SGLT2 inhibitor dapagliflozin reduces hyperfiltration and prevents glomerular filtration rate decline in rodent models of diabetic nephropathy

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INTRODUCTION

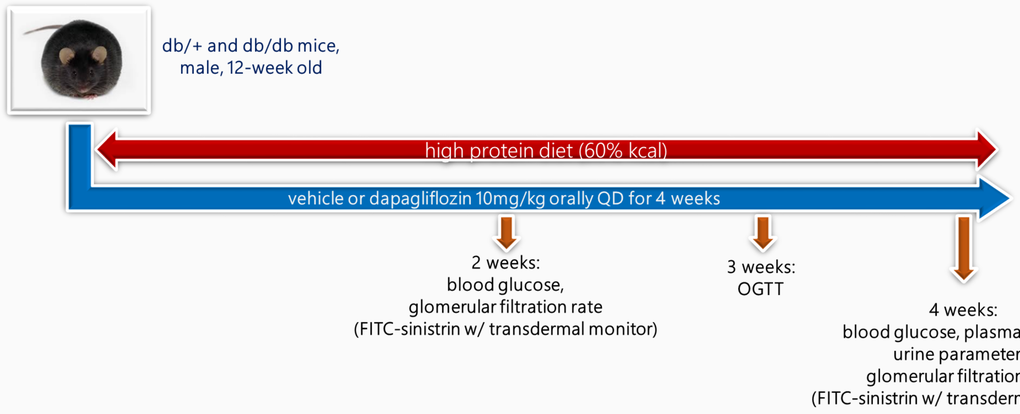
SGLT2 inhibitors (SGLT2i) may have protective effects on the kidney in diabetic nephropathy (DN). To evaluate the impact on kidney function, we here evaluated the effects of the SGLT2i dapagliflozin on glomerular filtration rate (GFR) in animal models of DN.

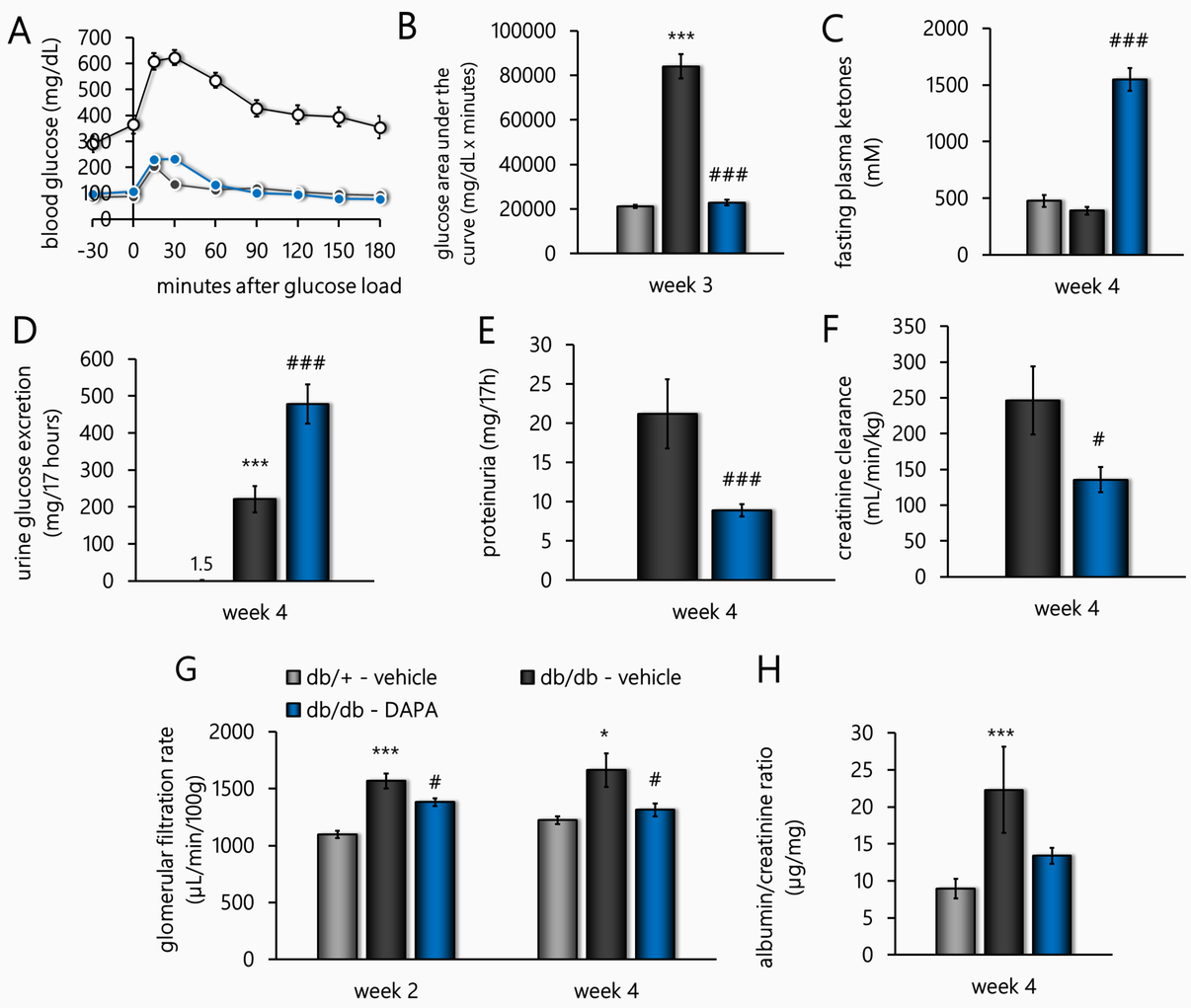
METHODS

To evaluate the effects on hyperfiltration, db/db mice fed a high protein diet (60%kcal from protein, known to accelerate DN) were treated with vehicle or dapagliflozin 10mg/kg orally once daily for 4 weeks. To evaluate the effects on GFR decline, uni-nephrectomized (Unx) Spontaneously Diabetic Torii (SDT) fatty rats were fed a 0.3% salt diet and treated without (control) or with dapagliflozin at 1mg/kg/day in the diet for 10 weeks. To measure GFR, animals were injected i.v. with FITC-sinistrin or FITC-inulin. Data are shown as mean ± SEM, n=8 per group.

RESULTS

1 Dapagliflozin reduces hyperglycemia and hyperfiltration in db/db mice on high protein diet

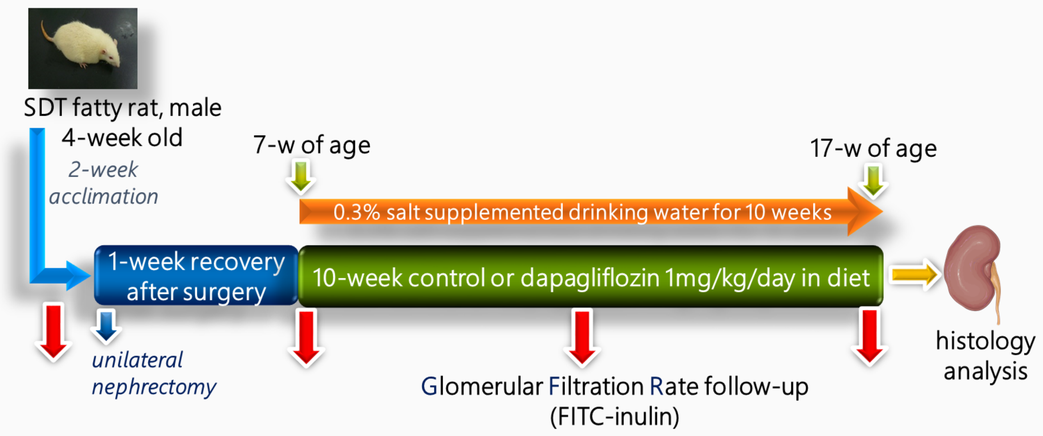


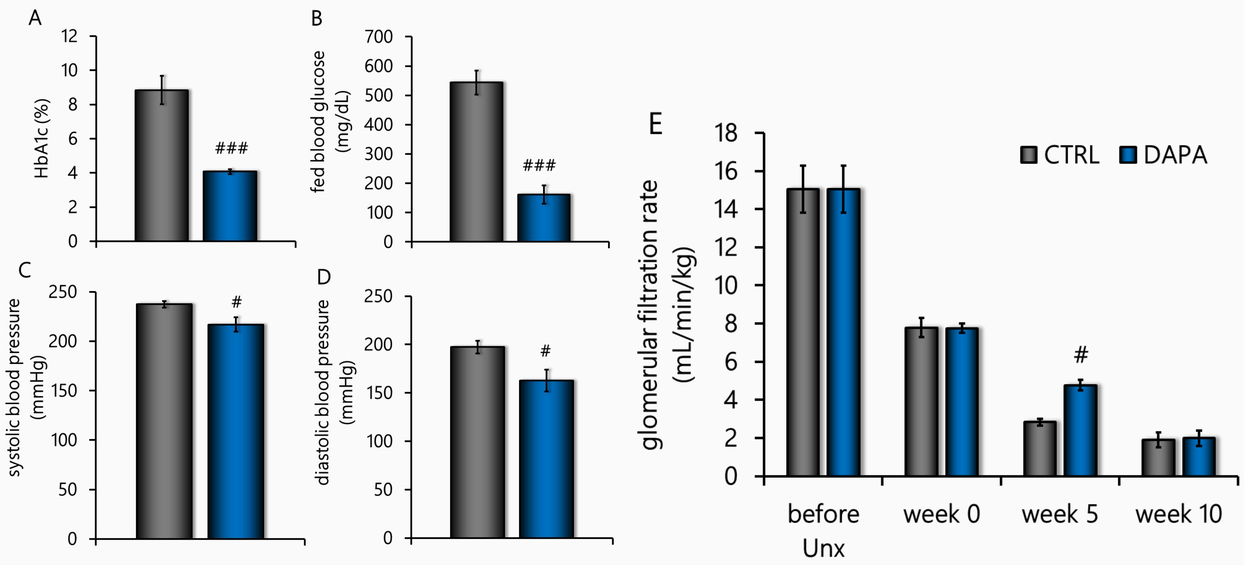


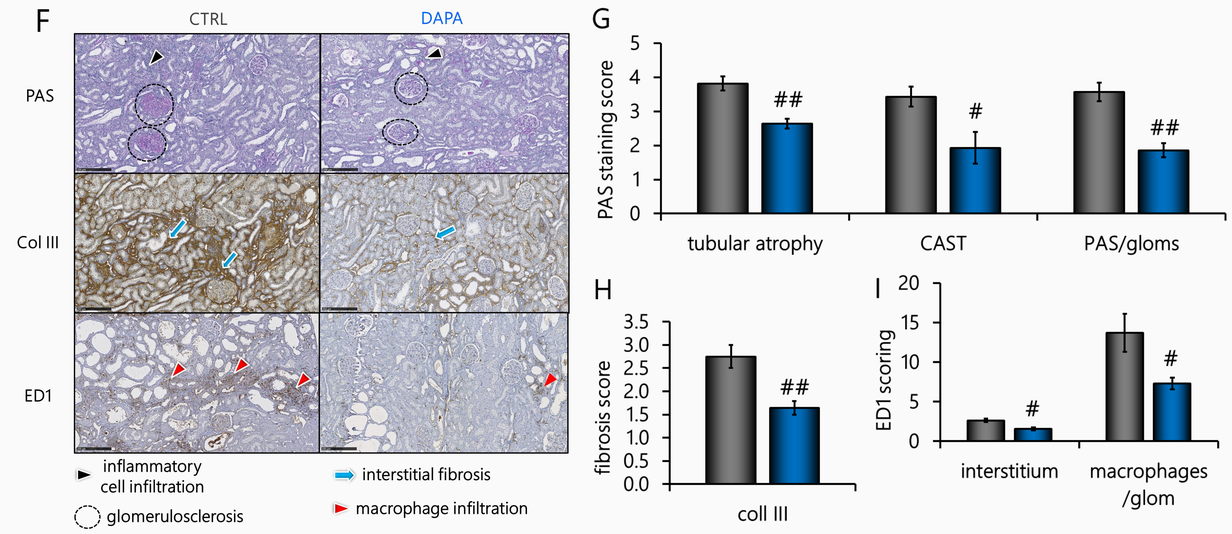
Blood glucose levels (A) and area under the curve (B) during an oral glucose tolerance test, fasting plasma total ketones bodies levels (C), urine glucose excretion (D), proteinuria (E) creatinine clearance (F), glomerular filtration rate (G) and albumin-to-creatinine ratio (H) in db/+ or db/db HPD fed mice treated with vehicle or dapagliflozin (DAPA) 10mg/kg QD for 4 weeks.

**p<0.05, ***p<0.001 db/+ - vehicle vs. db/db – vehicle; #p<0.05, ###p<0.001 db/db – vehicle vs. db/db - DAPA*

2 Dapagliflozin reduces HbA1c and blood pressure, prevents GFR decline and improves kidney lesions in Unx-SDT fatty rat on a 0.3% salt diet







HbA1c (A) and fed blood glucose (B) levels, systolic (C) and diastolic (D) blood pressure, glomerular filtration rate (E), representative PAS staining, Collagen III and ED1 immuno-staining (F), PAS staining (G), fibrosis (H) and ED1 scoring (I) in control (CTRL) or dapagliflozin (DAPA) treated Unx-SDT fatty rats on a 0.3% salt-supplement diet for 10 weeks.

#p<0.05, ##p<0.01 and ###p<0.001 CTRL vs. DAPA

CONCLUSION

- Dapagliflozin shows significant benefits on kidney dysfunction by reducing hyperfiltration and preventing GFR decline in animal models of DN.

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