Pterostilbene, a Resveratrol Derivative, Improves Ectopic Lipid Deposition in the Kidneys of Mice Induced by a High-Fat Diet

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Keywords
Diabetic kidney disease · Pterostilbene · Ectopic lipid deposition · Renal fibrosis · TGF-β1/Smad3 · SREBP-1/FAS signaling pathway

Abstract
Background: Diabetic kidney disease is a major cause of global end-stage renal diseases. Ectopic lipid deposition in the renal tissues of diabetic kidney disease is one major factor leading to renal fibrosis and chronic kidney disease. Pterostilbene has been reported to display lipid-lowing activity and participate in many kidney diseases. However, the influence of pterostilbene on the ectopic lipid deposition is unclear. We intend to explore the influence of pterostilbene on the ectopic lipid deposition in the kidneys of diabetic mice induced by high fat. Methods: A high-fat diet-induced diabetic mouse model was established to detect the alleviative effect of pterostilbene on the ectopic lipid deposition in the kidneys of diabetic mice. A biochemical analysis was conducted to examine the levels of urine albumin, urine creatinine, serum creatinine, and blood urea nitrogen in mice after pterostilbene treatment. Histological analysis was conducted to detect the degree of renal injury and fibrosis. Oil red O staining and immunohistochemical staining were carried out to evaluate lipid droplets and the expression of adipose differentiation-related protein in renal tissues of the mice treated by pterostilbene. The protein levels were assessed by Western blotting. Results: Pterostilbene inhibits the expression of the TGF-β1 and p-smad3 and suppresses the protein levels of SREBP-1 and FAS, and it ultimately reduces the ectopic lipid deposition, alleviates the renal tubular damage and renal fibrosis in the kidneys of diabetic mice induced by high fat, and improves kidney function. Conclusion: Pterostilbene alleviates renal fibrosis and ectopic lipid deposition in the kidneys of diabetic mice induced by high-fat diet by inhibiting the TGF-β1/Smad3 signaling.

Introduction

Diabetic kidney disease (DKD), as a serious complication of diabetes mellitus, is a major cause of global end-stage renal diseases [1]. Kidney disease develops in about 40% diabetic patients, the majority of whom may die from infections and cardiovascular diseases before effective renal replacement treatment [2]. A major pathologi-
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In this study, the function of pterostilbene against renal ELD and the related mechanisms were investigated in a mouse model induced by high-fat diet. Our findings might provide theoretical basis to support pterostilbene as a feasible medicine to alleviate ELD in kidney and improve kidney function.

Materials and Methods

Animal Model Establishment and Ethic Statement
Thirty male C57BL/6J mice (8-week-old, weighing 25–27 g) were bought from Hebei Invivo Biotech Co. Ltd. (license no. SCXK 2020-0002). Mice were raised in the animal laboratory of the Clinical Medicine Research Center of Hebei General Hospital. The 60% room was under a 12-h light/dark cycle, with food and water available. The experiment has been approved by the Ethics Committee of Hebei General Hospital (approval no. 2019E367; Shijiazhuang, China) and implemented in accordance with the International Regulations for the Administration of Laboratory Animals.

After allowed 1 week to adapt to the environment, 10 mice were given ordinary feed (D12450: 20% protein, 70% carbohydrate, 10% fat, 3.85 kcal/g, Beijing Huafukang Biotechnology Co., Ltd) and the remaining 20 mice were given high-fat feed (D12492: 20% protein, 20% carbohydrate, 60% fat, 5.24 kcal/g, Beijing Huafukang Biotechnology Co., Ltd). The mice were fed these diets for 12 weeks.

Drug Administration
Pterostilbene was dissolved in 20% PEG 400, followed by further dilution in double distilled water prior to use. The model (HFD) group was grouped again after 12 weeks of high-fat diet; 10 mice were still in the HFD group, and 10 mice were regarded as the high-fat + pterostilbene group (HFD + PTE group). The HFD + PTE group (n = 10) was given pterostilbene (50 mg/kg, Sigma-Aldrich, St. Louis, MO, USA) daily by gavage at a fixed time. Control group and HFD group were given corresponding doses of 0.9% sodium chloride solution containing 0.1% DMSO by gavage. After 6 weeks of intervention, the mice in each group were given fasting and water for 12 h overnight. The mice were weighed and given 2% pentobarbital sodium (45 mg/100 g) intraperitoneally to anesthetize the mice. Blood was collected from the blood collection tube by cardiac puncture. After routine fixation and disinfection, we opened the abdomen along the midline of the mouse’s abdomen and quickly removed the kidneys. The kidneys were rinsed with pre-cooled 0.9% sodium chloride solution, and a small piece was cut and placed in 4% paraformaldehyde. The rest of the tissues were packed in cryovials and quickly frozen with liquid nitrogen.
and then transferred to −80°C refrigerator for storage. After the sampling was completed, the blood collection tube was centrifuged at 3,000 rpm/min for 15 min. The upper serum was taken using a pipette, dispensed into EP tubes, and stored in a refrigerator at −80°C for later use.

Biochemical Analysis

Serum creatinine or blood urea nitrogen (BUN) levels were assessed using Creatinine Colorimetric Assay Kit (Abcam) or BUN detection kit (Asan Pharmaceutical, Seoul, Korea) following the instructions of the manufacturer. TCH and TG were measured by enzymatic colorimetric methods. Urine (24 h) were collected in metabolic cages for examining the level of urinary albumin and urinary creatinine by using albumin ELISA kit (ab108792, Abcam, Cambridge, UK) or Creatinine Colorimetric Assay Kit (ab204557, Abcam), respectively. Urine albumin-to-creatinine ratio (ACR) = urinary albumin (μg)/urinary creatinine (mg).

Histological Analysis

Kidney tissues were fixed in 10% neutral buffered formalin overnight. Four μm-thick sections were prepared after paraffin embedding. Then, kidney sections were stained with periodic acid-Schiff or Masson trichrome (MASSON). The criteria to score renal histological damage were as follows: 10 high-power fields (×400) in each group were randomly selected and photographed. None = 0; <10% = 1; 11–25% = 2; 26–75% = 3; and >75% = 4 to measure the degree of tubular injury and morphologic damage (tubular dilation, luminal necrotic debris, and epithelial necrosis). The extent of renal fibrosis was scored as 0, 1, 2, or 3 according to none, mild, moderate, and severe involvement, respectively.

Oil Red O Staining

Frozen sections (5 μm) of kidney tissues were first washed in PBS, followed by fixation with 4% paraformaldehyde for 30 min. Subsequently, the samples were stained with freshly prepared 60% oil red O (100% solution: 0.5 g of oil red O dissolved in 100 mL of isopropylene) for 30 min. Then samples were washed by PBS and counterstained with hematoxylin. An Olympus microscope (Olympus, Tokyo, Japan) was used to visualize the slides. The number and size of lipid droplets were quantified using ImageJ software.

Immunohistochemical Staining

The expression of adipose differentiation-related protein (ADRP) was detected by immunohistochemical staining. Endogenous peroxidases were inactivated by using 3% H2O2 for 5–10 min. Renal tissues were fixed in 4.5% buffered formalin, dehydrated, and embedded in paraffin. Tissue sections (4 μm) were rinsed with water and soaked in PBS for 5 min, followed by blocking with 5–10% normal goat serum for 10 min and incubation with primary anti-ADRP antibody (15294-1-AP, 1:200, Proteintech, Chicago, IL, USA) at 4°C overnight. Then, the sections were incubated with secondary antibody (SA00007-2, 1:100, Proteintech) for 30 min after being washed with PBS three times. Horseradish peroxidase (HRP)-streptavidin was added, and the sections were incubated at room temperature for another 30 min. Subsequently, diaminobenzidine solution dropwise was added and positive substances developed into brownish granules. The density was quantified using the image pro plus software.

Western Blotting

Renal tissues were homogenized in RIPA lysis buffer. After centrifugation, the protein level in supernatants was determined using a BCA protein assay kit (Abcam). Equal amounts of proteins were separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and subsequently transferred to the polyvinylidene difluoride membranes (Millipore, Burlington, MA, USA). The membranes were blocked in 5% nonfat milk for 1 h, followed by overnight incubation at 4°C with the following primary antibodies: SREBP-1 (14088-1-AP, 1:1,000, Proteintech), FAS (13098-1-AP, 1:1,000, Proteintech), TGF-β1 (21898-1-AP, 1:1,000, Proteintech), Smad3 (ab10854, 1:1,000, Abcam), p-Smad3 (ab52903, 1:2,000, Abcam), GAPDH antibody (10494-1-AP, 1:5,000, Proteintech) was used as the internal control. After being washed with TBS, membranes were incubated with a horseradish peroxidase-conjugated secondary antibody (ab97080, 1:5,000, Abcam) at room temperature for 1 h. Finally, an enhanced chemiluminescence (Thermo, Rockford, IL, USA) was used to visualize the bands.

Statistical Analysis

SPSS 26.0 software was used for statistical analysis. Data are expressed as the mean ± SD. One-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls (SNK) test was used for comparisons among multiple groups. p < 0.05 was considered statistically significant.

Results

Pterostilbene Improves Diabetes Symptoms of Mice

The chemical structure of pterostilbene was previously discovered [26] and shown in Figure 1a. We initially established the mouse model of diabetes to investigate the effects of pterostilbene on diabetic symptoms. Compared with the control group, an high-fat diet resulted in an increase in the body weight of mice in the HFD group, and pterostilbene treatment reduced the body weight of diabetic mice (Fig. 1b). The fasting blood glucose of mice in the model group was significantly increased and reached 15.4 mmol/L, which was then reduced after pterostilbene treatment (Fig. 1c). Compared to the control group, the diabetic mice in the HFD group displayed more urine volume and higher urinary glucose, which were reduced by pterostilbene (Fig. 1d, e). In conclusion, pterostilbene attenuated the diabetic symptoms of mice.

Pterostilbene Relieves Renal Tubular Injury and Fibrosis in Diabetic Mice

Then, renal tissues were stained with periodic acid-Schiff staining to observe the pathological changes after pterostilbene treatment. The results demonstrated that severe tubular damage as well as atrophy, dilation, and swelling of tubules appeared in the renal tissues of mice...
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Fig. 1. Pterostilbene improves diabetic symptoms of mice. 

(a) Chemical structure of pterostilbene. 
(b) Body weight. 
(c) Fasting blood glucose. 
(d) Urine volume and (e) urinary glucose of mice in control, HFD, HFD + PTE groups. 

Control HFD HFD + PTE

Fasting blood glucose, mmol/L

0 2 4 6 8 10 12 15 20

Control HFD HFD + PTE

Urine volume, mL/day

0 2 4 6 8 10

Control HFD HFD + PTE

Urinary glucose, g/dL

0 1 2 3 4 5

Control HFD HFD + PTE

Body weight, g

0 10 20 30 40

Control HFD HFD + PTE

Fig. 1. Pterostilbene improves diabetic symptoms of mice. a Chemical structure of pterostilbene. b Body weight. c Fasting blood glucose. d Urine volume and (e) urinary glucose of mice in control, HFD, HFD + PTE groups. n = 10 for each group. **p < 0.01, ***p < 0.001 versus control; ##p < 0.01 versus HFD.

Fig. 2. Pterostilbene relieves renal tubular injury and fibrosis of diabetic mice. 

(a) PAS staining showed the changes of renal tissues in each group. Scale bars, 20 μm. 
(b) Masson staining in renal tissues revealed the degree of renal fibrosis. Scale bars, 20 μm. n = 10 for each group. ***p < 0.001 versus control, ##p < 0.01 versus HFD. PAS, periodic acid-Schiff.

Control HFD HFD + PTE

Tubular score

0 1 2 3 4

Control HFD HFD + PTE

Tubular interstitial fibrotic score

0 1 2 3 4

Control HFD HFD + PTE
in the HFD group. However, compared with the model group, the mice treated with pterostilbene displayed significantly relieved renal tubular injury, as indicated by the quantification of tubular score (Fig. 2a). Furthermore, through Masson trichrome staining, we detected the deposition of ECM in renal tissues, which is a significant characteristic of renal tubulointerstitial fibrosis. The staining showed excessive accumulation of ECM in the renal tissues of diabetic mice, suggesting early renal fibrosis. Then, after pterostilbene treatment, ECM deposition was markedly reduced and renal fibrosis was alleviated (Fig. 2b). Taken together, we concluded that pterostilbene relieves renal tubular injury and fibrosis in diabetic mice.

Pterostilbene Alleviates Renal Dysfunction

Next, we investigated the protective influence of pterostilbene on renal function by assessing the levels of related indicators such as urine albumin, serum creatinine, and BUN. We discovered that the urine albumin level was elevated in the model group compared with the control group, which was remarkably reduced after pterostilbene treatment (Fig. 3a). Pterostilbene also reduced the urine ACR, thus mitigating the symptom of proteinuria (Fig. 3b). Similarly, treatment of pterostilbene downregulated the levels of serum creatinine and BUN in diabetic mice and ameliorated renal function (Fig. 3c, d). In addition, we examined the level of TG and TCH in serum. We found that in diabetic mice, the level of TG and TCH in serum was significantly increased relative to the control group, while pterostilbene treatment decreased their levels (Fig. 3e, f). In conclusion, pterostilbene alleviates blood lipids in diabetic mice induced by high fat and improves kidney function.

Pterostilbene Reduces ELD in Kidneys of Diabetic Mice

Subsequently, we stained frozen kidney tissue sections collected from the sacrificed mice with oil red O to observe the lipid distribution in renal tissues. A large number of stained lipid droplets could be seen in renal tissues of diabetic mice induced by high fat relative to the control group, while pterostilbene treatment decreased the area of the stained lipid droplets in renal tissues (Fig. 4a, b). This indicated that pterostilbene treatment alleviates ELD in the kidney. Immunohistochemistry was conduct-
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Fig. 4. Pterostilbene reduces ELD in kidneys of diabetic mice. **a, b** Oil red O staining was carried out to assess lipid droplets in renal tissues. The mean density of oil red O-positive areas was calculated in the control, HFD, and HFD + PTE groups. The first line refers to the staining of medullary segments, while the second line refers to the staining of cortical segments. Scale bars, 50 μm. **c, d** Immunohistochemical staining was performed to evaluate ADRP expression in renal tissues. The mean density of ADRP-positive areas was detected in the control, HFD, and HFD + PTE group. Scale bars, 100 μm. **e–g** Western blotting measured the levels of SREBP-1 and FAS proteins in the kidneys in the control, HFD, and HFD + PTE groups. n = 10 for each group. *p < 0.05, **p < 0.01 versus control; #p < 0.05, ##p < 0.01 versus HFD.

ed to determine ADRP expression in renal tissues. The results showed that ADRP expression was markedly increased in the model group compared to the control group but decreased in the PTE group (Fig. 4c, d). Furthermore, we also detected the levels of FAS and SREBP-1 proteins, which were key regulators of lipid synthesis [27]. Western blotting displayed that the levels of FAS and SREBP-1 proteins were elevated in renal tissues of the model group relative to the control group and were reduced after pterostilbene treatment (Fig. 4e–g). The above results confirm that pterostilbene can reduce the ELD in the kidneys of diabetic mice induced by a high-fat diet and adjust the level of SREBP-1/FAS.
Pterostilbene Inhibits the TGF-β1/smad3 Signaling in Diabetic Mice

TGF-β1 is confirmed to induce renal fibrosis by activating its downstream proteins, especially Smad3. We finally investigated the levels of p-Smad3/Smad3 and TGF-β1 proteins in the PTE group. Western blotting demonstrated that the levels of p-Smad3/Smad3 and TGF-β1 were upregulated in the renal tissues of the model group compared to the control group, while pterostilbene treatment downregulated the corresponding protein levels (Fig. 5a–c). Therefore, we concluded that pterostilbene inhibits the TGF-β1/smad3 signaling in diabetic mice induced by a high-fat diet.

Discussion

In the present study, we established diabetic mouse models induced by a high-fat diet to evaluate the effects of pterostilbene on renal fibrosis and ELD in the kidneys through some potential mechanisms. Pterostilbene treatment significantly decreases ECM deposition via the TGF-β1/Smad3 pathway and ameliorates ELD in the kidney through repressing the expression of FAS and SREBP-1 proteins in diabetic mice.

Hyperglycemia causes the apoptosis of renal tubular epithelial cells, which can further result in abnormal renal tubular reabsorption and secretion function and promote the atrophy of renal tubular epithelial cells and renal interstitial fibrosis [28]. This is the main factor in the progression of DKD [29]. Renal fibrosis is a major pathologic process of DKD, characterized by ECM accumulation [30]. In our study, we discovered renal tubular injury and ECM accumulation in diabetic mice; however, pterostilbene treatment relieved these symptoms. This indicated that pterostilbene alleviates renal injury and renal fibrosis. Furthermore, the previous study demonstrated that pterostilbene alleviates renal fibrosis via inhibiting TGF-β1/Smad3 pathway [31]. In our study, we discovered that the protein levels of TGF-β1, Smad3, p-Smad3 were elevated in diabetic mice, while were reduced in mice treated with pterostilbene. This suggested that pterostilbene exerts an anti-fibrotic effect on renal fibrogenesis through suppressing TGF-β1/Smad3 pathway. Additionally, pterostilbene was demonstrated to improve renal function in a mouse model of hyperuricemia nephropathy [26]. Therefore, in our study, we also investigated the influence of pterostilbene on renal function. We detected the levels of indicators related to renal function in diabetic mice. We discovered that in diabetic mice, the levels of serum creatinine, urine albumin, BUN, and the urine ACR were significantly increased, while were decreased after pterostilbene treatment. This suggested that pterostilbene improves renal function in diabetic mice.

ELD is a key factor that aggravates DKD-correlated renal injury [32]. TCH and TG are stored in lipid droplets [33]. In our study, oil red O staining demonstrated stained lipid droplets accumulated in renal tubules. ADRP, a major lipid droplet-related protein on the surface of lipid droplets, facilitates the formation of lipid droplets [34]. ADRP expression can be evaluated at the early stage of the formation of lipid droplets and then used for quantitative analysis of ELD [4]. In our study, ADRP expression in the renal tubules of diabetic mice was elevated, suggesting the occurrence of ELD in diabetic mice. Pterostilbene has been reported to reduce lipid deposition in the liver [35].

Fig. 5. Pterostilbene inhibits the TGF-β1/smad3 signaling in diabetic mouse kidneys. a–c Levels of p-Smad3/Smad3 and TGF-β1 proteins in renal tissues were determined by Western blotting. n = 10 for each group. ***p < 0.001 versus control; *p < 0.05 versus model.
Our study revealed that, in mice treated with pterostilbene, oil red O-stained lipid droplets were markedly attenuated and the expression of ADRP was also downregulated compared to that in the model group. The results confirmed that pterostilbene can also attenuate ELD in the kidneys of diabetic mice.

The occurrence of ELD is caused by abnormal lipid metabolism [36]. Key genes and enzymes associated with lipid synthesis such as SREBP-1 and its downstream FAS play significant roles in lipid deposition [37]. SREBP is a key transcription factor which regulates the synthesis of TCH and TG [38]. SREBP-1 dysregulation is associated with the pathogenesis of type 2 diabetes, fatty liver, and dyslipidemia [39]. Previously, SREBP-1 expression was found upregulated in renal tissues of mice with type 2 diabetes, and TG and TCH were discovered accumulated in the kidneys [40]. Upregulated expression of FAS and SREBP-1 leads to elevated lipid synthesis in the kidneys, thus causing glomerulosclerosis and tubulointerstitial fibrosis [40]. Our study showed that pterostilbene decreased the protein levels of FAS and SREBP-1 in diabetic mice. Overall, our findings indicated that pterostilbene reduces blood lipids and relieves ELD in kidney via repressing the SREBP-1-modulated FAS pathway.

Conclusion

In summary, our study explored the function of pterostilbene in kidneys of diabetic mice induced by high-fat diet. Pterostilbene alleviates renal fibrosis by inactivating TGF-β1/Smad3 pathway and improves renal ELD by repressing the SREBP-1-modulated FAS pathway in diabetic mice. Our study highlighted pterostilbene as a novel drug for effective treatment of ELD in kidney in DKD.

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Statement of Ethics

The experiment has been approved by the Ethics Committee of Hebei General Hospital (approval no. 2019E367; Shijiazhuang, China) and implemented in accordance with the International Regulations for the Administration of Laboratory Animals.

Conflict of Interest Statement

The authors declare that there are no competing interests in this study.

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Author Contributions

Wei Gu, Guangyao Song, and Jianlin Geng conceived and designed the study. Wei Gu, Linquan Yang, Xiaolong Li, Xing Wang, and Kunjie Zheng conducted experiments. Wei Gu, Chao Wang, Xiaoyu Hou, and Yunpeng Guan contributed to the writing of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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