Macitentan, a dual ET receptor antagonist, prevents nephropathy in type 2 diabetes

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Introduction: Alteration of endothelin (ET) system is a well-recognized mechanism of tissue damage in several chronic diabetic complications including diabetic nephropathy. We have previously demonstrated that, along with early alterations of blood flow in diabetes, ETs play key roles in augmented production of extracellular matrix proteins causing structural alterations. Here we investigated the preventive effects of macitentan, an orally active, tissue-targeting dual ET receptor antagonist on the prevention of diabetic nephropathy in type 2 diabetes.

Methods: db/db mice and there age- and sex-matched controls were examined after 2 and 4 months of diabetes. Groups of diabetic animals were treated with oral macitentan (25 mg/Kg/day) mixed with food. The animals were monitored with respect to blood glucose and creatinine. Urine analyses were performed for albumin. Following sacrifice the renal, retinal and cardiac tissues were analyzed for ET1, transforming growth factor β1 (TGF β1), vascular endothelial growth factor (VEGF), fibronectin (FN), EDB+ FN, Collagen 1(α)4 mRNA by real-time RT-PCR. Protein expressions were measured by ELISA and Western blot. Nuclear factor κβ (NFκβ) activation was assessed. Microscopic analyses were performed for mesangial matrix expansion.

Results: Diabetic animals showed hyperglycemia, glucosuria, increased urinary albumin and augmented serum creatinine levels. Diabetes further caused increased renal ET1, TGFβ1, VEGF, FN, EDB+FN, Collagen 1(α)4 mRNA expression and augmented FN and collagen protein production along with NFκβ activation. Furthermore, they demonstrated renal mesangial expansion by PAS stain. Most of the changes were pronounced after 4 months compared to two months of follow-up. Treatment with macitentan significantly prevented all such abnormalities.

Conclusion: Data from these experiments confirmed that ET system plays a significant role in the renal damage in diabetes. We also demonstrated that, treatment with macitentan can prevent the functional and structural changes in diabetic nephropathy.