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Empagliflozin Suppresses Urinary Mitochondrial DNA Copy Numbers and Interleukin-1β in Type 2 Diabetes Patients

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Objectives: Sodium-glucose co-transporter 2 (SGLT2) inhibitors improve cardiovascular and renal outcomes in type 2 diabetes mellitus (T2DM) patients. However, the mechanisms by which SGLT2 inhibitors improve the clinical outcomes remain elusive. Mitochondrial dysfunction and chronic inflammation play critical roles in the pathophysiology of T2DM and its complications. We evaluated whether empagliflozin, an SGLT2 inhibitor ameliorates mitochondrial dysfunction and inflammatory milieu of the kidneys in T2DM patients.

Methods: We prospectively measured copy numbers of urinary and serum mitochondrial DNA (mtDNA) nicotinamide adenine dinucleotide dehydrogenase subunit-1 (mtND-1) and cytochrome-c oxidase 3 (mtCOX-3) using quantitative polymerase chain reaction and urinary interleukin-1β (IL-1β) in healthy volunteers (n = 22), in SGLT2 inhibitor-naïve T2DM patients (n = 21) at baseline, and in T2DM patients after 3 months of treatment with empagliflozin (10 mg, n = 17 or 25 mg, n = 4).

Results: Both urinary mtDNA copy numbers and IL-1β were higher in the T2DM group than those in healthy volunteers. Urinary mtDNA copy numbers correlated with the diabetes duration (8.74 ± 7.60 years). Baseline copy numbers of serum mtCOX-3 in the T2DM group were lower than those in healthy volunteers. Empagliflozin induced marked reduction in both urinary and serum mtND-1 and mtCOX-3 copy numbers as well as in urinary IL-1β.

Conclusions: Our results suggest that empagliflozin could attenuate mitochondrial damage and inhibit inflammatory response in T2DM patients. This would explain the beneficial effects of SGLT2 inhibitors on cardiovascular and renal outcomes.