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Diabetic Autonomic Neuropathy and Cardiovascular Function

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Diabetic neuropathy has been defined as a set of clinical and subclinical syndromes that affect distinct regions of the nervous system, with differing clinical courses, singly or combined and possibly differing underlying aetiopathogenetic mechanisms. Each is characterized by generalized or focal damage to peripheral somatic or autonomic nerve fibers resulting from diabetes mellitus. The syndromes may be grouped under two general headings: generalized and focal neuropathies. The generalized neuropathies, i.e., distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) are common, usually chronic, frequently coexist and often progressive. The focal neuropathies are less common, usually acute in onset, and often self-limited.

Generalized Diabetic Neuropathy is the most common, underdiagnosed and poorly treated microvascular complication of diabetes mellitus. Diabetic neuropathy is a major factor in the impaired wound healing, erectile dysfunction, and cardiovascular dysfunction. More than half of all individuals with diabetes eventually develop neuropathy with a lifetime risk of one or more lower extremity amputations estimated in some populations to be up to 15%. Disease progression in neuropathy was traditionally clinically characterized by the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia with subsequent diminishment in oxygen tension and hypoxia.

Hyperglycemia clearly plays a key role in the development and progression of diabetic neuropathy as well as the other microvascular complications of diabetes. Excess intracellular glucose is processed by increased flux through one or more glucose metabolism pathways, and prolonged hyperglycemia can lead to increased oxidative and nitrosative stress, defective neurotropism, and autoimmune-mediated nerve destruction which could result to cellular damage in several ways. Cells within tissues that are prone to diabetic complications, such as endothelial cells, are not able to modulate glucose transport rates to prevent excessive accumulation of glucose in intracellular space. Another consequence of excess intracellular and extracellular glucose is the generation of advanced glycation end products (AGEs), via attachment of reactive carbohydrate groups to proteins, lipids, or nucleic acids. The main mechanisms behind the tissue damage caused by AGEs are intracellular

glycation, cross-link formation, and interaction with RAGEs. These groups tend to impair the biological function of proteins, thus affecting cellular function.

Cardiovascular Autonomic Neuropathy (CAN) has been linked to resting tachycardia, postural hypotension, exercise intolerance, reduced heart rate variability, enhanced intraoperative or perioperative cardiovascular liability, increased incidence of asymptomatic ischemia, silent MI, and decreased rate of survival after myocardial infarction. Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment, whereas abnormalities in heart-rate variability (HRV) are early findings of CAN. The prognostic value of resting heart rate is a useful tool for cardiovascular risk stratification and as a therapeutic target in high-risk patients.

In particular exercise intolerance due to CAN is a major problem, because of lifestyle guidelines, which recommend programs of exercise. Diabetic patients who are likely to have CAN should be tested for cardiac stress before undertaking an exercise program. Patients with CAN need to rely on their perceived exertion, not heart rate, because a "locked" heart rate and Left Ventricular dysfunction could co-exist, in order to avoid hazardous levels of intensity of exercise. Moreover in our studies we showed that CAN associated significantly with Left Ventricular Dysfunction. Cardiovascular diabetic autonomic neuropathy is a complication related to poorly controlled diabetes and includes abnormalities in heart rate control, vascular hemodynamics, and cardiac structure and function. Perioperative cardiovascular morbidity and mortality are increased 2- to 3-fold in patients with diabetes and preoperative cardiovascular autonomic screening of diabetic patient may help anesthesiologists identify those at greater risk of intraoperative complications.

Orthostatic hypotension is defined as a decrease in blood pressure (ie, >20 mmHg for systolic or >10 mmHg for diastolic) in response to postural change, from supine to standing. In patients with diabetes, orthostatic hypotension is usually a result of damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature.

Patients may present with light-headedness and presyncopal symptoms, or may remain asymptomatic despite significant drops in blood pressure. Orthostatic symptoms can also be misjudged as hypoglycemia and can be aggravated by several drugs, including vasodilators, diuretics, phenothiazines, and particularly TCAs and insulin.

Symptoms usually occur with advanced disease, and screening of diabetic patients for CAN is essential. The Cardiovascular Autonomic Reflex Tests (CARTs) are the gold standard. Restoration of autonomic balance is possible and has been shown with strict glycolic control, therapeutic lifestyle changes, increased physical activity, and diabetes treatment (ACE inhibitors, b-adrenergic blockers and potent antioxidants, such as a-lipoic acid).