

## The Role of Stress in the Pathogenesis of Diabetes Mellitus

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Non-communicable diseases (NCD) have emerged as a major health problem and accounts for 60% of all deaths worldwide. An estimated 8 to 14 million people die prematurely every year in developing countries due to preventable NCDs such as diabetes mellitus (DM), cancer, cardiovascular and respiratory diseases. DM is one of the fastest growing NCDs whose prevalence is seen in all the six inhabited continents of the globe and is the seventh leading cause of death worldwide. "Asian Indian Phenotype" is considered to be one of the major factor contributing to increased prevalence of DM in Asian Indians as it is associated with certain unique clinical and biochemical abnormalities.

DM is a metabolic disorder of multiple aetiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, action or both. Chronic supra physiological glucose concentration affects the secretion of  $\beta$ -cells, increases cellular resistance to insulin resulting in severe microvascular and macrovascular complications. These pathophysiological changes in multiple organ systems impose a tremendous burden on the individual with diabetes and on the health care system.

Genetic predisposition and life style modifications initiates a pathophysiologic cascade that culminates in DM. Exposure to chronic stressors predisposes individuals to develop diabetes and also worsens complications in diabetic subjects. Recently most of the researchers focus on the stress pathways that predisposes individuals to diabetes mellitus. Oxidative stress, a state of imbalance between free radical production and scavenging is intricately associated with diabetes mellitus. Hyperglycemia induced oxidative stress occurs through various mechanisms of which auto-oxidation of glucose, enhanced polyol pathway and glycation of proteins gains much importance.  $\beta$ -cells are more susceptible to oxidative damage as it has weak antioxidant defence than other cell types. Presently agents that scavenge free radicals or those that enhance endogenous antioxidants are finding immense applications in patient care.

Diabetes mellitus is also considered as an inflammatory disease. Activation of inflammatory pathways has emerged as an imperative link between diabetes mellitus and inflammation. Disordered metabolism triggers inflammatory cascade mechanism linking inflammation to insulin resistance and  $\beta$ -cell dysfunction. Up regulation of proinflammatory cytokines correlate with the risk of diabetes related vascular complications.

Endoplasmic reticulum (ER) stress is involved in the development of diabetes. A complex homeostatic signaling pathway, maintains a balance between the newly synthesized proteins and the capacity of the ER to aid in their maturation. Concrete evidence supports the findings that insulin secreting  $\beta$ -cell are sensitive to the adverse effects of perturbed ER function. Efficient Unfolded protein response (UPR) signaling is essential for the  $\beta$ -cell to meet the demands of varying levels of insulin synthesis. Persistent stimuli to  $\beta$ -cells arising from insulin resistance in target tissues brings ER stress. Signaling events in the death pathway downstream of ER stress aggravates the condition.

Minimizing stress, improving  $\beta$ -cell function, promoting glycemic control by enhancing insulin sensitivity are emerging as an attempt to prevent diabetes and its complications. In this context, identification of potential targets, development of novel therapeutic agents that can cross talk with multiple stress related pathways are in need of the hour to curtail the burden of diabetes and to improve life expectancy in diabetic subjects.

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