

AMERICAN DIABETES ASSOCIATION-ASP-YOUNG INVESTIGATOR INNOVATION AWARD IN GERIATRIC ENDOCRINOLOGY

Award Recipient:



RAJAGOPAL V. SEKHAR, MD
BAYLOR COLLEGE OF MEDICINE

PROJECT:

THE EFFECT OF TYPE 2 DIABETES AND AGING ON GLUTATHIONE SYNTHESIS AND OXIDATIVE STRESS

MENTORSHIP TEAM:

FAROOK JAHOOR, PHD GEORGE E. TAFFETT, MD

*M*y research goals as a physician-scientist are to study insulin-resistant metabolic syndromes and their complications, and to understand the mechanisms underlying their pathogenesis in an effort to identify effective therapies. An evolving area of research focus has been in the antioxidant glutathione (GSH) in the elderly and diabetic patients, as GSH depletion predisposes to increased damage mediated by oxidative-stress. To achieve this goal, I have a strong foundation both in clinical endocrinology with training at the Baylor College of Medicine, and in metabolic research at the United States Department of Agriculture/Children's Nutrition Research Center at Baylor, where I became skilled in stable isotope techniques and applied them to unravel the metabolic basis of the insulin-resistant HIV-lipodystrophy syndrome.

The incidence of diabetes has risen sharply across all age groups, including the elderly. Both type 2 diabetes mellitus (T2DM) and aging are associated with increased oxidative stress. Both populations have lower concentrations of GSH, a major component of antioxidant defenses, but the mechanisms responsible remain poorly understood. GSH depletion could result from increased consumption or diminished synthesis secondary to a shortage of glycine and cysteine (precursor amino acids). Based on preliminary data, we hypothesize: 1) diabetics and the elderly have lower GSH concentrations than younger healthy controls due to decreased synthesis; 2) the lower synthetic rate is due to decreased precursor availability (cysteine and glycine); 3) dietary cysteine and glycine supplementation will replenish the GSH pool by increased synthesis, thereby decreasing oxidative stress in the young healthy, young with T2DM, elderly healthy, and elderly with T2DM.

We will test our hypothesis with the following specific aims: 1) measure cysteine, glycine kinetics, GSH synthetic rate in erythrocytes and leukocytes, and plasma markers of oxidant damage and antioxidant capacity, in these four groups of 10 subjects each; and 2) determine the effect of dietary cysteine, glycine, and cysteine plus glycine supplementation on GSH synthesis and concentration, and markers of oxidant damage and antioxidant capacity, in these groups.

These studies will investigate, for the first time, the mechanism responsible for GSH depletion and its relationship to the metabolism of cysteine and glycine, and thus determine mechanisms associated with antioxidant consequences of GSH depletion common to both diabetes and aging, such as cataracts, retinopathy, nephropathy, and vascular and coronary artery disease. Additionally, the dietary interventions may contribute new approaches to the management of diabetic patients and the elderly by restoring GSH homeostasis, preventing complications associated with an impaired antioxidant status.

The American Diabetes Association-ASP-Young Investigator Innovation Award in Geriatric Endocrinology has given me the perfect opportunity to develop myself as an independent researcher at the interface between endocrinology and gerontology, and to achieve this goal I will be guided by a mentorship team consisting of experts in geriatric medicine, stable isotopes, and clinical research. To advance my learning in geriatric endocrinology, I will participate in the biology of aging lecture series and journal club at the Huffington Center of Aging at Baylor and also attend monthly aging laboratory meetings. My selection as a Williams Scholar will therefore facilitate my growth as an independent physician-scientist with a special focus on geriatric endocrinology.