Diabetic Complications Consortium

Application Title: Treatment of Diabetic Nephropathy Through Modulatin of Lipid Metabolism

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1. Project Accomplishments:

This project tests the hypothesis that hyperlipidemia, when combined with hyperglycemia, leads to diabetic nephropathy. We proposed to test this hypothesis in a mouse model of diabetic nephropathy that we developed (Attie and Alpers) that has become widely adopted in the nephrology field (6). To accomplish this goal, we developed a treatment protocol involving the administration of antisense oligonucleotides (ASOs) against the apoC3 gene. ApoC3 is an inhibitor of lipoprotein lipase activity and thus its repression leads to a dramatic lowering of plasma triglycerides. This treatment has been successful in the treatment of severe human hypertriglyceridemia syndromes (4)(5).

We accomplished the first aim of the project; the development of the treatment protocol that successfully reduced triglycerides in the mice. The second aim will be accomplished by February, 2019.

Specific Aims:

Specific Aim 1. Develop a treatment protocol involving antisense oligonucleotides against apoC3 to normalize triglyceride levels in the BTBR-ob/ob model of diabetic nephropathy.

- We will carry out a series of optimization experiments in BTBR-ob/ob mice to test dosages and duration of treatment to determine the proper protocol for administering the ASO therapy.

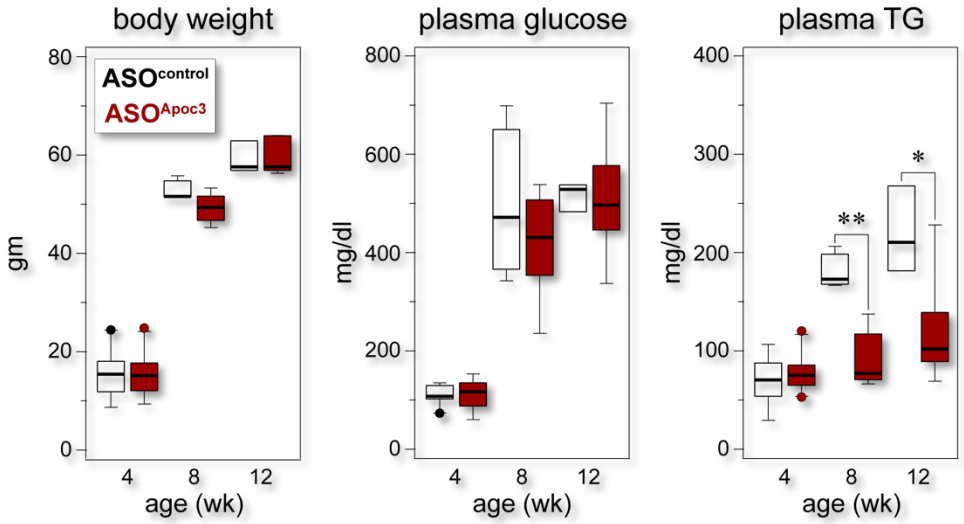

Figure 1. BTBR-ob/ob mice were treated with the ASOs against apoC3, beginning at about 3 weeks of age and then once per week until 12 weeks of age.

As shown in Figure 1, the ASO treatment was very effective at reducing triglyceride levels down to the normal range. In contrast, the ASO did not affect body weight or plasma glucose.

Specific Aim 2. Phenotype the kidneys of BTBR-ob/ob mice after successful treatment of their dyslipidemia.

- We will analyze the effects of antisense oligonucleotide therapy on plasma apoC3 levels, plasma triglycerides, and plasma cholesterol. We will also measure plasma glucose levels, and blood urea nitrogen, albumin, and creatinine in all of our experiments.
- We will collect urine and measure albumin, total protein, and urea.
- One kidney will be removed from each mouse and placed in formalin. Sections will be taken for analysis of nephropathy phenotypes by immunohistochemistry.
- We will analyze the kidneys for expression of oxidation-derived protein adducts by probing with a monoclonal antibody that recognizes these adducts in atherosclerotic lesions and in kidneys.

Altogether, we will have 17 mice harvested by mid-January, 2019. The measurements in the urine and plasma, and the analyses of the kidneys will then be carried out. We believe this experiment, whether we obtain a treatment effect on nephropathy or not, will be of high significance in answering a critical question in the field, namely, does hyperlipidemia contribute to diabetic nephropathy and can this disease be treated by lowering triglyceride levels?

2. Publications:

Please list any publications resulting from the project.

No publications. We plan to publish our results, whether or not the treatment is effective.