Dysregulation of LDL receptor by cyclooxygenase-2 contributes to podocyte injury in streptozotocin induced diabetic rats

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Background

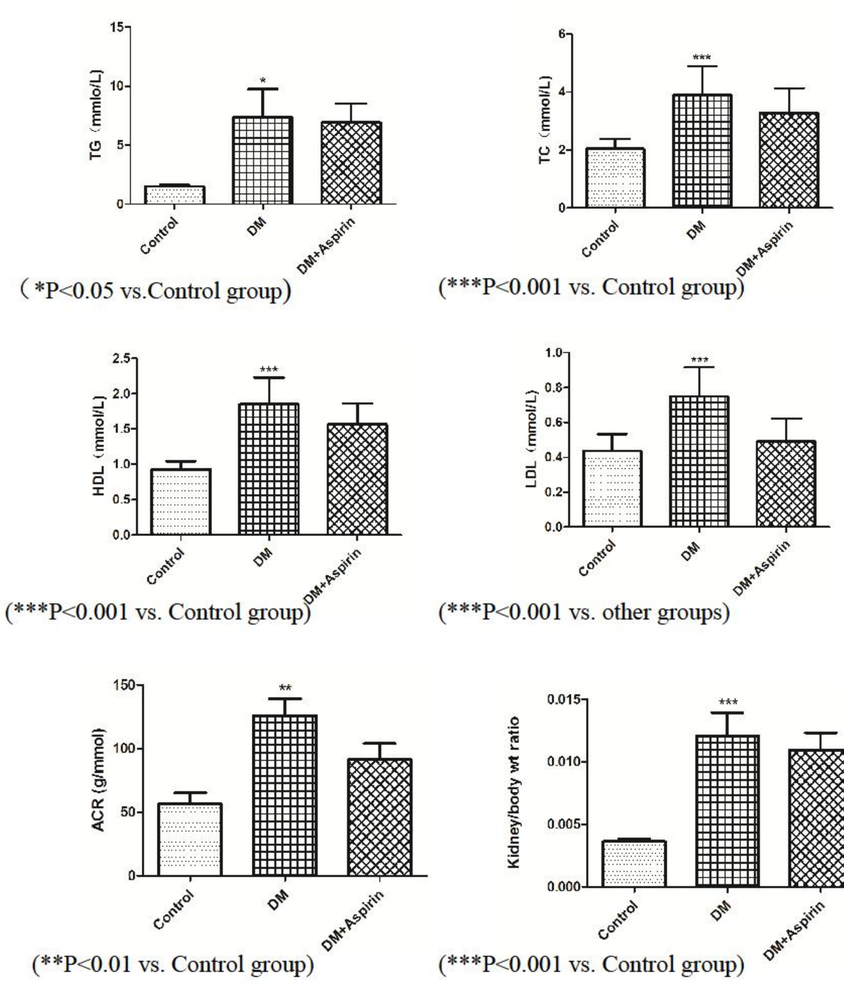
Podocyte injury and resulting microalbuminuria are early hallmarks of diabetic nephropathy(DN). Lipid disorder play crucial roles in podocyte injury of DN. This study was designed to investigate whether cyclooxygenase-2(COX-2)is involved in podocyte injury by disrupting the low-density lipoprotein receptor (LDLr) pathway.

Methods

Eight-week old male Sprague-Dawley rats were treated for 12 weeks by dividing into three groups: nondiabetic rats (Control), streptozotocin-induced diabetic rats (DM), and diabetic rats treated with Aspirin (DM+ Aspirin). The plasma lipid profile was checked by clinical biochemistry assay. The ratio of urinary microalbumin to creatinine (ACR) was detected by enzyme-linked immunosorbent assay. Intracellular lipid accumulation was evaluated by Oil Red O staining, Filipin staining, and a free cholesterol quantitative assay. The glomerular podocyte injury and the expression of molecules related with LDLr pathway was evaluated by electron microscope, immunohistochemical staining, immunofluorescent staining, and Western Blot.

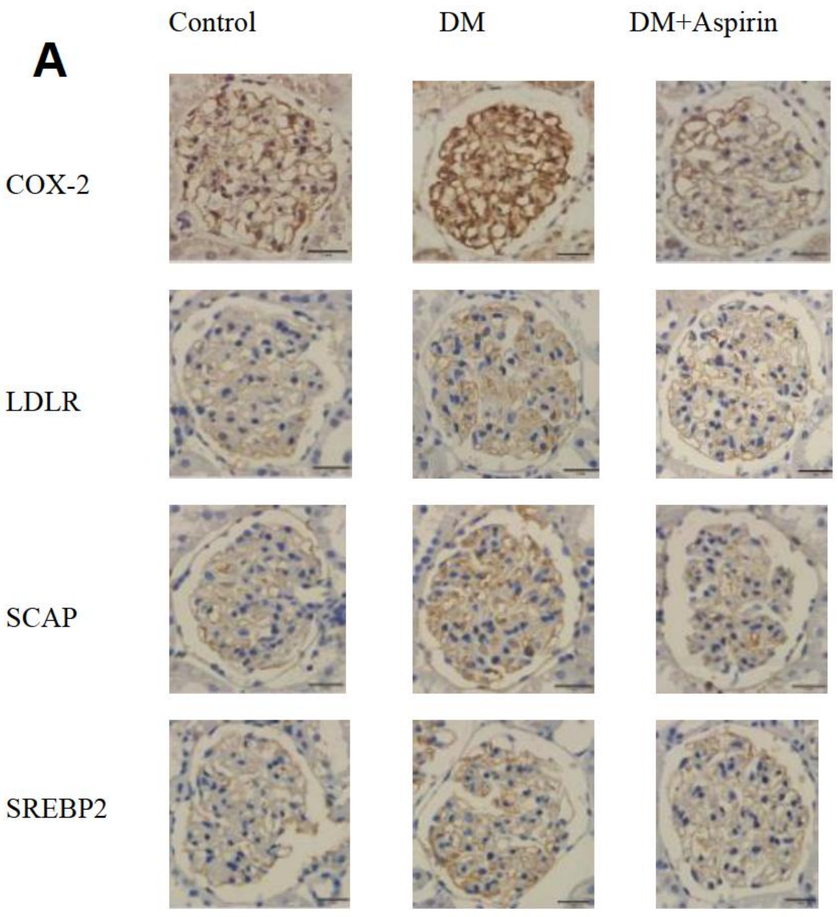
Results

1. There were increased levels of plasma lipids, urinary ACR, and kidney weight-to-body weight ratio in DM rats compared with Control, which was inhibited by Aspirin.



（TG, triglyceride; TC, total cholesterol; HDL， high-density lipoprotein; LDL, low-density lipoprotein; ACR,Albumin/Creatinine ratio.Values were represented as the means±SD.）

2. Increased protein expressions of COX-2, LDLr, sterol regulatory element–binding protein (SREBP), cleavage activating protein (SCAP), and SREBP-2 were observed in DM rats compared with the controls, which were decreased in DM+Aspirin.



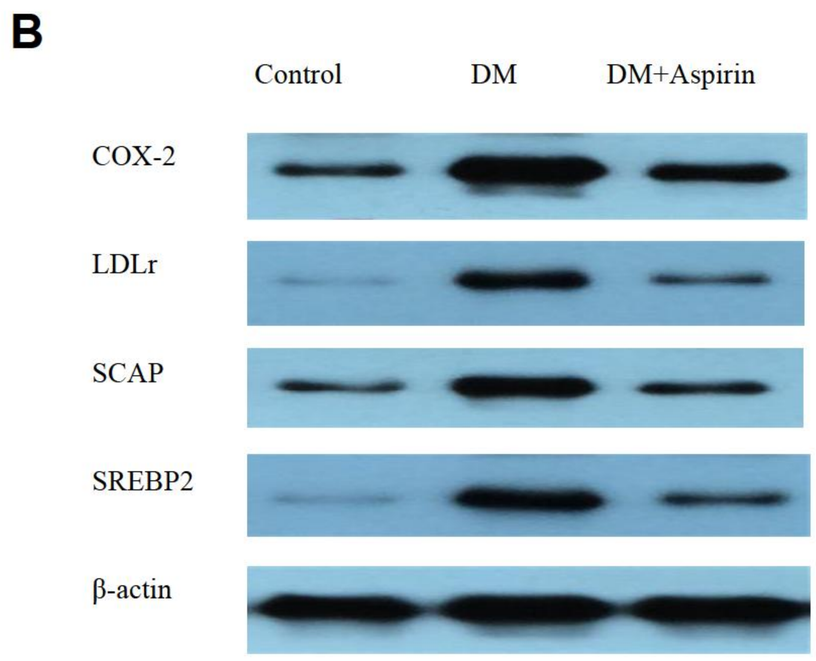


Fig.1 The protein expressions of COX-2 and LDLr pathway were evaluated by immunohistochemical staining (A,brown color,original magnification ×400） and Western Blot （B）.

3. Low levels of two podocyte biomarkers were detectable in DM rats.And electron microscope showed obvious foot process effacement in DM rats.However, these change were significantly inhibited by an inhibitor of COX-2, Aspirin.

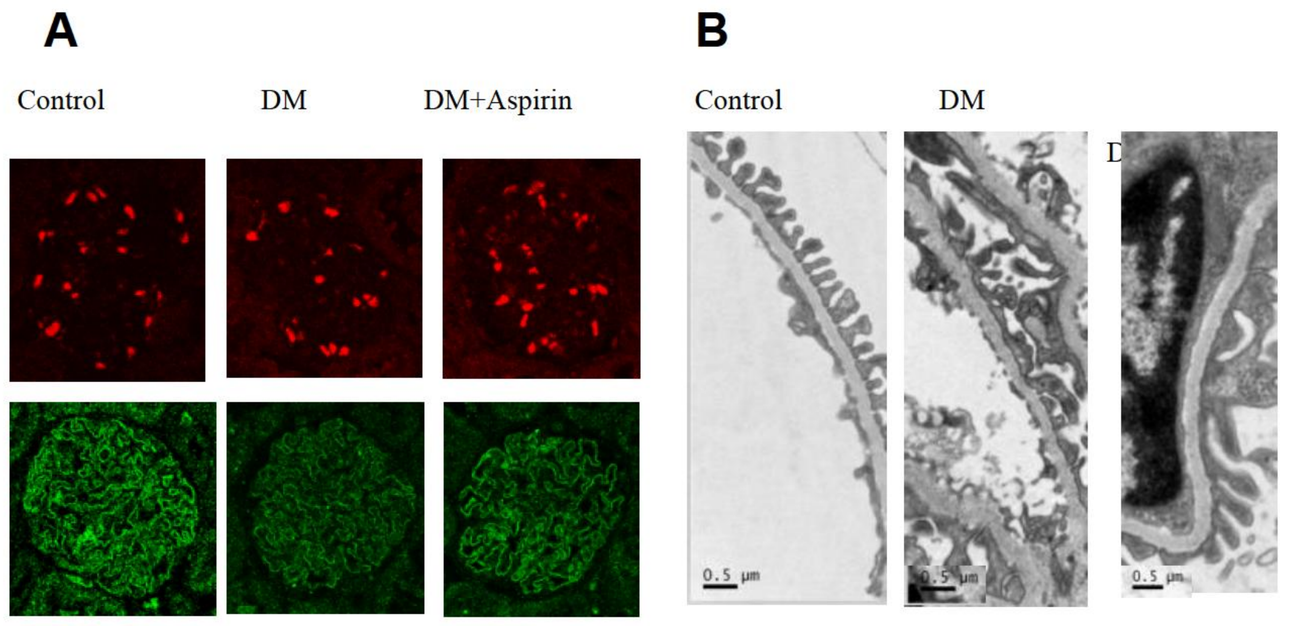


Fig.2 The protein expressions of WT-1and nephrin were evaluated by immunofluorescent staining(A,magnification×400).The fusion of foot processes were evaluated by electron microscope(B,magnification ×12000).

4. Free cholesterol quantitative assay revealed overt intracellular lipid accumulation in DM rats compared to the control, which was overridden by Aspirin.

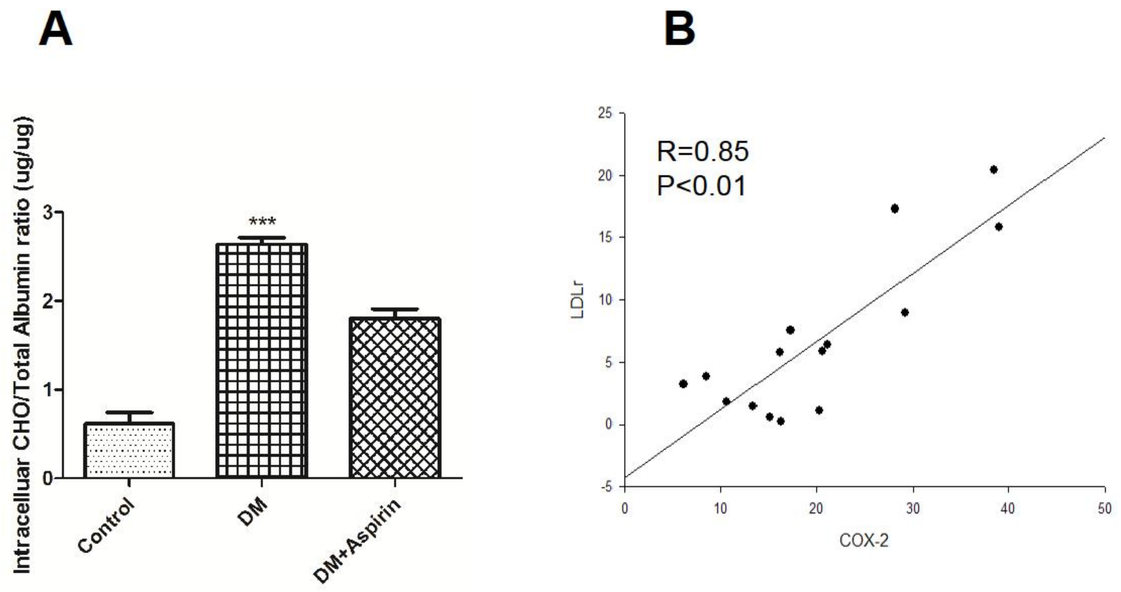


Fig.3 Intracellular CHO,Intracellular cholesterol ; ***P<0.001 VS. other groups (A) . Correlation analysis of protein expressions of COX-2 with LDLr(B) .

Conclusions

Dysregulation of LDLr pathway contributes to podocyte injury in diabetic nephropathy, which might be mediated through the increased COX-2 expression.

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