Renal protective effects of non-steroidal mineralocorticoid antagonist FINERENONE in western-diet induced Kidney Disease

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Introduction and Purpose of study

- Mineralocorticoid receptor (MR) overactivation plays a crucial role in the pathogenesis of chronic kidney disease as well as cardiovascular disease. The purpose of the present studies were to determine the effects of the non-steroidal MR antagonist Finerenone on kidney disease in a mouse model of western diet (42 kcal% milk fat + 34% sucrose + 0.2% cholesterol) induced obesity and insulin resistance.

Methods

- **Intervention study**

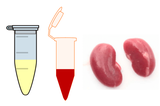
2-month old C57BL/6J

12-weeks

- Control diet (CD)
- Western-diet (WD)

12-week +/- Finerenone

- Control diet (CD)
- Control diet + Finerenone (CD+FN)
- Western-diet (WD)
- Western-diet + Finerenone (WD + FN)



Results

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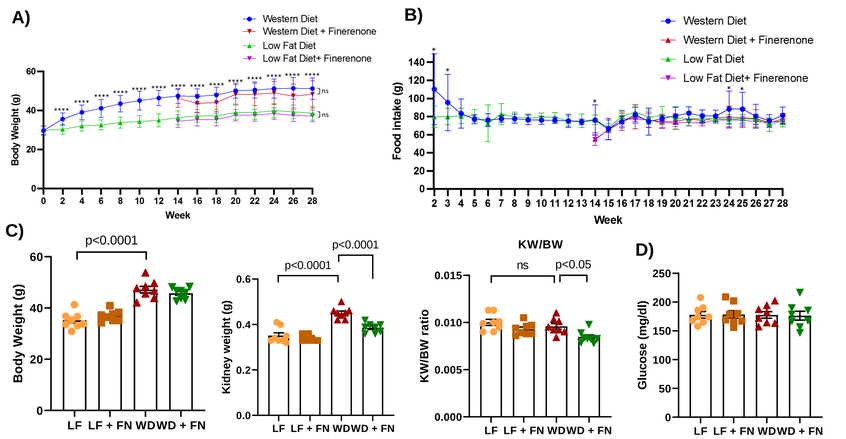

Figure 1: Metabolic parameters of mice fed control diet (CD) and western-diet (WD) administered with and without finerenone (FN) for 24-weeks. A) Body weight B) food intake measured every week during the entire study period. C & D) body weight, kidney weight and blood glucose measured at the time sacrifice the mice. Statistical significance was calculated by one-way ANOVA and significant differences indicated as asterisk (*), p values * p<0.05, **p<0.001, ***p<0.0001, n=6-8 per group.

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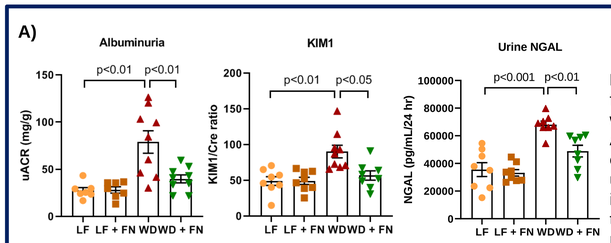

Figure 2: Administration of finerenone ameliorated the western-diet induced kidney injury. A) 24 hour metabolic cage urine collected from mice, measured urinary albumin (uACR), kidney injury molecule (KIM1) normalized to creatinine ratio and excretion of neutrophil gelatinase-associated lipocalin (NGAL). n=6-8 per group.

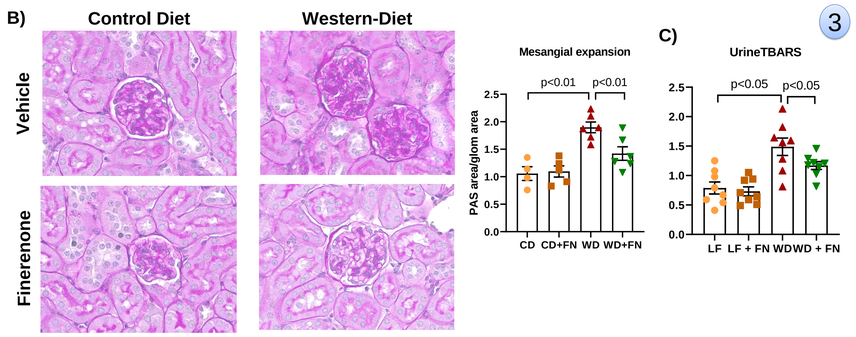

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Figure 3: Administration of finerenone ameliorated the western-diet induced kidney injury. B) Representative images of Periodic acid-Schiff (PAS) staining and bar graph analysis indicating the mesangial expansion score of kidney sections with 40X magnification length. C) 24-hour urine analyzed for oxidative stress marker TBARs. n=6-8 per group, values presented as mean ± SEM with variance is calculated using one-way ANOVA and statistical significance designated as p values of p<0.05.

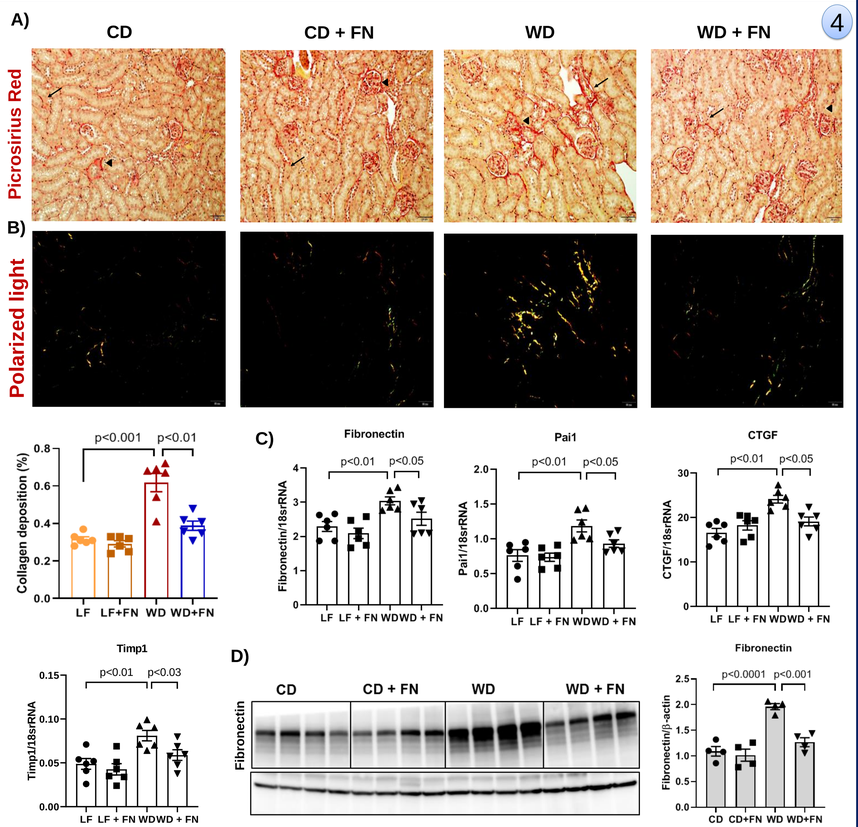

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Figure 4: Administration of finerenone reduced fibrosis in western-diet induced kidney disease. A) Collagen-specific Picrosiriusred (PSR) staining images showing the positive staining area in tubulointerstitium (arrow) and around glomeruli (arrowhead). B) Polarized light microscopic images of PSR stained kidney sections indicating the deposition of collagen-I & III and bar graph indicating the quantification of fibrosis. Magnification length is 20X and n=6 per group. C) RT-qPCR performed to describing the gene expression of markers related to fibrosis. D) Westernblot analysis indicating the protein expression of fibronectin and quantification. values presented as mean ± SEM with variance is calculated using one-way ANOVA.

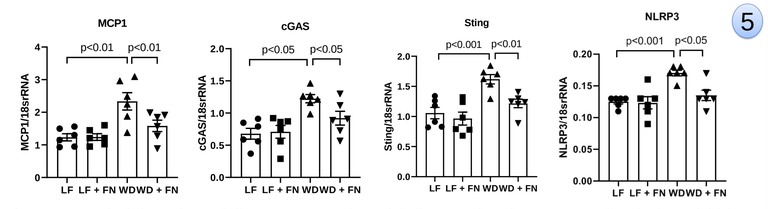

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Figure 5: Administration of finerenone reduced inflammation in western-diet induced kidney disease. RT-qPCR performed to describing the gene expression of markers related to inflammation. n=6 per group. Statistical significance was calculated by one-way ANOVA .

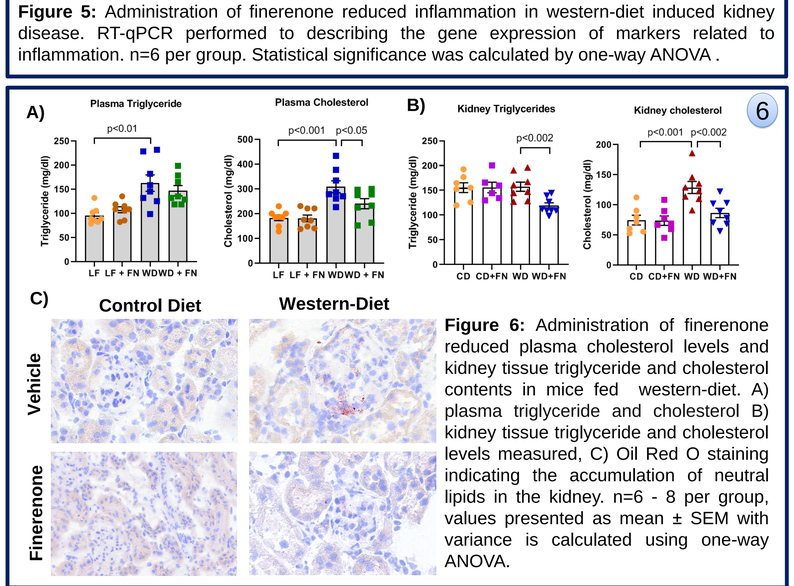

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Figure 6: Administration of finerenone reduced plasma cholesterol levels and kidney tissue triglyceride and cholesterol contents in mice fed western-diet. A) plasma triglyceride and cholesterol B) kidney tissue triglyceride and cholesterol levels measured, C) Oil Red O staining indicating the accumulation of neutral lipids in the kidney. n=6 - 8 per group, values presented as mean ± SEM with variance is calculated using one-way ANOVA.

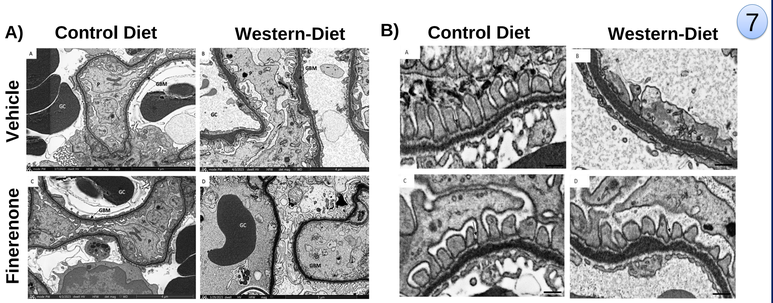

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Figure 7: Administration of finerenone preserved the glomerular ultra structure and podocyte foot processes . A) EM Images demonstrating thickened glomerular basement membrane (GBM) B) Normal distribution and structure of foot processes, filtration slits and slit diaphragm bridges (arrow). Magnifications x 35,000.

Conclusion

- Overall, our intervention data shows that administration of Finerenone exhibits renal protective role and prevent the progression of kidney disease in a mouse model of diet induced obesity and insulin resistance.

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