Diabetic Complications Consortium

Application Title: Glucose regulation of hypertriglyceridemia

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1. Project Accomplishments:

We have studied the effects of streptozotocin-induced diabetes and glucose reduction on hepatic production of triglyceride. The uncertain issue is the importance of gene regulation versus substrate delivery in liver production of triglyceride in the setting of diabetes. We have shown the following:

1. Insulin deficient diabetes does not modulate gene regulating de novo liver fatty acid synthesis.
2. Although plasma triglyceride is increased with diabetes, this is not associated with increased liver triglyceride secretions.
3. Streptozotocin-induced diabetes leads to a marked reduction in liver lipoprotein lipase activity in peripheral tissues.

2. Specific Aims:

Aim 1 is to determine why glucose reduction reduces triglyceride levels in diabetic mice.
Aim 2 will determine the effects of acute hypertriglyceridemia and insulin-deficient diabetes on HDL composition and function.

Aim 1. We have complete Aim 1 and a manuscript in revision is appended to this progress report. We have studied control mice and mice with modulation of lipoprotein lipase (both deletions and transgenic overexpression). Despite several studies using mice with defects in insulin receptors that have shown the essential role(s) of insulin signaling in de novo triglyceride synthesis, we have found no similar effects in animals with insulin deficiency, but sufficient amounts of insulin to maintain life. Liver secretion of triglyceride was not altered and we found no reduction in FASN or SCD1, genes within the pathway of de novo synthesis

Factors affecting plasma triglyceride removal from plasma were altered in diabetic mice. Postprandial lipemia was markedly increased with diabetes. This was associated with greater lipoprotein lipase mRNA levels and activity in skeletal muscles.

We then studied mice with altered lipoprotein lipase production. Mice with a heterozygous deletion of lipoprotein lipase had much more markedly hyperlipidemia than did wild type mice. In concert with this, mice with additional lipoprotein lipase due to transgenic expression in skeletal muscle were protected form diabetes-induced hypertriglyceridemia.

Aim 2. We also assessed effects of diabetes on circulating levels of HDL and HDL composition. In our model we found no significant effect of diabetes on HDL lipid or protein composition. Perhaps this reflected the relatively minor increased in triglyceride levels in our diabetic mice. Or diabetes mediated changes in HDL might require the presence of cholesteryl ester transfer protein.

3. Publications:

Lipolysis, and not hepatic lipogenesis, is the primary modulator of triglyceride levels in streptozotocin-induced diabetic mice. Florian Willecke, Diego Scerbo, Prabhakara Nagareddy, Joseph C Obunike, Tessa J Barrett, Mariane L. Abdillahi, Chad M. Trent, Lesley Ann Huggins, Edward A Fisher, Konstantinos Drosatos, Ira J. Goldberg. Athero, Thomb, Vasc Biol. Accepted pending editorial revisions