Quantitative Image Analysis Reveals the Benefits of Dapagliflozin on Glomerulosclerosis, Podocytes Effacement and Kidney Fibrosis in the SDT Fatty Rat Model of Diabetic Nephropathy

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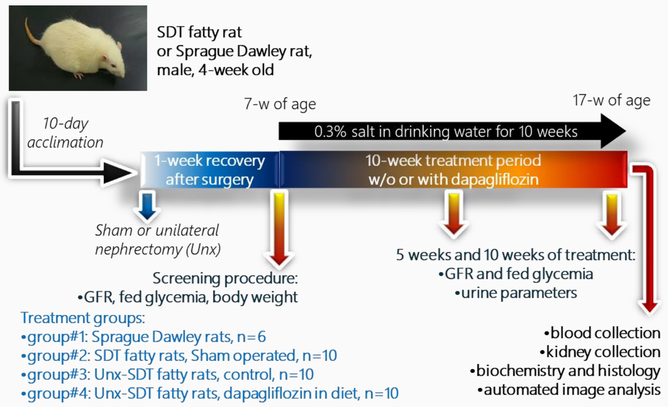
BACKGROUND:

We aimed to optimize drug efficacy studies in the Spontaneously Diabetic Torii (SDT) fatty rat, a type 2 diabetic model, using quantitative image analysis of kidney. To demonstrate the accuracy of our imaging methods, dapagliflozin (DAPA) was evaluated in SDT fatty rats with unilateral nephrectomy (Unx).

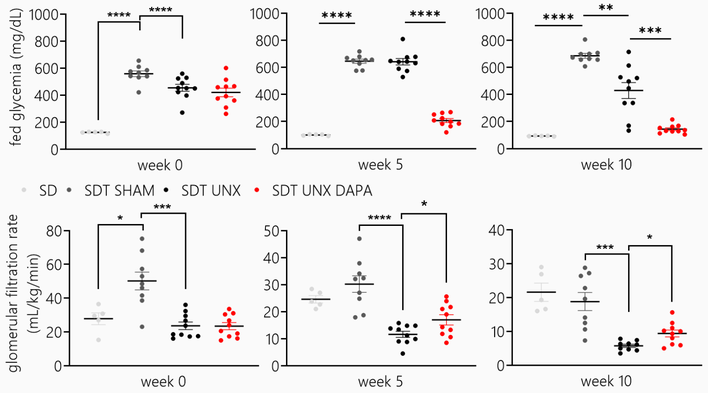
METHODS:



Unx SDT fatty rats from CLEA Japan Inc. were fed a 0.3% salt diet and treated without or with DAPA for 10 weeks. Sham operated SDT fatty rats and Sprague Dawley (SD) rats were used as controls. Glomerular Filtration Rate (GFR) and urine parameters were measured at baseline (week 0), 5 weeks, and 10 weeks. Kidneys were collected at 10 weeks for histology and automated image analysis, including quantitative glomerulosclerosis and tubular impairments (Nephropath AI, Aiosyn), Podocyte Exact Morphology Measurement Procedure (PEMP, Nipoka) and quantitative digital pathology of fibrosis (FibroNest platform, Pharmanest, Inc).

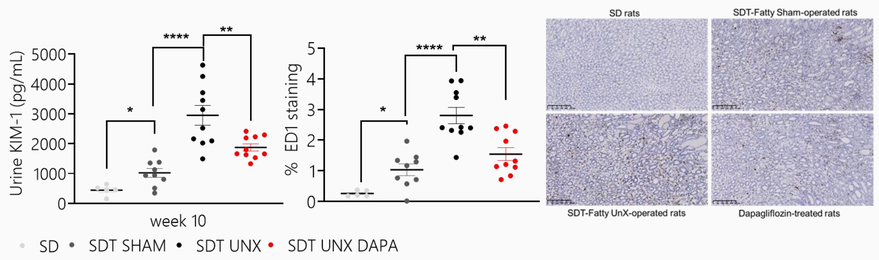
RESULTS:

1 Dapagliflozin strongly reduces hyperglycemia and prevents GFR decline in Unx SDT fatty rats



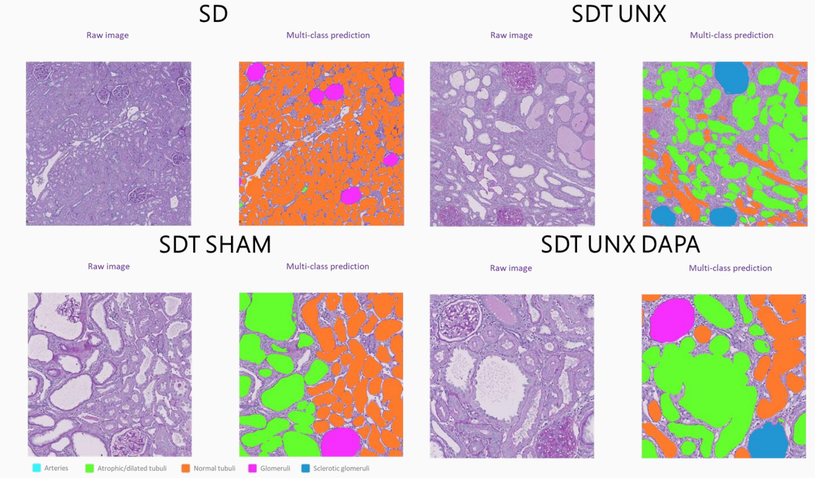
Fed glycemia (upper panel) and glomerular filtration rate (lower panel) in SD rats, sham or Unx SDT fatty rats on a 0.3% salt diet without or with dapagliflozin for 10 weeks. **p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001*

2 Dapagliflozin reduces urine KIM-1 levels and kidney inflammation in Unx SDT fatty rats



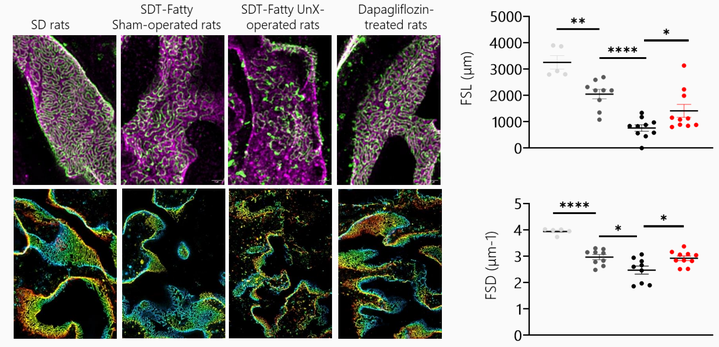
Urine KIM-1 (left panel) and kidney inflammation assessed with ED1 immunohistochemistry (right panel) in SD rats, sham or Unx SDT fatty rats on a 0.3% salt diet without or with dapagliflozin for 10 weeks. **p<0.05, **p<0.01 and ****p<0.0001*

3 Nephropath AI demonstrates that dapagliflozin reduces tubuli impairment and glomerulosclerosis in Unx SDT fatty rats



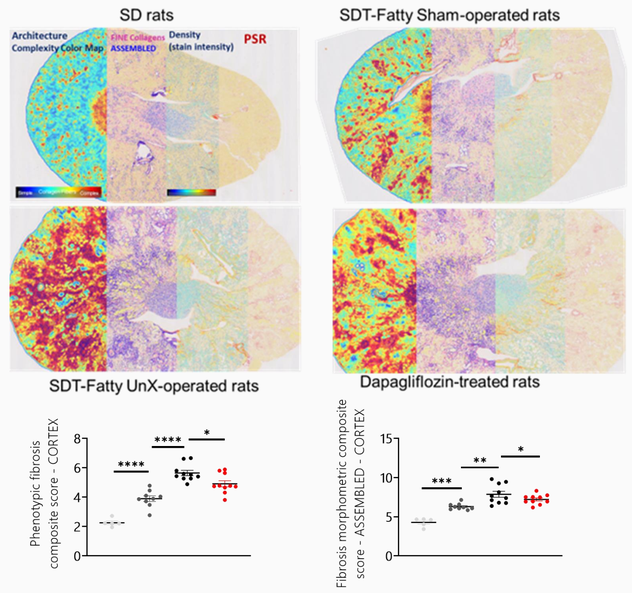
Representative raw PAS staining and Nephropath AI multi-class prediction images (upper panel), number of atrophic and dilated tubuli and sclerotic glomeruli (lower panel) in SD rats, sham or Unx SDT fatty rats on a 0.3% salt diet without or with dapagliflozin for 10 weeks. **p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001*

4 PEMP reveals that dapagliflozin improves podocyte effacement in Unx SDT fatty rats



Representative images of double staining for podocin/integrin α3 and maximum intensity projection with color coding for depth (left panel); Filtration Slit Length (FSL) and Filtration Slit Density (FSD) determined by PEMP (right panel) in SD rats, sham or Unx SDT fatty rats. **p<0.05, **p<0.01 and ****p<0.0001*

5 FibroNest platform uncovers the antifibrotic effects of dapagliflozin in the renal cortex of Unx SDT fatty rats



Representative pictures showing the panels illustrating original Sirius Red images and image analysis layers (upper panel), and phenotypic fibrosis composite scores (lower panel) assessed with PharmaNest's high resolution quantitative digital pathology in SD rats, sham or Unx SDT fatty rats.
**p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001*

CONCLUSION

Quantitative image analysis reveals the benefits of DAPA on glomerulosclerosis, podocytes effacement and kidney fibrosis in Unx SDT fatty rat. This experimental setting will help evaluating the efficacy of drugs targeting diabetic nephropathy.