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Heme oxygenase is a molecular switch that ameliorates diabetic nephropathy when up-regulated

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Impaired insulin signaling and deregulated glucose metabolism are associated with kidney dysfunction. Our recent studies indicate that up-regulating Heme-Oxygenase (HO) potentiates insulin signaling and improve glucose metabolism in different animal models of type-1 and type-2 diabetes. This was accompanied by: (1) the attenuation of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and chemokines (MCP-1 and MIP-1α); (2) the suppression of transcription factors/mediators of oxidative stress (NF-κB, activating-protein (AP)-1, AP-2 and c-Jun-N-terminal-kinase and 8-isoprostane); (3) the potentiation of fundamental proteins implicated in the insulin signal transduction pathway like IRS-1, PI3K and PKB; (4) the reduction of insulin/glucose intolerance (IPITT); (5) the enhancement of insulin sensitivity, and (6) the inability of insulin to enhance *GLUT4* was overturned. These were associated with the amelioration of renal histological lesions such as glomerulosclerosis, tubular necrosis, tubular vacuolization, interstitial macrophage-M1 infiltration and the abrogation of pro-fibrotic/extracellular-matrix proteins like collagen and fibronectin that deplete nephrin, an important transmembrane protein which forms the scaffolding of the podocyte slit-diaphragm allowing ions to filter but not proteins. Correspondingly, proteinuria/albuminuria decreased while creatinine clearance significantly increased suggesting improved renal function. These data suggest that HO may be considered and important switch that can be potentiated rescue kidney damage in diabetes.

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