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SGLT2 Inhibitors Alleviated Podocyte Damage in Lupus Nephritis by Decreasing Inflammation and Enhancing Autophagy

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Objectives : The protective role of sodium glucose cotransporter 2 (SGLT2) inhibitors in renal outcomes has been revealed by large cardiovascular outcome trials among patients with type 2 diabetes. However, the effect of SGLT2 inhibitors on lupus nephritis (LN) and its underlying mechanisms remain unknown.

Methods : We applied empagliflozin treatment to lupus-prone MRL/lpr mice to explore the renal protective potential of SGLT2 inhibitors. An SGLT2 knockout monoclonal podocyte cell line was generated using the CRISPR/Cas9 system to examine the cellular and molecular mechanisms.

Results : In MRL/lpr mice treated with empagliflozin, the levels of mouse anti-dsDNA IgG-specific antibodies, serum creatinine and proteinuria were markedly decreased. For renal pathology assessment, both the glomerular and tubulointerstitial damages were lessened by administration of empagliflozin. The levels of SGLT2 expression were increased and colocalised with decreased synaptopodin in the renal biopsy samples from patients with LN and MRL/lpr mice with nephritis. The SGLT2 inhibitor empagliflozin could alleviate podocyte injury by attenuating inflammation and enhance autophagy by reducing mTORC1 activity. Nine patients with LN treated with SGLT2 inhibitors with more than 2 months of follow-up showed that the use of SGLT2 inhibitors was associated with a significant decrease in proteinuria from 29.6% to 96.3%. Moreover, the estimated glomerular filtration rate (eGFR) was relatively stable during the treatment with SGLT2 inhibitors.

Conclusions : This study confirmed the renoprotective effect of SGLT2 inhibitors in lupus mice, providing more evidence for non-immunosuppressive therapies to improve renal function in classic autoimmune kidney diseases such as LN.