PROXIMAL CONVOLUTE TUBULE INJURY IN HAPTOGLOBIN 2-2 GENOTYPE IN DIABETIC NEPHROPATHY PATIENTS AND MICE

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The haptoglobin (Hp) genotype (1-1, 2-2) is a major determinant of nephropathy progression in diabetes mellitus patients. Hp 2-2 diabetic mice have impaired Hb clearance, increased iron deposits and oxidative stress in the proximal tubules (PCT), leading to increased renal injury. However, the precise mechanism of the PCT injury in diabetic nephropathy (DN) remains elusive. In the kidney, $1,25(OH)_2D3$ suppresses the inflammatory response to renal tubular injury and requires normal renal expression of the α-klotho protein. In this study, we set out to test the hypothesis that the increased renal iron deposits in the PCT of Hp 2-2 DN affects the α-klotho-Vitamin D receptor (VDR) axis and thereby exacerbates the PCT injury generated by the iron deposits. Immunohistochemical analysis of human and mouse kidney biopsies along with western blot analysis showed that the increased iron deposits in the PCT of Hp 2-2 genotype were accompanied with significantly decreased α-klotho and VDR renal expression but significantly increased 1-α-hydroxylase renal expression. In conclusion, the Iron-Klotho-VDR axis is a major player in the mechanism contributing to iron-mediated PCT injury in diabetic Hp 2-2 mice and patients. Targeting this axis may open the way for new ideas regarding the pathogenesis and treatment of DN.