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Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates nephropathy in diabetic rats.

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Abstract

BACKGROUND: Diabetic nephropathy is a major risk of end-stage kidney disease. Many complex factors relate to the progression of diabetic nephropathy. Using nonobese type 2 diabetes model rats, we confirmed that oxidative stress was a crucial factor. Because recent studies suggest that vitamin D could suppress oxidative stress, we explored whether the active vitamin D analog, maxacalcitol, could also attenuate oxidative stress and prevent the progression of diabetic nephropathy.

METHODS: Diabetic rats aged 20 weeks were divided into 3 groups and treated with insulin, maxacalcitol, and vehicle. At age 30 weeks, blood and urine analyses, renal histology, immunohistochemistry, real-time polymerase chain reaction, and western blot were performed.

RESULTS: Although maxacalcitol reduced albuminuria and mesangial matrix expansion, no significant differences were observed in blood pressure and creatinine clearance among the 3 treatment groups. Systemic and intrarenal oxidative stress was reduced by maxacalcitol therapy. Expressions of nuclear factor-κB and nicotinamide adenine dinucleotide phosphate oxidase in the kidney also decreased in the insulin-treated and maxacalcitol-treated groups but increased in the vehicle-alone group. In addition, the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) decreased and Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1 (Keap1) increased in the vehicle-treated group; however, these expressions were restored in the maxacalcitol- and insulin-treated groups.

CONCLUSIONS: It is suggested that maxacalcitol attenuates the progression of diabetic nephropathy by suppression of oxidative stress and amelioration of the Nrf2-Keap1 pathway in nonobese type 2 diabetes without significant changes in blood pressure and glomerular filtration rate.

KEYWORDS: Keap1; Nrf2; blood pressure; diabetic nephropathy; hypertension; oxidative stress; vitamin D.

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