together, with the principal cell as the core, water molecules formed a functional coordination mechanism across the membrane with the "AQP2/AQP3+AQP4 network".

A recent study showed that weak expression of AQP2, AQP3 and V2R were revealed in renal medulla of rats of high-fat food, and it has been suggested that excess lipid accumulation may lead to lipotoxicity and may be the major driver of water reabsorption dysfunction (Wang *et al*., 2019). In addition, long-term fat accumulation further leads to tubular diseases (Wang, *et al*., 2022). However, the direct mechanism by which obesity contributes to kidney damage based on downregulation of AQPs expression remains elusive. Accordingly, we aimed to copy the mode of high-fat nutritional obesity in this study, and determine potential cross-talk between the water balance and obesity-related kidney disease.

MATERIAL AND METHOD

Laboratory animals and protocols

All experimental procedures and protocols in this study were approved by Animal Ethics Committee of Ningxia Medical University, China.

Sprague Dawley (SD) rats were obtained from the Laboratory Animal Center, Ningxia Medical University and Ningxia Hui Autonomous Region, and bred in the Laboratory Centre. To avoid the impact of gender on this experiment, healthy and male SD aged about 8 weeks and weighting about 240g were used at the beginning of the experiment (n=30). All animals were bred in-house and had free access to clean water and rat chow for the duration of the study. After one week of adaptive feeding, the rats were randomly divided into two groups, Normal Diet (ND, n=15) and High-fat Diet (HFD, n=15), respectively. ND was fed with normal rat chow, the fat of which accounted for 10 % of the total calories. Meanwhile, HFD was fed with High-fat Diet, where the fat accounted for 66 % of the total calories (Carbohydrate: 15.48 %; Protein: 18.08 %; Fat: 66.43 %, lard-saturated fatty acid mainly). Animals were housed in steel cages in a controlled temperature room at 23±2 °C, exposed to a daily 12-hour light–dark cycle (lights on at 07:00 a.m. and off at 07:00 p.m.). Hereditary obesity (ND) and obesity-resistant (HFD) were artificially eliminated during the study.

During 90-day feeding, the body weight of ND and HFD rats were recorded every 10 days. A blood sample was collected at end of the experimental period. UREA, HDL and LDL were measured by standard methods using an autoanalyzer (JCA-BM6010/C, Sysmex CA-620, Japan). Meanwhile, the samples of kidney and adipose tissue were collected and immediately fixed with 4 % paraformaldehyde solution (PH7.4), and shortly afterward, blocks were cut from various parts of the samples for HE, Masson staining and immunolight microscopy.

Electron microscopy

Samples of renal cortex, outer medulla and inner medulla were collected. For transmission electron microscopy, fresh specimens, about 1 mm^3 in size, were fixed in 4 % phosphate buffered glutaraldehyde for 2 h at 4 °C. Subsequently, these were immersed in 1% solution of osmium tetroxide in a phosphate buffered at 4 °C.The specimens were then dehydrated in ascending grades of ethanol and embedded in Epoxy, and sectioned in ultra-thin slice. Sections were stained with uranyl acetate and observed using transmission electron microscopy (Zeiss, Oberkochen, Germany).

Immunolight microscopy

For immunolight microscopy, specimens were dehydrated through a graded series of alcohol, cleared and embedded in paraffin wax, and sectioned at 5 μm used for immunohistochemical staining. The sections were dewaxed and rehydrated; an antigen retrieval procedure was performed to unmask antigens by treating the samples three times in a microwave oven at medium-high fire for 5 min each time in 10 mM citrate buffer, pH 6. After cooling to room temperature, the sections were treated with 3 % hydrogen peroxide (H_2O_2) in distilled water for 30 min and then washed three times with PBS for 10 min each. The sections were incubated in blocking reagent for 1 h and incubated overnight at 4 °C with anti-F4/80 diluted 1:1000 (Boster, Wuhan, China). The primary antibody was diluted in 10 mM PBS supplemented with 0.1 % BSA and 0.3 % Triton X-100 [10 mM PBS (7mM Na_2HPO_4, 3mM NaH_2PO_4, 150 mM NaCl, pH 7.4)]. Subsequently, the sections were rinsed with 10 mM PBS for 3×10 min and incubated with biotinylated anti-rabbit IgG (ZSGB-BIO, Beijing, China, dilution: 1:200) secondary antibody for 2 h at room temperature. Then, the sections were rinsed with 10 mM PBS for 3×10 min and incubated with horseradish peroxidase streptavidin (ZSGB-BIO, Beijing, China, dilution: 1:200) tertiary antibody for 2 h at room temperature followed by coloration with diaminobenzidine (DAB; ZSGB-BIO, Beijing, China) for 30 s to visualize positive reaction. Counterstaining was with hematoxylin staining. The sections were carried out using bright microscopy (NI-V, Nikon, Japan).

Western blot

Kidney tissue lysates were obtained in Total Protein Extraction Kit (KeyGEN, Nanjing, China). The total protein concentration was measured using a BCA Protein Assay Kit (KeyGEN, Nanjing, China). Total protein lysates (~30 μg) were used for immunoblotting studies. After blocking, membranes were incubated overnight with the primary antibody anti-AQP2/AQP4/Smad2/ADRP/CD36 (Abways, Shanghai, China; 1:1000), anti-AQP3 (Boster, Wuhan, China; 1:1000), anti-TGFb1 (Abmart, Shanghai, China; 1:1000) and then with a goat anti-rabbit immunoglobulin G (Abways, Shanghai, China; 1:10000) conjugated to peroxidase. Immunoreactivity was detected using the Enhanced Chemiluminescence (ECL) Western Blotting Analysis System (Amersham Imager 600, GE Healthcare, DE, USA) according to the manufacturer's instructions. To confirm equal loading, each membrane was also analyzed for GAPDH protein expression. Densitometry was performed and the values were plotted as AQP2, AQP3, AQP4, TGFβ1, Smad2, ADRP, CD36/GAPDH, respectively.

Statistical analysis

Measurements results of general physiological parameters were performed by unpaired t-test (two tailed). All data are presented as the mean±SEM (standard error of the mean), $*P<0.05$, $**P<0.01$, $***P<0.001$.

RESULTS

Establishment of high-fat diet-induced obesity in rats

During 90 days feeding, the data on body mass of ND and HFD rats were recorded every 10 days. The body weight of SD rats during the first 60 days were no significant difference between ND and HFD groups. However, the body mass of rats in HFD group from day 60 onwards was difference compared with ND group ($P<0.05$) (Fig.1A). Light microscopy of adipose tissue at ND and HFD rats on paraffin section was shown by HE staining, comparison of adipocyte size at ND and HFD rats was markedly difference ($P<0.001$) (Fig.1B). The concentration of HDL, LDL and UREA in serum of ND and HFD rats were measured by standard methods using an autoanalyzer. HDL and UREA were decreased in the HFD as compared with the ND rats ($P<0.01$) (Fig.1C&D). In addition, LDL was increased in the HFD as compared with the ND rats ($P<0.05$) (Fig.1C&D).

Pathomorphology of renal corpuscles and glomerular filtration barrier

Light microscopy of renal cortex at ND and HFD rats on paraffin section were examined by HE staining. It was found that HFD rats had a larger glomerular area and volume than that of ND rats ($P<0.05$) (Fig. 2A). Meanwhile, glomerular filtration barrier in the renal corpuscle at ND and HFD rats were observed by means of transmission electron microscope. Compared with ND, the number of foot processes (FP) in HFD was smaller and shorter, and the adjacent foot processes were diffused and widened. Although the glomerular basement membrane (BM) was complete and continuous, it was slightly thinning. In addition, there were abundant red blood cells (RBC) in the vascular lumen, but there were also free flocculent proteins (Fig. 2B).

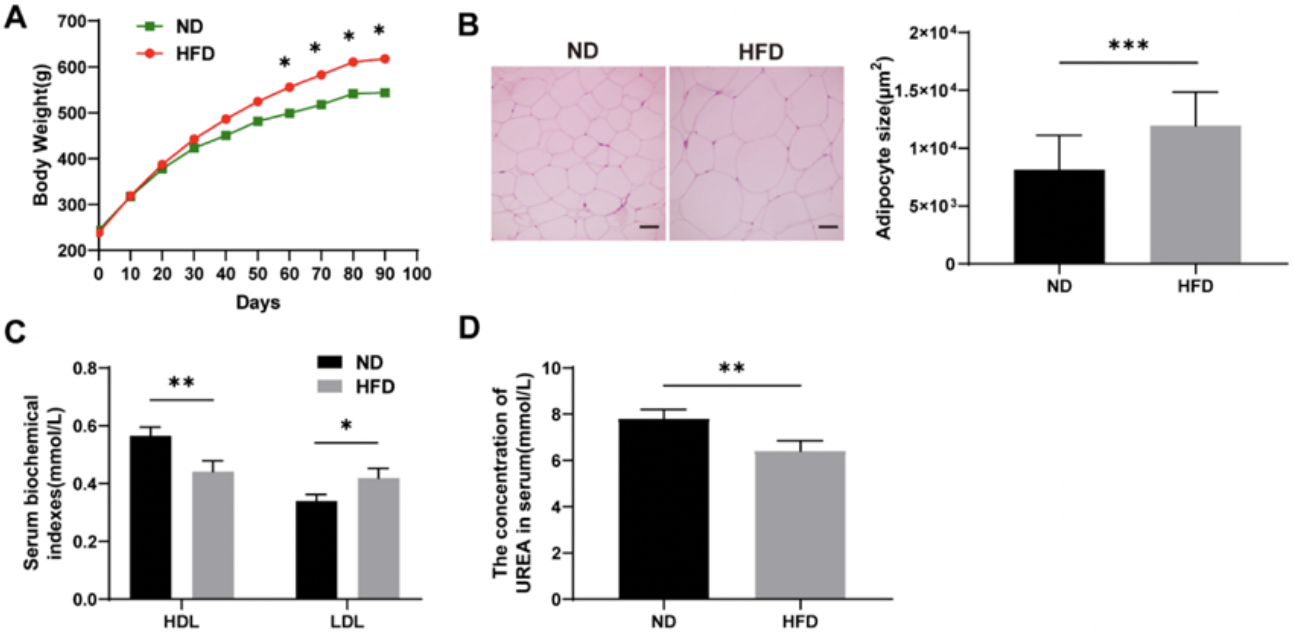

Fig. 1. Establishment of high-fat diet-induced obesity in rats. **A.** Changes in body weight of rats (ND, Normal Diet; HFD, High-fat Diet), after 90-day of high-fat diet feeding, the rats of obesity resistance were eliminated according to body weight sorting. **B.** Histologic features of adipose tissue at ND and HFD rats in HE staining on paraffin section; and comparison of adipocyte size at ND and HFD rats. **C.** The concentration of HDL and LDL in serum of ND and HFD rats. **D.** The concentration of UREA in serum of ND and HFD rats. Scale bar =50mm.*P<0.05, **P<0.01, ***P<0.001, HFD compared with ND, n=15 each group.

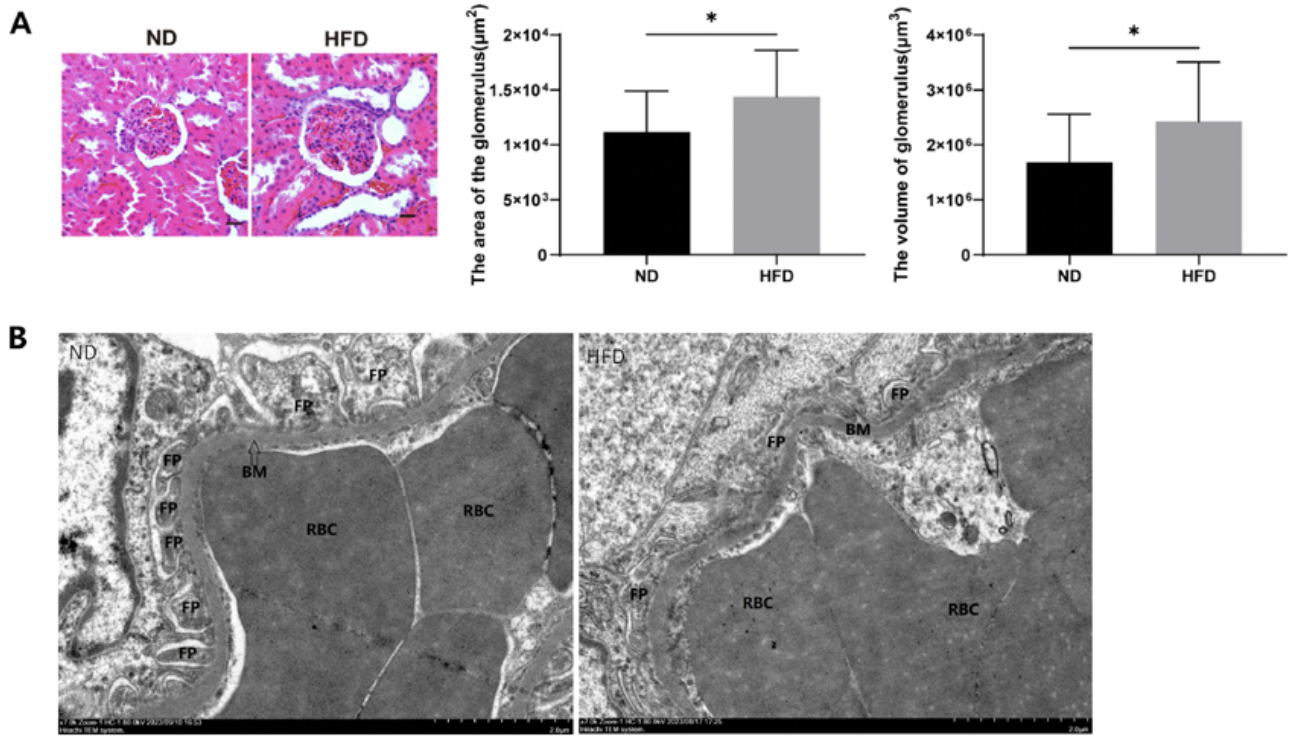

Fig.2. Pathomorphology of renal corpuscles and glomerular filtration barrier in rats induced by high-fat diet. **A.** Histologic features of glomerulus at ND and HFD rats in HE staining on paraffin section; and the area and volume of the glomerulus at ND and HFD rats. Scale bar =20 mm.*P<0.05, ***P<0.001, HFD compared with ND, n=5 each group. **B.** Observation of glomerular filtration barrier in the renal corpuscle at ND and HFD rats with transmission electron microscope. FP, Foot Process; RBC, Red Blood Cell; BM, Basement Membrane.

Renal fibrosis and ultrastructure of collecting duct epithelial cells

Light microscopy of renal cortex, outer medulla and inner medulla at ND and HFD rats were examined by Masson staining on paraffin section. It was shown that HFD rats had a higher degree of interstitial fibrosis in renal cortex, outer medulla and inner medulla compared with ND, respectively (Fig. 3A). Epithelial cells in cortex collecting duct (CCD), outer medullary collecting duct (IMCD) and inner medullary collecting duct (OMCD) were observed by means of transmission electron microscope. Compared with ND, epithelial cells in HFD dissolved in local areas, edema was obvious, and the intracellular matrix showed a larger area of low electron density edema. Chromatin dissociation occurred in the nucleus (N) of epithelial cells, and mitochondria appeared (M) swollen, enlarged, and relatively reduced in number. In addition, rough endoplasmic reticulum (RER) expanded, its membrane space widened and ribosome degranulated. Occasionally, microbodies (Mi) were seen (Fig. 3B).

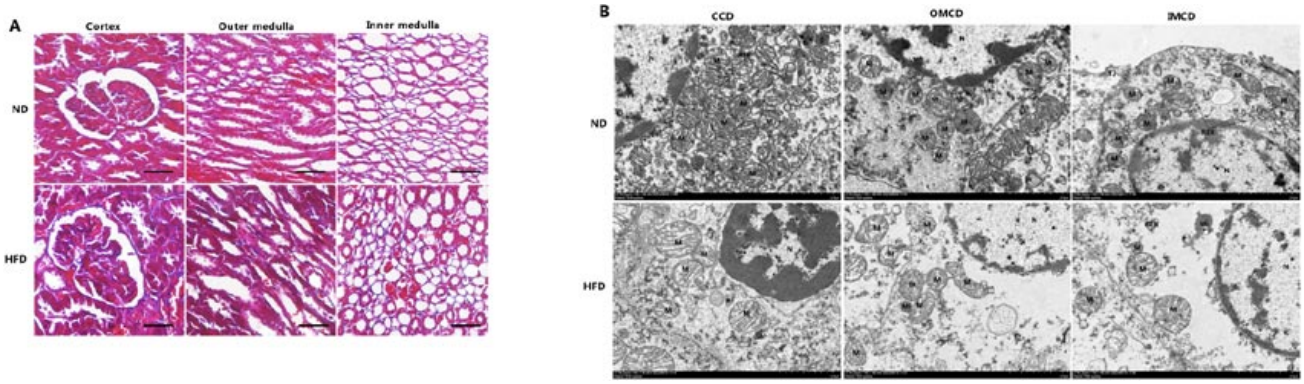

Fig. 3. Renal interstitial fibrosis and ultrastructure of collecting duct epithelial cells in rats induced by high-fat diet. **A.** Degree of fibrosis in cortex, outer medulla and inner medulla of ND and HFD rats by Masson staining on paraffin section. Scale bar =50 μm. **B.** Comparative observation of epithelial cells in cortex collecting duct (CCD), outer medullary collecting duct (IMCD) and inner medullary collecting duct (OMCD) of ND and HFD rats with transmission electron microscope. **N.** Nucleus; **M.** Mitochondria; **REM.** Rough Endoplasmic Reticulum. **Mi.** Microbody.

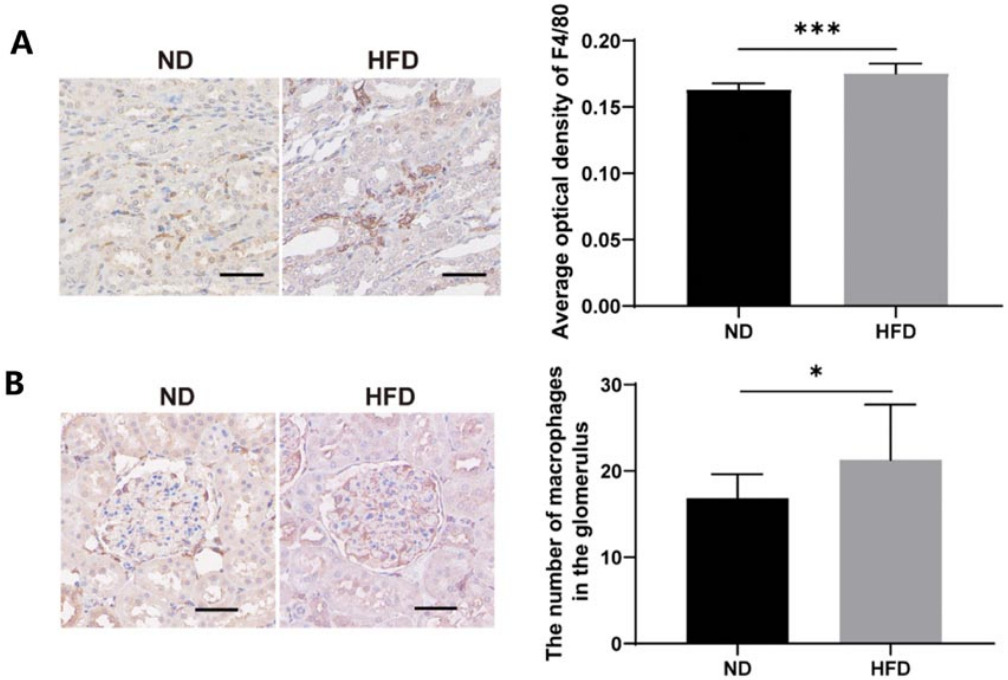

Fig. 4. Immunohistochemical detection of F4/80 (macrophages) in the kidney of rats induced by high-fat diet. **A.** The number of macrophages in the junction of renal cortex and medulla between ND and HFD rats. **B.** The number of macrophages in glomerulus between ND and HFD rats. Scale bar =50 μm.*P<0.05, ***P<0.001, HFD compared with ND, n=5 each group.

Detection of F4/80 (macrophages) in the kidney

The relative number of macrophages in the kidney of rats induced by high-fat diet was measured by immunohistochemical detection of F4/80, counterstaining with hematoxylin staining was used to identify negative segments. It was found that HFD rats had a higher degree of average optical density of F4/80 in the junction of renal cortex and medulla than that of ND (P<0.001) (Fig. 4A). The number of macrophages in glomerulus in HFD was difference compared with ND (P<0.05) (Fig. 4B).

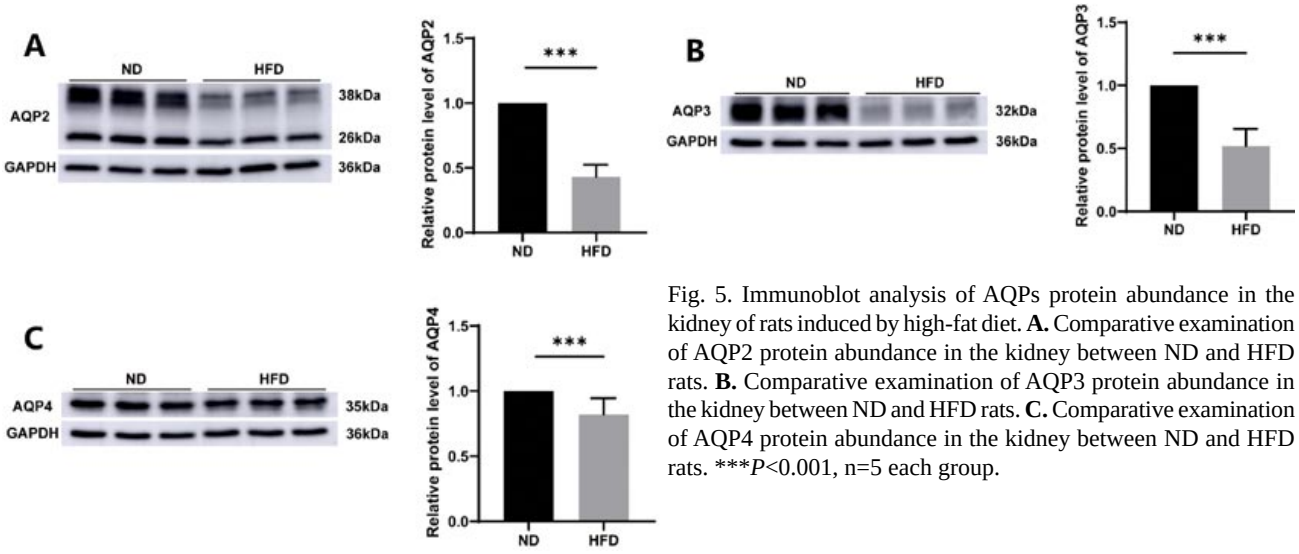

Fig. 5. Immunoblot analysis of AQPs protein abundance in the kidney of rats induced by high-fat diet. **A.** Comparative examination of AQP2 protein abundance in the kidney between ND and HFD rats. **B.** Comparative examination of AQP3 protein abundance in the kidney between ND and HFD rats. **C.** Comparative examination of AQP4 protein abundance in the kidney between ND and HFD rats. ***P<0.001, n=5 each group.

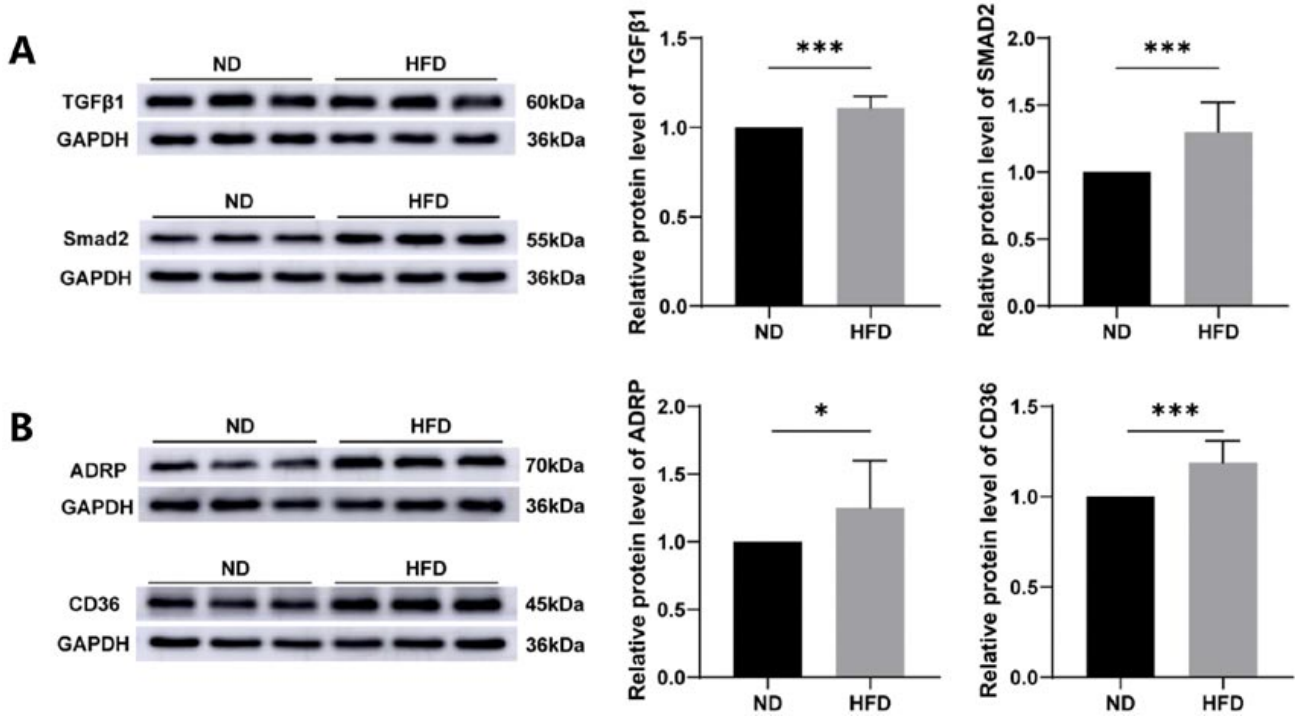

Fig. 6. Immunoblot analysis of TGFβ1, Smad2, ADRP and CD36 protein abundance in the kidney of rats induced by high-fat diet. **A.** Comparative examination of TGFβ1 and Smad2 protein abundance in the kidney between ND and HFD rats. **B.** Comparative examination of ADRP and CD36 protein abundance in the kidney between ND and HFD rats. *P<0.05, ***P<0.001, n=5 each group.

Examination of AQPs, TGFβ1, Smad2, ADRP and CD36 protein abundance in the kidney

AQPs protein abundance in the kidney of rats induced by high-fat diet were examined by western blot analysis. It was shown that AQP2 (Fig. 5A), AQP3 (Fig. 5B) and AQP4 (Fig. 5C) protein abundance in the kidney were all decreased in the HFD as compared with the ND rats, and observed significant differences respectively (P<0.001). A deeper understanding of factors associated with fibrosis and inflammation would provide useful information for AQPs downregulation, mainly including TGFβ1, Smad2, ADRP and CD36. It was found that TGFβ1 and Smad2 protein abundance in the kidney of HFD rats were significant increased in the HFD as compared with ND rats (P<0.001) (Fig. 6A). Meanwhile, the abundances of ADRP and CD36 protein in kidney of HFD rats were increased and significantly different compared with ND rats (P<0.001) (Fig. 6B).

DISCUSSION

There have been a number of prior studies that reported the detrimental effects of obesity on the kidney. Accumulating evidence has suggested that obesity and kidney disease are closely related, and kidney diseases caused by obesity include glomerular injury and renal tubular injury, which of the latter will be the focus of our discussion further. Obesity can cause renal tubular damage, such as renal tubular hypertrophy, the appearance of lipid cytoplasmic inclusions, tubulointerstitial inflammation and fibrosis (Vallon & Thomson, 2012; Declèves *et al*., 2014; Wang *et al*., 2022). Essentially, dissolved materials in the liquid fraction of plasma are formed into a filtrate by the action of kidneys. In this way, the kidneys remove waste by renal corpuscle and recycle filtered nutrients and lots of water by renal tubules and collecting ducts (namely uriniferous tubules). Tubulointerstitial inflammation and fibrosis caused by long-term fat accumulation in obesity inevitably affect the recovery of filtered nutrients and water. Whereas, it was shown that losing weight through drugs or daily diet adjustment can treat renal tubular damage in animal models (Sun *et al*., 2020). Especially, uriniferous tubules have been proved to play a role in body water reabsorption based on AQPs (Kortenoeven & Fenton,2014; Moeller *et al*., 2016). So how does the tubulointerstitial inflammation and fibrosis specifically influence the renal AQPs thereby lead to kidney damage caused by obesity? And there are only a few studies on the structural and functional impairment of the uriniferous tubules associated with obesity. Here, we established the mode of obesity by long-term fat accumulation and set to explore the mechanism between the water balance based on AQP2, AQP3 and AQP4 in collecting ducts and obesity-related kidney disease.

In this study, we demonstrated that long-term HFD feeding can induce kidney injury in Sprague Dawley (SD) rats. Our data showed that 90-day HFD feeding induced obesity in SD rats that exhibited high levels of circulating LDL, low levels of circulating HDL and UREA. Importantly, these HFD-fed rats also exhibited pathological damage in kidney, e.g. histologic change of adipose, glomerulomegaly (including area and volume), glomerular filtration barrier defect, tubulointerstitial inflammation and fibrosis, mitochondrial swelling and enlargement in epithelial cells of collecting ducts. Consistent with previous reports, kidney accumulation of lipids causes lipotoxicity that set the stage for renal injury (Vallon & Thomson, 2012; Wang *et al*., 2022; Sun *et al*., 2020).

It was shown that that obese individuals had a higher glomerular hyperfiltration, renal plasma flow and filtration fraction compared to metabolically healthy normal-weight subjects (Alizadeh *et al*., 2019). Consequently, the original urine composition and osmotic pressure in obese individuals, that is, the "internal environment" is abnormal. Whereby the reabsorption process of uriniferous tubules at all levels is very special and complicated, and the damage to the uriniferous tubules itself is great. In addition, it has been found that the damage of renal interstitium (here can be regarded as " uriniferous tubule interstitium") in obese individuals predicts the decline of renal function in CKD patients in advance (Kitada *et al*., 2020). The damage of uriniferous tubule interstitium is equivalent to the destruction of the "external environment" of the uriniferous tubules, and it is extremely unfavorable to the transport of substances in the original urine. In short, the abnormal "inner/outer environment" of uriniferous tubules in obesity may have the potential to induce irreversible lesions on its structure and function.

Adipose tissue is now considered as an endocrine organ producing biologically active molecules that promote the onset of obesity-related disease, and excess lipid accumulation may be the major driver of renal injury (Declèves & Sharma, 2015; Wang *et al*., 2022). Depending on the body's needs, the filtrate can be reabsorbed via the uriniferous tubules whereby resulting in the final urine concentration. As previously mentioned, this process is tightly regulated, mainly by AVP/V2R-AQP2/AQP3+AQP4 in hypothalamic-pituitary-renal axis, which allows the body to adapt to periods of water load or water restriction (Stanton & Koeppen, 2004; Kortenoeven & Fenton, 2014).

Essentially, uriniferous tubules are tubule surrounded by monolayer epithelial cells, which can reabsorb and secrete some components in urine. Alternatively, the filtrate can be reabsorbed via principal cells of uriniferous tubules based on AQPs in a normal physiological state (Kortenoeven &

Fenton, 2014). Obesity-related kidney disease was characterized interstitial inflammation and fibrosis in this study and it may thus set the stage for renal failure later in life. Here, it was showed that 90-day HFD feeding induced obesity in SD rats that exhibited downregulation of AQPs at the molecular level, including AQP2, AQP3 and AQP4. As mentioned, water molecules enter principal cells via AQP2 expressed on the apical plasma membrane and exit principal cells via AQP3 and AQP4 expressed on the basement membrane (Stanton & Koeppen, 2004; Poulsen *et al*., 2013; Kortenoeven & Fenton, 2014). On this basis, it was suggested that long-term HFD feeding causes kidney injury at least in part as a result of the obvious edema observed in the epithelial cells in this study.

In addition, TGFβ1 and Smad2 expression in the kidney of HFD rats were significant increased in the HFD as compared with ND rats. Meanwhile, expression of ADRP and CD36 in kidney of HFD rats were increased and significantly different compared with ND rats. In the obese state, adipose tissue around the kidneys would be releasing excess pro-inflammatory adipokines (Reilly & Saltiel, 2017). In other words, the state of long-term fat accumulation is characterized by what has been called low-grade systemic inflammation, which in turn has the potential to increase renal inflammation and fibrosis, as well as downregulation of AQPs. A number of prior studies reported that upregulation of AQPs protein can reduce urine volume and improve kidney function in rats with renal fibrosis (Lovisa *et al*., 2015; Liu *et al*., 2018). Together these manifestations suggest that the abnormal "inner/outer environment" and AQPs downregulation of renal tubules in obesity plays a critical role in driving the molecular events leading to renal tubular injury.

Taken together, we investigated the mechanism whereby long-term high-fat diet (HFD) feeding induces renal injury in rats. Our data showed that 90-day HFD feeding induced obesity in rats that exhibited multiple pathological damage in kidney, especially, downregulation of AQPs protein level, including AQP2, AQP3 and AQP4, high expression of TGFβ1, Smad2, ADRP and CD36. Accordingly, we further emphasized on the mechanism between the tubulointerstitial inflammation and fibrosis and AQPs, revealing a potential intervention strategy for the clinical treatment in future. In short, these observations suggest that long-term HFD feeding causes kidney injury at least in part as a result of the tubulointerstitial inflammation and fibrosis and AQPs downregulation (Fig.7). Certainly, diets with high-fat contents have multiple ways to induce kidney injury by a number of prior studies and accumulating evidences. Further studies could focus on the molecular functions of vasopressin type-2 receptor and hormone vasopressin, combining with *in vitro* and *ex vivo*.

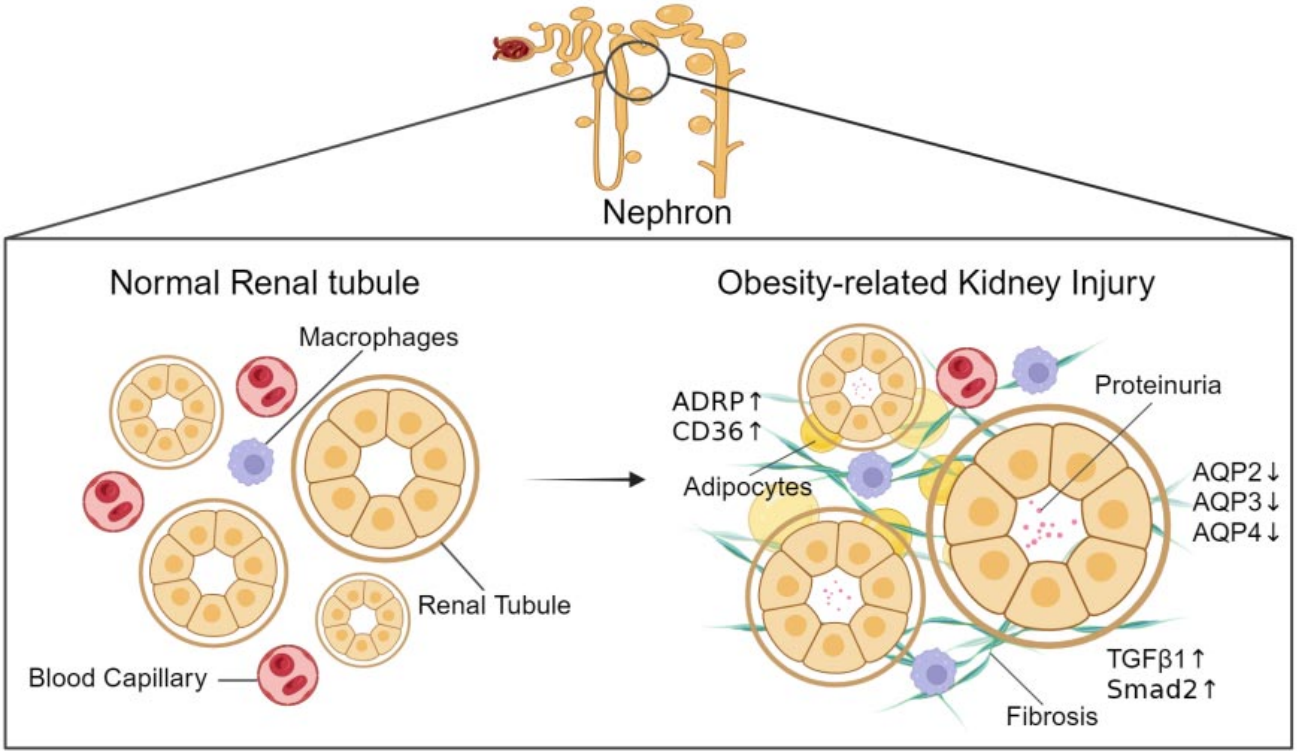

Fig. 7. Schematic illustration of the underlying mechanism by which obesity contributes to kidney injury based on AQPs.

LIANG, J.; WANG, J.; LIN, X.; LONG, J.; YANG, K. & ZHAO, C. Estudio sobre el mecanismo de daño renal causado por la obesidad basado en la regulación negativa de la expresión de AQP en ratas. *Int. J. Morphol., 43(2)*:622-631, 2025.

RESUMEN: La obesidad es un factor de riesgo significativo para el desarrollo de la enfermedad renal crónica (ERC). Básicamente, los materiales disueltos en la fracción líquida de la sangre se transforman en un filtrado por la acción del glomérulo. De esta manera, el riñón elimina los desechos y recicla los nutrientes filtrados (incluida el agua) a través de los túbulos urinarios (es decir, los túbulos renales y los conductos colectores), que pueden reabsorber y secretar algunos componentes en la orina. Cuando se produce una acumulación de grasa en el tiempo en el riñón, acelera una serie de daños renales, p. ej. inflamación y fibrosis. Se ha sugerido que la acumulación excesiva de lípidos conduce a lipotoxicidad y puede ser el principal impulsor de la disfunción de la reabsorción de agua. Además, la acumulación de grasa a largo plazo conduce a enfermedades tubulares. Sin embargo, el mecanismo directo por el cual la obesidad contribuye al daño renal basado en la regulación negativa de la expresión de AQP sigue siendo difícil de alcanzar. Nuestros datos mostraron que la alimentación HFD de 90 días indujo obesidad en ratas que exhibieron múltiples daños patológicos en el riñón, especialmente, la regulación negativa del nivel de proteína AQP, incluyendo AQP2, AQP3 y AQP4, alta expresión de TGFβ1, Smad2, ADRP y CD36. En consecuencia, enfatizamos aún más en el mecanismo entre la inflamación tubulointersticial y la fibrosis y las AQP causadas por lipotoxicidad, revelando una posible estrategia de intervención para el tratamiento clínico en el futuro.

PALABRAS CLAVE: Obesidad; Daño renal; Túbulos uriníferos; AQP; Lipotoxicidad.

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