American Diabetes Association-ASP Young Investigator Innovation Award in Geriatric Endocrinology

AWARD RECIPIENT

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PROJECT

"Hyperglycemia as a Driver of Altered High-Density Lipoprotein Metabolism After Menopause"

MENTORSHIP TEAM

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Aging is the loss of physiological function that increases the probability of death. Much aging research has focused on cellular aspects of aging, but reversing the mechanisms of aging in humans also requires addressing the root cause of mortality in the elderly, coronary heart disease (CHD). For women after menopause, CHD is the primary cause of death.

Despite dramatic improvements in the prevention and treatment of CHD in the general population, elderly women and patients with diabetes have an increased risk of death from CHD. This risk may result from additional CHD risk factors associated with elevated plasma triglycerides (TG). Elevated TG contributes to TG-enriched high-density lipoprotein (HDL) particles, which are more rapidly cleared and less protective against CHD. The transfer of TG into HDL is mediated by cholesterol ester transfer protein (CETP). Hyperglycemia is a major driver of elevated TG, but the impact of this process on HDL biology has been difficult to study in rodents because mice and rats lack CETP.

My American Diabetes Association (ADA)-ASP award will support research using a mouse strain that has been made transgenic for human CETP. These animals have a "humanized" lipoprotein profile with lower HDL, increased low-density lipoprotein (LDL), and elevated TG. These experiments aim to determine the extent to which hyperglycemia-induced TG elevations alter HDL metabolism in female CETP mice using in vivo clamp techniques and metabolic tracers for glucose and lipids. The impact of hyperglycemia on fatty acid synthesis, TG production, lipoprotein assembly, HDL levels, and control points in TG metabolism will be compared between age-matched female "humanized" mice and "non-humanized" littermates. Next, the effect of menopause induced by surgical ovariectomy on glucose-mediated changes in TG-HDL metabolism will be tested. These "humanized" animals can serve as an important bridge between basic science research and human disease.

Beginning to understand the ability of estrogen to coordinate metabolic signals with regard to glucose-mediated and insulin-mediated changes in TG-HDL metabolism will be an important outcome of these studies, and will likely have implications for many aspects of understanding how menopause alters cardiovascular risk. The molecular mechanisms of how this metabolic control is coordinated will be the subject of future experiments, and will undoubtedly serve as the roots of future studies in years to come. Through the guidance of my mentorship team and the support from the ADA-ASP Young Investigator Innovation Award in Geriatric Endocrinology, this research will be the foundation for my continuation in geriatric endocrine research.