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Effect of Ameliorating Renal Hypoxia Mechanism on Canagliflozin to Delay the Early Stage of Diabetic Kidney Disease

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DESCRIPTION

Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitor canagliflozin improved renal oxygenation levels in newly diagnosed T_2DM patients with normal renal function independent of changes in renal blood perfusion [1]. Two forms of functional Magnetic Resonance Imaging Renal Blood Oxygen Level-Dependent MRI (BOLD-MRI), which can detect changes in the oxygenation state of renal tissues in a non-invasive and highly sensitive manner [2]. Arterial Spin Labelling-Magnetic Resonance Imaging (ASL-MRI), which can accurately and noninvasively quantify the renal blood perfusion [3]. To compare the changes in renal oxygenation levels and blood perfusion of kidney in 25 newly diagnosed type 2 diabetic patients with normal renal function before and after canagliflozin or glimepiride treatment lasting 24 weeks. BOLD-MRI image analysis showed that canagliflozin significantly decreased the renal cortex R_2^* values (17.57 ± 1.88 1/s *vs*. 15.1 ± 1.25 1/s, change from baseline, p=0.0005, and change *vs*. glimepiride control, p=0.004) after 24 weeks. In addition, the medulla R_2^* decreased from 46.59 ± 9.31 to 32.96 ± 5.51 1/s (change from baseline, p=0.002, and change *vs*.glimepiride control, p=0.02) after 24 weeks of canagliflozin treatment and from 42.08 ± 8.56 to 40.08 ± 9.31 1/s (p=0.42) after 24 weeks of glimepiride treatment. Taken together, these results showed that canagliflozin improved renal cortical and medullary oxygen levels by 22.3% (p=0.005) and 29.2% (p=0.0002), respectively, and these decreases were significantly more pronounced than in the glimepiride control group (p=0.0004 and p=0.02, respectively). However, ASL-MRI image analysis results showed that neither drug regimen significantly affected the Renal Blood Flow (RBF), compared with the baseline level, all p>0.05. These results strongly indicate canagliflozin could improve renal hypoxia in diabetic patients with normal renal function, and this effect was not dependent on renal blood perfusion.

The changes in eGFR levels and metabolic outcomes of 25 newly diagnosed T_2DM patients with baseline Egfr>90 ml/min/1.73 m^2 and UACR<30 mg/g, who accepted canagliflozin (n=12) or glimepiride (n=13) treatments at the basis of lifestyle intervention plus metformin and completed the 24-week follow-up. The baseline mean eGFR of the patients was greater than 120 ml/min/1.73 m^2, indicating that most patients in this study were in a relatively high GFR stage. Canagliflozin treatment rendered eGFR levels significantly lower than in the glimepiride treatment group at 24 weeks (124.30 ± 7.31 ml/min (or) 1.73 m^2 *vs*.118.58 ± 4.50 ml/min (or) 1.73 m^2) (change from baseline, p=0.04, and change *vs* glimepiride control, p=0.048). Canagliflozin alleviated GFR levels only in patients with relatively high eGFR levels; it had no effect in patients with normal GFR levels. Moreover, this result was consistent of the research on patients with T_1DM [4]. This also

suggested that the decrease in eGFR levels caused by canagliflozin in newly diagnosed T_2DM patients with normal renal function may be protective. Furthermore, the FBG, HbA_1C, and body weight of the patients decreased significantly after 12 and 24 weeks of treatment in both groups. The HbA_1C and FBG levels were similar in both groups. Canagliflozin significantly decreased the serum UA level compared to the glimepiride-treated controls at 24 weeks (p=0.002). Likewise, the body weight of the patients decreased to a greater extent in the canagliflozin group than in the glimepiride control group at both 12 weeks (p=0.005) and 24 weeks (p=0.002). The DBP of the patients also improved to a greater extent in the canagliflozin group than in the glimepiride control group at both 12 weeks (p=0.05) and 24 weeks (p=0.001).

Overall, these results suggest that the $SGLT_2$ inhibitor canagliflozin, if used in the early stages of T_2DM, could provide protection against early diabetic nephropathy by improving chronic renal hypoxia and metabolic status.

CONFLICT OF INTEREST

Saijun Zhou and Pei Yu are full-time employees of Chu Hsien-I Memorial Hospital of Tianjin Medical University. Both authors were fully involved in the planning and writing of the letter and approved the final version for submission.

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