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Dapagliflozin Alleviates Diabetic Kidney Disease via Hypoxia Inducible Factor 1/Heme Oxygenase 1-Mediated Ferroptosis

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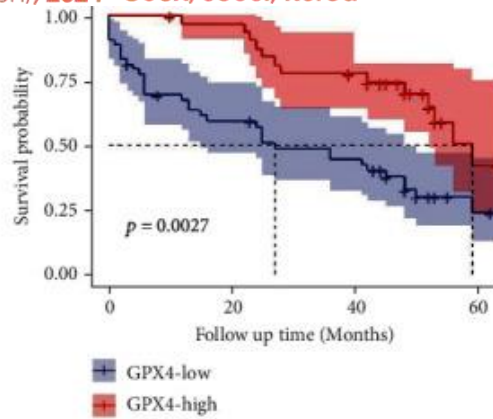
Objectives : Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) showed excellent renoprotective effects; however, the underlying mechanism remains not fully understood. Previous studies have revealed the importance of ferroptosis, which is closely related to oxidative stress, in the progression of DKD. Glutathione peroxidase 4 (GPX4) is the mainstay in regulating ferroptosis. The current study investigated the predictive value of kidney GPX4 expression level in DKD progression, and hypothesized that SGLT2i could relieve ferroptosis and thereby alleviate renal injury in DKD due to their antioxidative stress effects.

Methods : The GPX4 level in kidney samples of 85 biopsy-proven DKD patients was measured and associations between the GPX4 level and clinicopathological parameters as well as renal outcomes were analyzed. HK-2 cells and db/db mice were used to investigate the mechanisms of the renoprotective effects of SGLT2i.

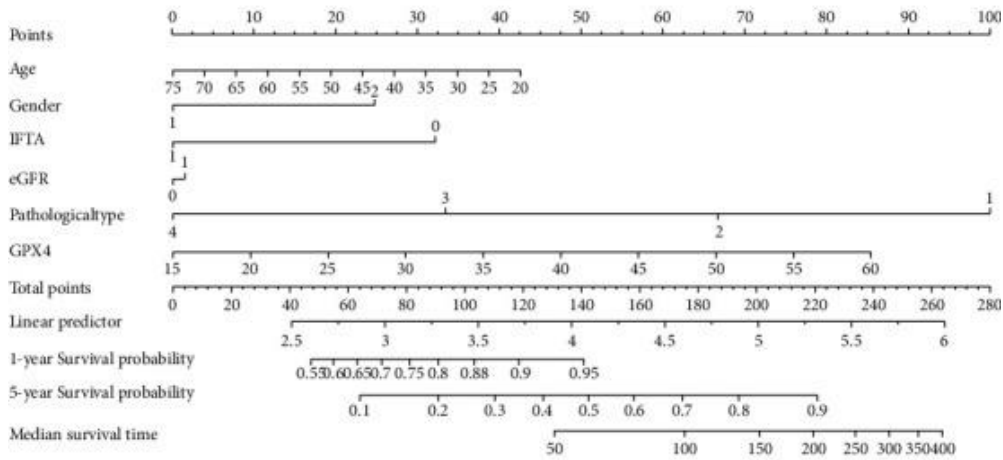
Results : The GPX4 level was significantly lower in DKD patients than healthy controls, and correlated with proteinuria, serum creatinine and eGFR. GPX4-low patients showed a significantly higher probability of developing ESKD compared with GPX4-high patients. Moreover, after adjusting for other potential predictors, the GPX4 level was still an independent predictor of developing ESKD. Typical changes of ferroptosis were found in db/db mice and high glucose/high fat (HG/HF)-treated HK-2 cells. Furthermore, increased expression of hypoxia inducible factor 1 α (HIF1 α) and heme oxygenase 1 (HO1) was observed in db/db mice and HG/HF-treated HK-2 cells as well. Dapagliflozin treatment significantly ameliorated the ferroptosis-related changes via attenuating overactivation of the HIF1 α /HO1 axis in vivo and in vitro. Besides, downregulation of the HIF1 α /HO1 axis alleviated ferroptosis, while overexpression of HIF1 α and HO1 aggravated ferroptosis induced by HG/HF in HK-2 cells.

Conclusions : Kidney tubulointerstitial GPX4 level was associated with the disease severity and progression of DKD, and SGLT2i played a renoprotective role in DKD through alleviating HIF1 α /HO1-mediated ferroptosis.

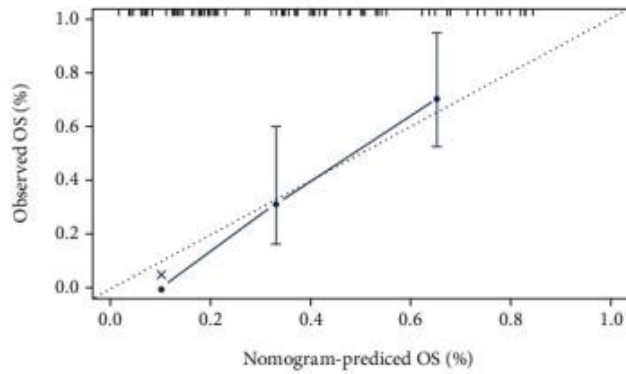
IMG_3091.jpeg



(a)



(b)



$n = 76$ (41 - 35), $p = 6.20$ subjects per group
Grey: actual

X-axis sampling operation added, $N = 1000$
Based on observed predicted

(c)

