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Empagliflozin attenuates epithelial to mesenchymal transition through senescence in a peritoneal dialysis model

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Objectives : Epithelial to mesenchymal transition (EMT) is considered as one of the senescence processes; reportedly, anti-senescence therapies effectively reduce EMT. Some models have shown anti-senescence effects with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitor. Therefore, our study investigated the anti-senescence effects of empagliflozin as a SGLT2 inhibitor in a peritoneal fibrosis model and their impact on EMT inhibition.
Methods : For in vitro study, human peritoneal mesothelial cells (HPMCs) were isolated and grown in a 96-well plate. The cell media were exchanged with serum-free M199 medium with D-Glucose, with or without empagliflozin. All experiments were carried out in male mice. Mice were randomly classified into three treatment groups based on peritoneal dialysis (PD) or empagliflozin. We evaluated changes in senescence and EMT markers in HPMCs and PD model.
Results : HPMCs treated with glucose transformed from cobble stone to spindle shape, resulting in EMT. Empagliflozin attenuated these morphologic changes. Reactive oxygen species production, DNA damage, senescence, and EMT markers were increased by glucose treatment; however, cotreatment with glucose and empagliflozin attenuated these changes. For the mice with PD, an increase in thickness, collagen deposition, staining for senescence or EMT markers of the parietal peritoneum was observed, which however, was attenuated by cotreatment with empagliflozin. p53, p21, and p16 increased in mice with PD compared to that in the control group; however, these changes were reversed by empagliflozin.
Conclusions : Empagliflozin effectively attenuated glucose-induced EMT in HPMCs through a decrease in senescence. Cotreatment with empagliflozin improved peritoneal thickness and fibrosis in a PD model.