Diabetic Complications Consortium

Application Title: Liver X Receptor in Diabetic Nephropathy and Cardiomyopathy

Principal Investigator: Moshe Levi

1. Project Accomplishments:

We found that LXR agonism that induces cholesterol influx had a highly beneficial effect in kidney disease in DBA/2J mice fed a western diet and made diabetic with multiple dose STZ. We found the same effects with SREBP inhibition that prevents cholesterol and fatty acid synthesis and CD36 inhibition that prevents cholesterol and fatty acid uptake.

Specific Aims:

Specific Aim: to determine the effects of LXR activation, SREBP inhibition, or simultaneous LXR activation plus SREBP inhibition, or CD 36 inhibition, and LXR activation in diabetic kidney disease in mice.

RESULTS

We found that in DBA/2J mice fed a western diet and made diabetic with multiple low dose streptozotocin (DBA/WD/STZ), there are marked increases in serum triglycerides, total cholesterol, and LDL-cholesterol (**Figures 1-3**). Treatment with the SREBP inhibitor FGH10019, CD36 inhibitor SSO, or LXR activator GW3965 all markedly decreased serum triglycerides, total cholesterol, and LDL-cholesterol (**Figures 1-3**).

Figure 1.

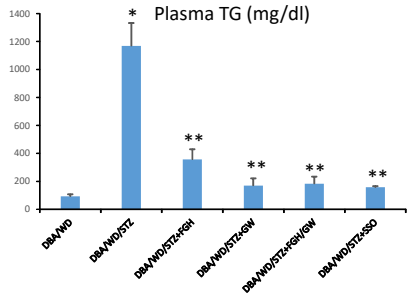


Figure 2.

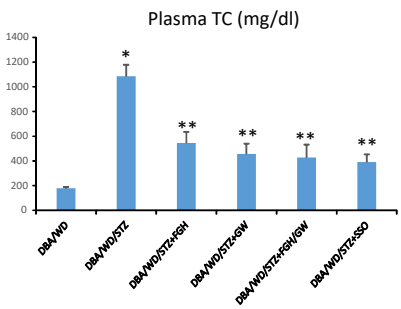
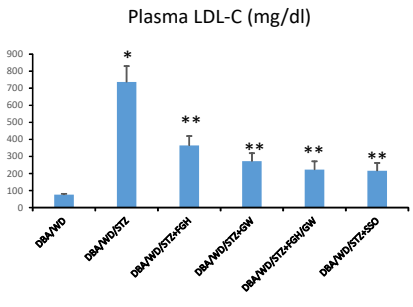
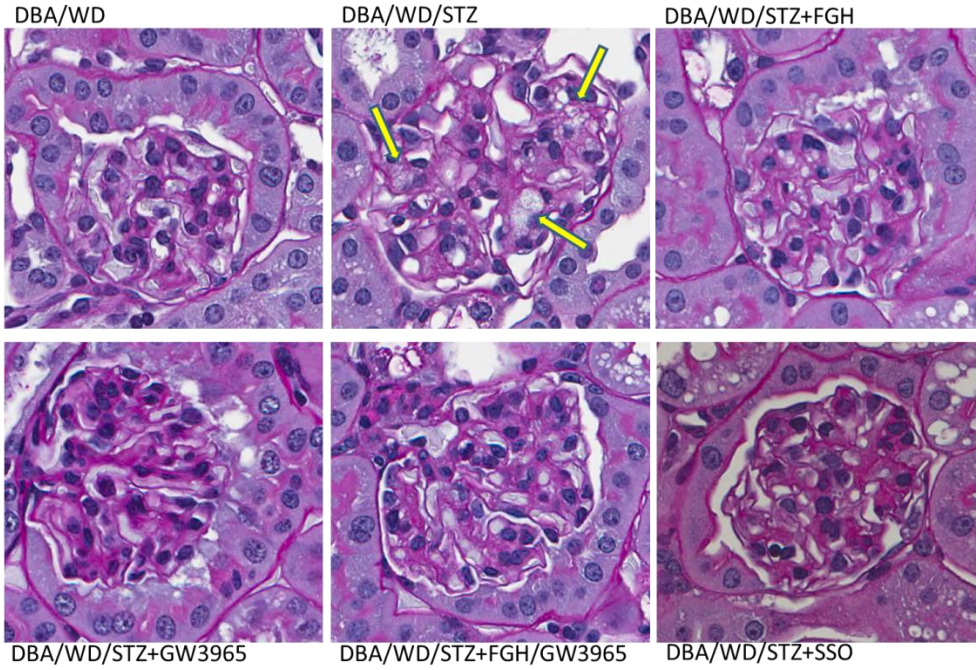


Figure 3.



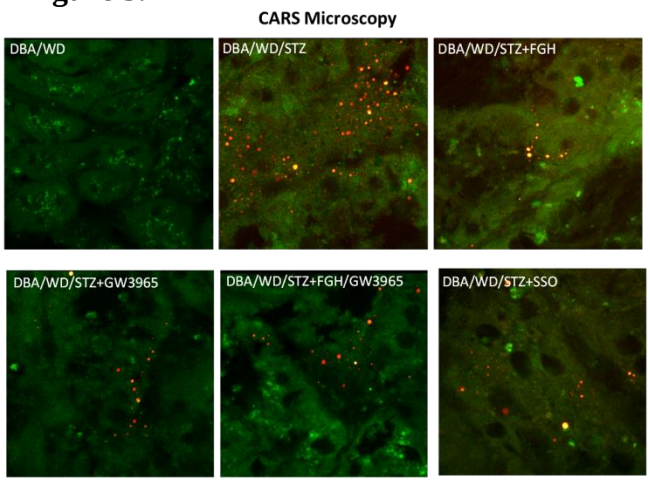
DBA/WD/STZ mice have marked alterations in glomerular pathology as determined by PAS staining. SREBP inhibition, LXR activation, or both in combination decrease in the foam cells and the mesangiolysis. CD 36 inhibition alone also has the same beneficial effects (**Figure 4**).

Figure 4.



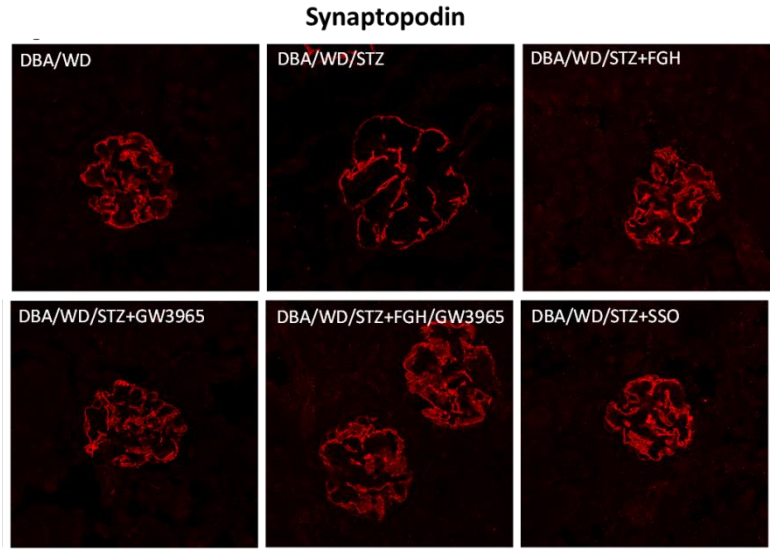
Label free imaging with Coherent Anti Stokes Raman Spectroscopy (CARS) Microscopy shows marked neutral lipid accumulation in the kidneys of DBA/WD/STZ mice, which is inhibited by SREBP inhibition, LXR activation, or both, and CD 36 inhibition (**Figure 5**).

Figure 5.



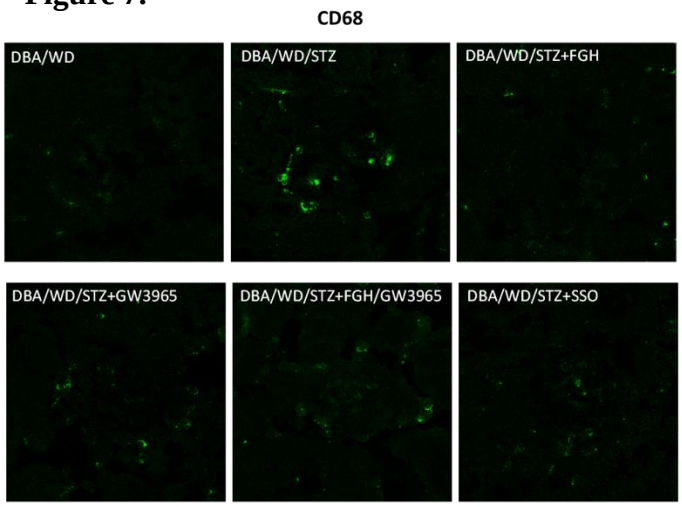
Immunofluorescence microscopy for the podocyte marker synaptopodin shows that there is a marked decrease in the kidneys of DBA/WD/STZ mice, which is inhibited by SREBP inhibition, LXR activation, or both, and CD 36 inhibition (**Figure 6**).

Figure 6.



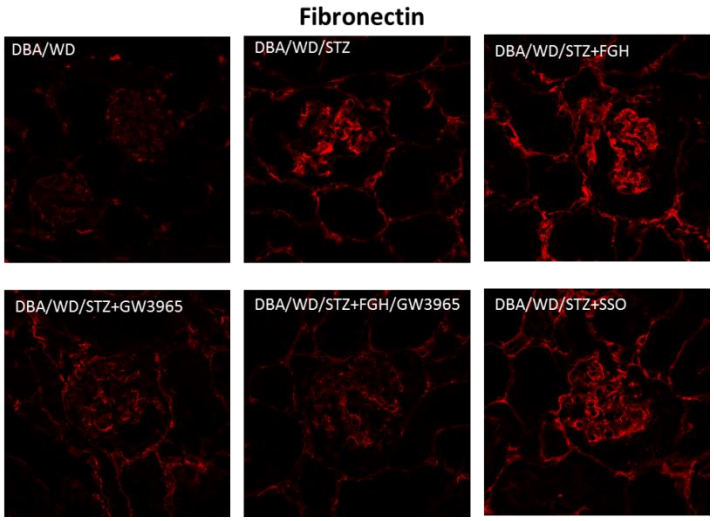
Immunofluorescence microscopy for the macrophage marker CD68 shows that there is a marked increase in the kidneys of DBA/WD/STZ mice, which is inhibited by SREBP inhibition, LXR activation, or both, and CD 36 inhibition (**Figure 7**).

Figure 7.



Immunofluorescence microscopy for the extracellular matrix protein fibronectin shows that there is a marked increase in the kidneys of DBA/WD/STZ mice, which is inhibited by LXR activation, but not SREBP or CD36 inhibition (**Figure 8**).

Figure 8.



2. Publications:

Manuscript with additional data is in progress.