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Long Term Treatment of GLP-1 Analogue Exendin-4 Ameliorates Diabetic Nephropathy through Improving Metabolic Syndrome in *db/db* Mice

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Glucagon like peptide (GLP-1) is one of the gut incretin hormones and also considered a potential therapeutic agent for type 2 diabetes because it stimulates insulin secretion in a glucose-dependent manner, inhibits glucagons secretion and delays gastric emptying, which together result in reduced circulating glucose. However, this peptide is almost immediately degraded within 1 min by DPP-IV. GLP-1 not only attenuates dyslipidemia but also improves insulin resistance in both animal and man with type 2 diabetes. The present studies were aimed at examining the effect of GLP-1 using long acting GLP-1 analogue exendin-4 on the development and progression of diabetic nephropathy (DN) in db/db mice.

Male *db/db* mice and db/m mice at 8 wks of age were divided into five groups. Diabetic *db/db* mice received exendin-4 for 8 weeks (0.5 or 1 nmol/kg/day, n=8, respectively) while the control *db/db* mice (n=6) received only vehicle. Nondiabetic db/m mice also received exendin-4 for 8 weeks (1 nmol/kg/day, n=8) while the control db/m mice (n=6) received the vehicle. After 8 weeks, fasting blood glucose, HbA1C, BUN and creatinine concentrations were not significant different among *db/db* mice. The change of increasing body weight and periepididymal fat mass were significantly lowered in exendin-4 treated *db/db* mice ($p<0.01$, respectively). In *db/db* mice treated with 1 nmol/kg exendin-4, 24hr urinary albumin excretions were significantly decreased compared to those in *db/db* mice treated with 0.5 nmol/kg exendin-4 and control *db/db* mice ($p<0.005$). Serum triglyceride, free fatty acid and insulin concentration were decreased in *db/db* mice treated with 1 nmol/kg exendin-4 compared with other groups ($p<0.05$) accompanying with improving fatty liver. Intraperitoneal GTT was improved in *db/db* mice treated with 1 nmol/kg exendin-4 compared with other groups ($p<0.05$). Renal histology studies further demonstrated that glomerular hypertrophy, mesangial matrix expansion, TGF-b1 expression, and type IV collagen accumulation were significantly decreased in *db/db* mice treated with 1 nmol/kg exendin-4. Furthermore, there was less 24 h urinary 8-OH-2′-Dg concentration in *db/db* mice treated with 1 nmol/kg exendin-4 compared to those in other groups. On the contrary, there were no such differences between db/m mice treated with or without exendin-4.

Taken together, exendin-4 seems to be strongly associated with the prevention of diabetic nephropathy through improving metabolic syndrome in a dose-dependent manner. Our results suggest that exendin-4 could provide a therapeutic role in diabetic nephropathy resulting from type 2 diabetes.