Introduction  
Diabetic nephropathy (DN) has become the primary cause of end-stage renal disease worldwide [1]. Pigment epithelium-derived factor (PEDF) is an endogenous anti-inflammatory factor in vivo [2], which can inhibit the expression of pathogenic factors — transforming growth factor β1 and connective tissue growth factor, and suppresses extracellular matrix protein production in diabetic kidney, suggesting an antifibrogenic activity [3]. PEDF can reduce albuminuria through the blockade of VEGF expression in the diabetic kidney [2]. In addition, PEDF has been shown to have anti-angiogenic and anti-oxidant properties in cell culture and animal models [4, 5].

Recently, some researchers reported that metformin, as the first-line hypoglycemic drugs for the treatment of type 2 diabetes mellitus (DM), can prevent and delay the occurrence and progress of diabetic nephropathy.
through some mechanisms, which include anti-inflammatory, anti-oxidant, anti-fibrosis, and some other non-hypoglycemic action mechanisms [6–8].

In this study, we aim to observe its reno-protective effect and possible underlying mechanisms of metformin in diabetic rats so as to provide an experimental basic for the use of metformin in the clinical prevention and treatment of diabetic nephropathy.

Materials and methods

Reagents

The following reagents were used: STZ (Sigma, USA), metformin and glyburide (Shanghai Shiguibao Medicine Co., Ltd., China), TG, and LDL-C kits (Beijing BHKT Clinical Reagent Co., Ltd.), urine creatinine (Ucr) and urea nitrogen (BUN) kits (Jiancheng Technology Co., Nanjing, China), urinary albumin (Ualb) kit (Tianjing, Xiehe Medicine Co., Ltd., China), urinary PEDF ELISA test kit (Shanghai Dr. Dean Biotechnology Co., China), TRIzol, primers, and real-time PCR kit (TaKaRa, China), Western blot kits (Shanghai Beyotime Biotechnology Co., Ltd.).

Experimental method

Establishment of the experimental mode

We followed the experimental methods of Ye et al. (2015) [9]. Forty-four male SD rats (180–200 g, SPF grade) aged 8 weeks were purchased from the Experimental Animal Center of Anhui Medical University (Anhui, China). All the animals had free access to water under condition of relative humidity of 40–60 % and temperature of 20–30, and were maintained in a 12/12 h light-dark natural cycle during the experiment period. SD rats were fed a high-fat diet (basal diet +10 % lard compound +2 % cholesterol, 50 % calories from fat) for 4 weeks followed by a single intraperitoneal injection of a low dose of streptozotocin (STZ, 30 mg/kg in 10 mmol/L citrate buffer, pH 4.4) after an overnight fast. Normal control rats (n = 10) received an injection the same volume of citrate buffer alone. Only the animals with glucose levels higher than 16.7 mmol/L were considered diabetic and selected for further studies. One week later, diabetic rats were randomly assigned into three groups (n = 10): group DM treated with metformin 300 mg/(kg×d), group GLY injected with glyburide 5 mg/(kg×d) for 8 weeks.

Care, use, and treatment of all animals in this study were in strict agreement with the rules in the care and use of laboratory animals set forth by Anhui Provincial Hospital Affiliated to Anhui Medical University. Every effort was made to reduce the number of animals used and their suffering.

Biochemical detections

Biochemical detections were approached as described previously [9]. Urine samples were collected from the rats housed in metabolic cages for 24 h to measure urinary albumin (Ualb), urinary sediment PEDF (Upedf), and urinary creatinine (Ucr). Ualb was measured by radioimmunoassay. Radiimmunoassay was used to test Ualb. Enzyme-linked immunosorbent assay was used to test Upedf. Ucr was tested by Jaffe’s assay. Urinary albumin and urinary sediment PEDF were expressed as urinary Ualb/Ucr (UACR) and Upedf/Ucr (UPCR) to eliminate the impact of urine volume, respectively. Data’s were calculated using the following equations:

\[
\text{UACR (mg/g)} = \frac{\text{Ualb (mg/L)}}{\text{Ucr (umol/L)}} \times \frac{\text{the molecular weight of Cr (113.12 g/mol)}}{10^{-6}}.
\]

\[
\text{UPCR (pg/g)} = \frac{\text{Upedf (pg/L)}}{\text{Ucr (umol/L)}} \times \frac{\text{the molecular weight of Cr (113.12 g/mol)}}{10^{-6}}.
\]

The blood sample was preserved at -80 after centrifugation for the detection of FBG, HbA1c, serum BUN, TG, and LDL-C. High-performance liquid chromatography was used to detect HbA1c. Insulin (INS) was detected by the radioimmunoassay method. BUN was detected by the urease method. The serum TG, LDL and FBG were detected by automatic microplate reader.

Electron microscopic observation

1 mm² renal cortex was fixed in 2.5 % glutaraldehyde to produce 4 µm thick sections. Ultrathin sections were observed by electron microscopy at a magnification of ×10,000. Three glomeruli were observed per section. Collected 10 photos from each glomerulus randomly and measure glomerular basement membrane (GBM) thickness, taking the average, was calculated as GBMT of the corresponding group.

Image processing and analysis program (Image Pro Plus 6.0) was used to assess the GBM and the part of fused foot process. Foot process fusion rate (FRFP) = the whole length of GBM/the grand total length of fused foot process covered in the corresponding GBM. FRFP was calculated and used to finally assess a mean FRFP per group [10].

Western blot analysis

Western blot analysis was performed as described previously [11]. Briefly, the renal tissue was lysed with the RIPA lysis buffer to obtain extracts of renal protein. Electrophoresis for the protein samples was performed on 10 % SDS-PAGE gels, and then the samples were transferred onto a polyvinylidene fluoride (PVDF) membrane for sealing for 2 h 50 µg of protein from each sample was blotted by an anti-PEDF antibody. The same PVDF membranes were stripped and incubated with an anti-β-actin antibody. Image acquisition system was used to obtain Images, the band intensities were quantified using Image J software.

Renal Tissue PEDF mRNA Expression

The levels of mRNA were analyzed in renal tissue using a real-time PCR approach as described previously [12]. Total RNA was extracted using TRIzol reagent (Invitrogen) according to the manufacturer’s protocol. Primers specific for PEDF (forward 5'-TC-GCATAGACCTCCGAG AGATTA-3'; reverse 5'-ATCAGAGTCCAAGCCATACGT-3') and β-actin (forward 5'-CACCCCGCAG TACAACCTTC-3'; reverse 5'-CCCATACCCACCACATCACC-3').
PCR was performed using the reverse transcription kit and SYBR Premix Ex Taq II. Results were normalized to the β-actin mRNA levels and represented using the comparative threshold cycle method. The cycle threshold (Ct) value of fluorescence units was used to analyze the mRNA levels by the 7500 software. The relative quantitative method ($2^{ΔΔCt}$) was used to calculate the relative changes in gene expression.

### Statistical Analysis

Data processing was performed using SPSS 16.0 (SPSS Inc., USA). The results were calculated and expressed as group means ± SD. One-way analysis of variance was used to perform significant differences among groups and Student-Newman-Keuls test was used for comparison between individual groups. Individual differences among groups were analyzed by Dunnett’s test. A p value of < 0.05 was considered statistically significant.

### Results

**Effect of metformin on serum biochemical and urinary indices in diabetic rats**

After 8 weeks, compared with NC group, the diabetic rats showed a profound elevation in the level of FBG, HbA1c, TG, LDL-C, and BUN and INS (p < 0.05). All measured biochemical parameters above in MET group and GLY group decreased significantly (p < 0.05) as compared with group DM, there were no significant differences in FBG and HbA1c between group MET and group GLY. UACR and UPCR levels in DM group increased obviously compared with NC group. The indicators above in MET group and GLY group were significantly decreased compared to those in the DM group (p < 0.05), there were significantly decreased in group MET than those in group GLY (table 1).

**Effect of metformin on renal histology in diabetic rats**

The renal tissue obtained from NC group showed a normal mesangial matrix, the structure of glomerular podocytes remained clear, the foot processes showed no fusion. The glomerular basement membrane (GBM) was thickened diffusely and its the architecture became ambiguous, the foot processes were swollen and fused significantly at the meanwhile, some foot processes were completely ruined and even disappeared in the DM group. Compare with DM group, both GBMT and FRFP of glomerular were alleviated in the MET and GLY groups (p < 0.05). Compared to GLY group, the pathological changes of glomerular were more alleviated in MET group (p < 0.05) (figure 1(a)).

### Effect of metformin on renal tissue PDE7 mRNA expressions in diabetic rats

As compared to that in NC group, the renal PDE7 mRNA expressions was down-regulated significantly in DM group (p < 0.05). Administration of metformin or glyburide significantly inhibited renal PDE7 mRNA expressions as compared to DM group, which was more prominent in group MET than those in group GLY (p < 0.05) (figure 2(c)).

### Discussion

PEDF is a member of the serpin superfamily, which is a neurotrophic factor secreted by adipocytes, and it could block the development and progression of experimental diabetic nephropathy [2]. Initially identified in the conditioned medium of human retinal pigment epithelial cells, it is currently believed that PEDF is abundantly expressed in kidney, liver, and adipose tissue [13].

PEDF has been shown to be a highly effective inhibitor of angiogenesis in cell culture and animal models, not only reduces advanced glycation end product, angiotensin II or leptin-induced vascular endothelial growth factor (VEGF) expression, but also inhibits the biological actions of other factors, thus exerting an important

### Table 1. Effect of metformin on Indices of Serum Biochemical and Urinary Indices Levels in diabetic rats

| Item         | NC group (n = 10) | DM group (n = 10) | MET group (n = 10) | GLY group (n = 10) |
|--------------|------------------|------------------|-------------------|-------------------|
| FBG (mmol/l) | 4.45 ± 1.07      | 15.60 ± 1.56*    | 11.75 ± 0.98*     | 11.78 ± 1.42*     |
| HbA1c (%)    | 4.13 ± 0.89      | 12.41 ± 0.61*    | 8.78 ± 0.32*      | 8.85 ± 1.07*      |
| TG (mmol/l)  | 0.58 ± 0.19      | 1.52 ± 0.52*     | 0.88 ± 0.27*      | 1.14 ± 0.39*      |
| LDL-C (mmol/l)| 0.54 ± 0.19      | 1.16 ± 0.18*     | 0.82 ± 0.15*      | 1.03 ± 0.80*      |
| BUN (mmol/l) | 6.91 ± 2.52      | 18.95 ± 0.98*    | 11.30 ± 2.02*     | 14.03 ± 2.55*     |
| UACR (mg/g)  | 34.09 ± 2.92     | 136.31 ± 6.84*   | 98.92 ± 5.40*     | 110.10 ± 6.76*    |
| UPCR (pg/ml) | 0.15 ± 0.01      | 0.83 ± 0.15*     | 0.28 ± 0.07*      | 0.40 ± 0.05*      |

Notes: * — p < 0.05, versus NC group; † — p < 0.05, versus DM group; ‡ — p < 0.05, versus MET group.
Figure 1. Effect of metformin on renal histology in diabetic rats. The pathological changes in kidneys under electron microscope among four groups (× 10,000) (a); GBMT (b); FRFP (c)
Notes: normal rats; DM: STZ rats; MET: STZ + metformin (300 mg/kg per day) treatment rats; GLY: STZ + glimepiride (5 mg/kg per day) treatment rats; all values were expressed in mean ± SD. * — p < 0.05, versus NC group; # — p < 0.05, versus DM group; ! — p < 0.05, versus M1 group.

Figure 2. Effect of Metformin on the Renal Tissue PEDF Protein and mRNA Expressions in Rats.
The Relative PEDF protein levels (a) (b); Renal PEDF mRNA levels (c)
Notes: normal rats; DM: STZ rats; MET: STZ + metformin (300 mg/kg per day) treatment rats; GLY: STZ + glimepiride (5 mg/kg per day) treatment rats; all values were expressed in mean ± SD. * — p < 0.05, versus NC group; # — p < 0.05, versus DM group; ! — p < 0.05, versus M1 group.
role in protecting blood vessels, inhibiting inflammation and oxidative stress [4, 14, 15]. It was reported that PEDF suppresses AGE-elicited endothelial cell damage through its anti-oxidative properties and blocks the progression of experimental diabetic retinopathy (DR) [5, 16].

However, the protective effect of PEDF in early experimental diabetic nephropathy has not been demonstrated in vivo. Joshua [3] provided the first evidence that a PEDF gene delivery ameliorates proteinuria in STZ-induced diabetic rats in vivo. AGE-induced RAGE gene expression, ROS generation, inflammatory and fibrogenic gene expression (MCP-1, TGF-β, fibronectin and type IV collagen mRNA levels) were significantly increased in diabetic kidney, which were suppressed by administration of PEDF, it suggests that PEDF could play a protective role against diabetic nephropathy by attenuating the deleterious effects of AGES via the down-regulation of RAGE expression [5, 18–20].

Previous study showed that metformin treatment increased PEDF expression in both prostate cancer cells and tumor tissue [21]. Turan et al demonstrated that metformin is effective in preventing ovarian hyperstimulation syndrome (OHSS) and its severity (VEGF expression and vascular permeability) by up-regulating PEDF expression [22].

Akin S. et al. reported that patients with newly diagnosed diabetes is associated with obvious increase in serum PEDF levels after metformin treatment [23]. In this study, the levels of serum BUN, UACR, FRFP and GBMT in DM rats were higher than those in group NC. These indexes were significantly decreased after metformin or glyburide treatment for 8 weeks, and the former is superior than the latter, but the value of FBG, HbA1c in MET group had no significant differences compared with GLY group, which indicated that metformin has a remarkable protective effect on the kidney independent of its hypoglycemic effect.

And the underlying mechanisms of metformin renoprotection are not clear completely, which may be related to its effects in activating AMP, activating protein kinase, inhibiting inflammation and oxidative stress, lightening lipid deposition, and so forth [25].

In present study, the UPCR, protein and mRNA expressions of PEDF in group DM were obviously decreased compared with group NC, which were up-regulated by MET or GLY treatment, and that was greater in group MET than that in group GLY. It suggests that metformin can up-regulate the expressions of PEDF protein and mRNA in renal tissue of DM rats partially independent of hypoglycemia, which maybe also contribute to its renoprotection in some extent. At present, the mechanism is not clear that metformin increasing the expression of PEDF in renal tissue, and there is no report about the direct effect of metformin on the expression and secretion of PEDF in diabetic kidney tissue [23].

In the early stage of diabetes, the expression of PEDF is decreased, hyperglycemia maybe is responsible for the decrease of PEDF in the diabetic kidneys [3, 24]. Many studies have demonstrated that activating PPAR-γ signaling pathway played pivotal role in PEDF’s beneficial effects [25–29]. PPAR-γ knockdown could reduce PEDF expression [30]. The decrease of PEDF was significantly down-regulated and the increase of NF-κB and MMP-9 was down-regulated by systemically administration of PPAR-γ agonist [31].

Our observations indicate that PEDF induces macrophage apoptosis and necrosis through the signaling of PPAR-γ [25]. Ishibashi et al. demonstrated for the first time that PEDF could block the AGE-induced apoptotic cell death of podocytes by suppressing RAGE expression and subsequent ROS generation partly via PPAR-γ activation. All of the beneficial effects of PEDF on AGE-exposed podocytes were blocked by the treatment of GW9662, an inhibitor of PPAR-γ [32]. PEDF increment on human endothelial cells was blocked by the preincubation with GW9662, which resulted in the promotion of angiogenesis [30]. Moreover, it had been suggested that PEDF could interact with PPAR-γ for the regulation of angiogenesis and lipid metabolism in hepatocellular carcinoma [33], and it is necessary for protective roles of PEDF in OGD cardiomyocytes [34]. These results highlight the crucial of PPAR-γ pathway in regulating PEDF expression.

Previous studies demonstrated that metformin activated AMPK which subsequently activates and upregulates PPAR-γ [35–37]. Qu et al. have shown that metformin can effectively inhibit the mRNA and protein expressions of MCP-1, IL-6, and TNF-α in LPS-induced VSMCs through the upregulation of PPAR-γ activity [38]. Previous studies have also shown that metformin can inhibit LPS-induced pulmonary inflammatory responses in mice by upregulating PPAR-γ activity [39]. In addition, metformin modulates CIS-induced hepatic damage by mitigating oxidative, and decreased caspase-3, MAPK activity and NF-kB level via a PPAR-γ-dependent pathway [40]. These are proposed that metformin increases the PEDF express by up-regulating PPAR-γ pathway, attenuates the deleterious effects of oxidative and fibrogenic, and exerting certain renal protective effects.

**Conclusion**

Taken together, metformin significantly alleviated proteinuria and renal podocyte lesions in diabetic rats induced by STZ, which may be due to that metformin increases the PEDF express by up-regulating PPAR-γ pathway, attenuates the deleterious effects of oxidative and fibrogenic, and exerting certain renal protective effects.

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**Conflicts of interests.** Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

**Availability of data and materials**
The data’s and models used to support the findings of this study are available from the corresponding author upon request.

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Резюме. Актуальність. Діабетична нефропатія стала основною причиною термінальної стадії ниркової недостатності. Фактор пігментного епітелію (ФПЕ) є ендоцитичною тканиною, а також продукцією білка позаклітинного матрикса в нирці за наявності цукрового діабету.

Мета дослідження. Вивчити вплив метформіну на експресію ФПЕ у тканині нирок з цукровим діабетом 2-го типу.

Метаболічні показники. Глюкоза крові натще (ГН), глікованого гемоглобіну (HbA1c), термінальних продуктів глюкозвоночної засихової активності (TPP) в групі МЕТ і групі ГЛІ порівняно з групою ФР. Крім того, зменшилися показники трігліцеридів, екскреції альбуміну із сечею і ФПЕ, сили зниженої гломерулярної продукції (ГПП).

Результати. На восьмому тижні рівні глюкометричних показників, дані гістопатологічного дослідження нирок і рівні експресії ФПЕ у нирковій тканині в групі МЕТ i ГЛІ вірогідно знизилися порівняно з групою ФР. МЕТ і ГЛІ порівняно з групою ФР. Крім того, зменшу-

Загалом 30 щурів із діабетом 2-го типу були розподілені перитонеальним введенням 30 мг/кг стрептозотоцину. індукували дієтою з високим вмістом жиру і внутрішньо перитонеальним введенням 30 мг/кг стрептозотоцину. Загалом 30 щурів із діабетом 2-го типу були розподілені ні на 3 групи, які отримували метформін 300 мг/кг (30 мг/кг) (група ГЛІ, n = 10) або фізіологічний розчин (група ФР, n = 10). Крім того можливі основні захисні механізми при ураженні нирок by PPARs. PLoS One. 2015 Nov 4;10(11):e0142303. doi: 10.1371/journal.pone.0142303.

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Оригінальні дослідження /Original Researches/

Резюме. Актуальность. Диабетическая нефропатия стала основной причиной терминальной стадии почечной недостаточности. Фактор пигментного эпителия (ФПЕ) является эндогенным противовоспалительным фактором вживую, который может подавлять экспрессию патогенных факторов — трансформирующего фактора роста β, и фактора роста соединительной ткани, а также продукцию белка внеклеточного матрикса в почках при наличии сахарного диабета, что указывает на антифброгенную активность. 

Цель исследования: изучить влияние метформина на экспрессию ФПЭ в ткани почек крыс с сахарным диабетом 2-го типа и установить его возможные основные защитные механизмы при поражении почек. 

Материалы и методы. Десять самцов крыс линии Sprague–Dawley были рандомизированы в качестве нормальной контрольной группы. Сахарный диабет 2-го типа индуцировали посредством диеты с высоким содержанием жира и внутриперитонеального введения 30 мг/кг стрептозотоцина. Всего 30 крыс с диабетом 2-го типа были разделены на 3 группы, которые получали метформин 300 мг/кг/сут (группа MET, n = 10), глибенкламид 5 мг/кг/сут (группа ГЛИ, n = 10) или физиологический раствор (группа ФР, n = 10) в течение восьми недель. Анализировали различные биохимические показатели, данные гистопатологического исследования почек и уровни экспрессии ФПЭ в почечной ткани.

Результаты. На восьмой неделе уровни глюкозы крови натощак, гликированного гемоглобина, триглицеридов, экскреции альбумина и ФПЭ с мочой, сывороточного креатинина и азота мочевины крови в группе MET и группе ГЛИ достоверно снизились по сравнению с группой ФР, достоверных различий в показателях глюкозы крови натощак и гликированного гемоглобина между группой MET и группой ГЛИ не обнаружено. При гистологическом исследовании выявлено улучшение гломерулярных патологических изменений, вызванных сахарным диабетом, после лечения MET и ГЛИ по сравнению с группой ФР. Кроме того, уменьшилась экскреция альбумина и ФПЭ с мочой, наблюдалась меньшая выраженность патологических изменений в клубочках и повысилась экспрессия белка и мРНК ФПЭ почечной ткани в группе MET по сравнению с группой ГЛИ.

Выводы. Метформин снижает экскрецию альбумина с мочой у крыс с диабетом, улучшает морфологию и уменьшает выраженность структурных поражений подоцитов. Это может быть частично связано с его ролью в восстановлении экспрессии ФПЭ и ингибировании экскреции ФПЭ с мочой.

Ключевые слова: сахарный диабет 2-го типа; диабетическая болезнь почек; метформин; фактор пигментного эпителия; глибенкламид