Dapagliflozin reduces glomerular hyperfiltration and improves urine parameters in db/db mice on high protein diet, a 4-week model of diabetic nephropathy

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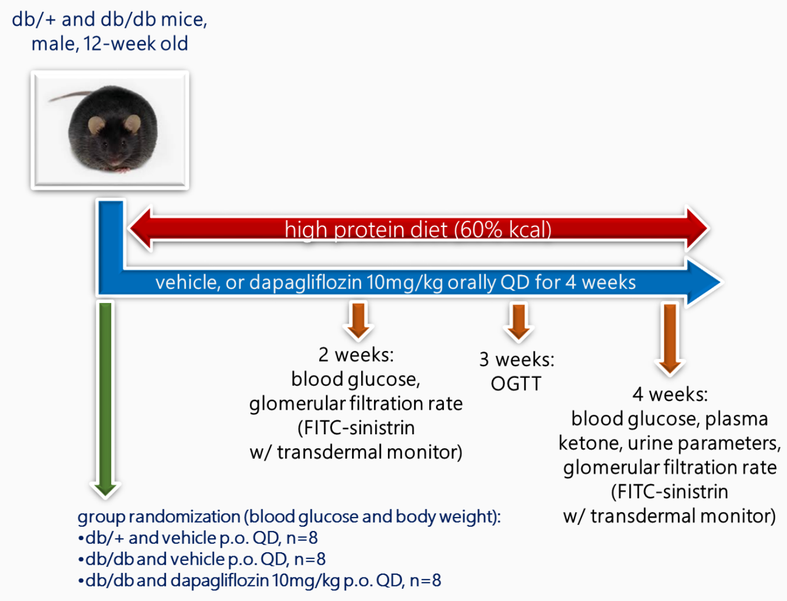
BACKGROUND:

Preclinical animal models of glomerular hyperfiltration and diabetic nephropathy (DN) are needed for rapidly evaluating novel drugs targeting these complications. In this goal, obese and diabetic db/db mice are routinely used, but require several weeks to only show mild-albuminuria and early kidney disorders seen in human DN. Since high protein diet (HPD) are known to accelerate DN in human and animal models, we therefore developed a 4-week HPD fed db/db mouse model, in which the sodium glucose cotransporter 2 inhibitor dapagliflozin (DAPA) was evaluated.

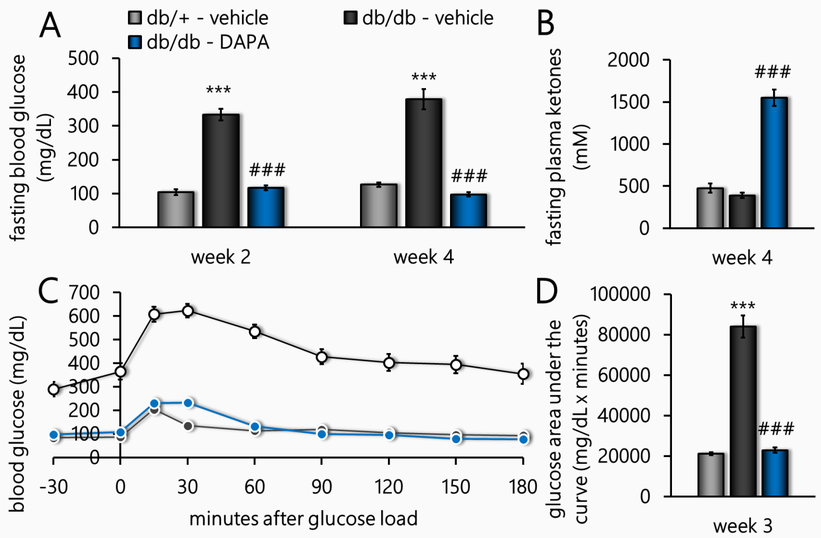
METHODS:

12-week old db/db male mice were placed on a HPD (60%kcal from protein) and treated with vehicle or dapagliflozin 10mg/kg orally (n=8 per group) once daily for 4 weeks. Non-diabetic db/+ males on HPD treated with vehicle were included as negative control. Oral glucose tolerance test (OGTT), biochemical assays and glomerular filtration rate (GFR), assessed with FITC-sinistrin i.v. injection and Medibeacon transdermal monitors, were performed. Data are shown as mean ± SEM.



RESULTS:

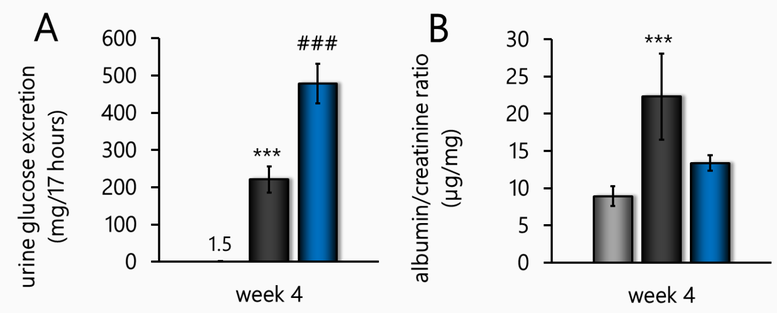
1 Dapagliflozin normalizes fasting glycemia and glucose tolerance, and raises plasma ketone bodies in HPD db/db mice



4-hour fasting blood glucose levels at 2 and 4 weeks of treatment (A), plasma ketone bodies at 4 weeks (B), oral glucose tolerance test (C) and glucose area under the curve (D) at 3 weeks of treatment in control db/+ and db/db mice treated with vehicle or dapagliflozin 10mg/kg QD orally.

****p<0.001 vs. db/+ and ###p<0.001 vs. db/db w/ vehicle*

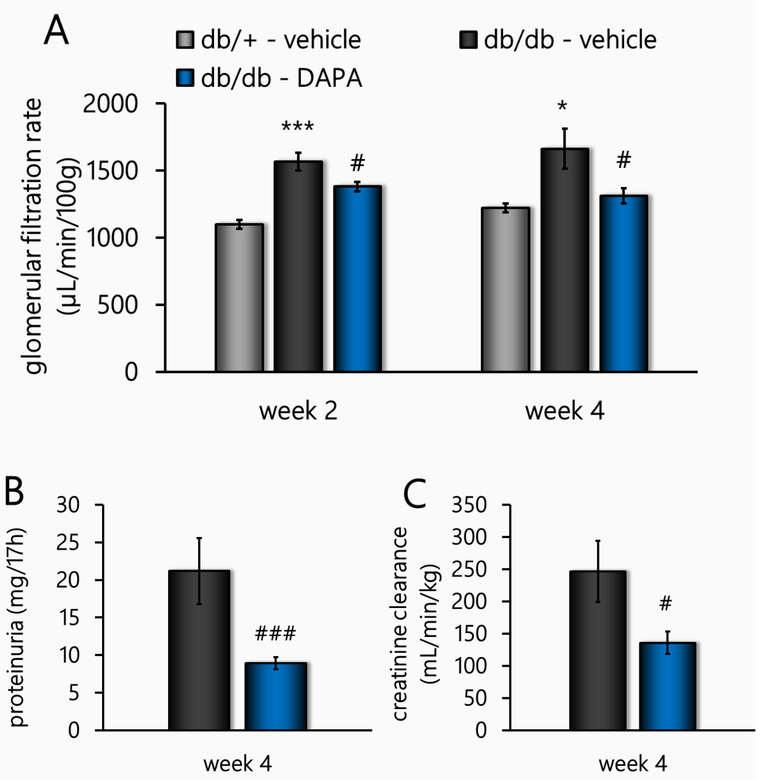
2 Dapagliflozin increases urine glucose excretion and reduces albumin/creatinine ratio in HPD db/db mice



Urine glucose excretion (A) and albumin/creatinine ratio (B) at 4 weeks of treatment in control db/+ and db/db mice treated with vehicle or dapagliflozin 10mg/kg QD orally.

****p<0.001 vs. db/+ and ###p<0.001 vs. db/db w/ vehicle*

3 Dapagliflozin reduces glomerular filtration rate, creatinine clearance and proteinuria in HPD db/db mice



Glomerular filtration rate measured by FITC-sinistrin and transdermal monitors (A), proteinuria (B) and creatinine clearance (C) in control db/+ and db/db mice treated with vehicle or dapagliflozin 10mg/kg QD orally. Proteinuria and creatinine clearance could not be determined in db/+ - vehicle for technical reason.

**p<0.05, **p<0.01 and ***p<0.001 vs. vehicle*

CONCLUSION

- The present data indicate that DAPA shows significant benefits on kidney dysfunction in the 4-week HPD fed db/db mouse model.
- This fast model should be useful to rapidly evaluate drugs targeting diabetic nephropathy and glomerular hyperfiltration.