



# Diabetic Autonomic Neuropathy

Alaka Deshpande

## ABSTRACT

Neuropathy is a debilitating complication of diabetes. Neuropathy can be motor, sensory, and autonomic. There is a wide variation in the prevalence of diabetic autonomic neuropathy (DAN), depending upon the definition and criteria used for diagnosis. The sympathetic and parasympathetic nerves supply various organ systems modulating their functions. Therefore, DAN has wide spectrum of clinical presentation.

The clinical manifestations differ depending upon the systemic involvement. The management consists of lifestyle modifications, control of hyperglycemia, and simple physical measures along with supportive care.

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## INTRODUCTION

Neuropathy is a debilitating complication of diabetes. Neuropathy can be motor, sensory, and autonomic. It can be classified as:

- Bilaterally symmetrical polyneuropathy.
- Focal or multifocal neuropathy.

Diabetic autonomic neuropathy falls in the first category. It can be further classified as<sup>1</sup>

- Subclinical: Detected by physiological tests.
- Clinical: Diabetic patient presenting with symptoms and signs of neuropathy after excluding other causes.

Medical literature reports wide variation in the prevalence of DAN, depending upon the definition and criteria used for diagnosis. The other confounding factor is age of the patient. The sympathetic and parasympathetic nerves supply various organ systems modulating their functions. Therefore, DAN has wide spectrum of clinical presentation. The DAN can affect cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor, and neuroendocrine systems.

Honorary Professor of Medicine

**Corresponding Author:** Alaka Deshpande, A-8, Shri Sahawas 90 Feet Road, Ghatkopar (E), Mumbai-400077, Maharashtra India, Phone: +919869168886, e-mail: alakadeshpande@rediffmail.com

## PATHOGENESIS

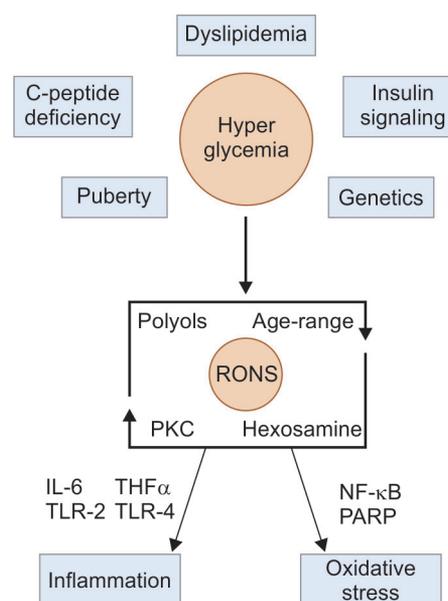
As in the case of most of the complications of diabetes, multiple factors contribute to the pathogenesis of damage to the nerves both peripheral and autonomic nerves. The whole cascade starts with uncontrolled hyperglycemia. As nicely depicted by Verrotti et al<sup>2</sup> in Fig. 1, hyperglycemia induces various alternating metabolic pathways, resulting in production of oxidative stress and chronic inflammation causing irreparable damage to tissues. The hyperglycemia is responsible for mitochondrial overproduction of reactive oxygen and nitrogen species (RONS). RONS induce deoxyribonucleic acid (DNA) damage which overstimulates polyadenosine diphosphateribose polymerase (PARP) with endothelial dysregulation.

Chronic hyperglycemia leads to irreversible advanced glycosylation end-products (AGEs). Experimentally, it has been shown that AGEs have collagen linking activity which may be responsible for vascular complications.

The AGEs bind to Receptor for Advanced Glycation End products (RAGE) and activate these. The RAGE activation is pro-inflammatory. In addition, vascular complications like occlusion result into ischemic damage of the nerves. Peripheral nerve repair is impaired in diabetes.

## CLINICAL FEATURES

Sympathetic and parasympathetic nerves supply all the visceral organs; therefore, the signs and symptoms of DAN depend on the organ system that is involved. The



**Fig. 1:** Pathogenesis  
Courtesy: Verrotti et al<sup>2</sup>

prevalence of this neuropathy is difficult to determine. It depends on the definition, the diagnostic criteria used, and the population studied.

Common manifestations due to DAN are:

- Cardiovascular autonomic neuropathy (CAN)
- Gastrointestinal
- Genitourinary
- Sudomotor
- Renal
- Arthropathy
- Pupillary
- Neuroendocrine
- Central nervous system

### Cardiovascular Autonomic Neuropathy

Sympathetic and parasympathetic nerves control multiple cardiovascular functions including blood pressure.

Reduced heart rate variability is noted early in DAN. However, there are multiple risk factors contributing to the same, e.g., age, smoking, duration of diabetes, and control of hyperglycemia. Later on, as the vagal impairment sets in resting tachycardia and a fixed heart rate are common manifestations.

A fixed heart rate unresponsive to stress, moderate exercise or sleep indicates complete cardiac denervation. The CAN impairs exercise tolerance by blunting the heart rate and blood pressure response. Diabetics with multiple risk factors and preclinical coronary artery disease may be subjected to stress imaging testing so that hazardous exercise program can be avoided.<sup>3</sup>

### Intra- and Perioperative Cardiovascular Instability

Patients with CAN may more often require vasopressor support than those without CAN. The normal autonomic response of vasoconstriction and tachycardia do not compensate for vasodilatory effect of anesthesia. There is an association between CAN and severe intraoperative hypothermia which impairs healing. The anesthesiologist and the surgeon should be alerted to CAN complications, particularly reduction in hypoxia-induced ventilatory drive.

### Orthostatic Hypotension

It is defined as a fall in systolic blood pressure of >30 mm Hg or > 10 mm Hg in diastolic blood pressure in response to change in posture from supine to standing accompanied by symptoms of dizziness, faintness, even syncope. These symptoms may be misdiagnosed as due to hypoglycemia. It is therefore necessary that clinicians should pay more attention to DAN.

### Silent Myocardial Ischemia

Cardiovascular autonomic neuropathy impairs appreciation of ischemic pain, thereby delaying the recognition and treatment. The electrocardiograph of a diabetic patient with exertional chest pain has shown prolongation of time of perception of chest pain from the onset of ST depression (angina perceptual threshold). Due to this unawareness, a diabetic patient with CAN may continue to exercise despite increasing ischemia. The studies have shown 28% cases with CAN had silent ischemia as against 10% cases without CAN.

### Autonomic Cardiopathy

Cardiovascular autonomic neuropathy may be associated with diastolic and systolic dysfunctions in the absence of cardiac disease. Cardiovascular autonomic neuropathy can be evaluated more accurately by cardiac radionuclide imaging. Metaiodobenzylguanidine (MIBG) (the nonmetabolized norepinephrine analog) is actively taken up by postganglionic sympathetic nerve terminals of myocardium. Several studies have shown reduced myocardial MIBG uptake in patients with CAN.

### Treatment

It aims at primarily prevention of disease progression. Hence, modifiable risk factors, such as hyperglycemia, hyperlipidemia, hypertension, and smoking need to be controlled. The ACCORD trial links intensive glycemic control to increased mortality. Therefore, target glycated hemoglobin level should be achieved gradually.

- Nonpharmacological measures
  - Increased consumption of water
  - Slow postural changes
  - Elevation of head end by up to 30 cm
  - Dorsiflexion of feet or hand grip exercise should be performed before standing
- Pharmacotherapy
  - Mineralocorticoid Fludrocortisone 0.1 to 0.4 mg/day
  - Alpha adrenoceptor agonist Midrodin used for postural hypotension, but it may cause severe supine hypertension so patients should not use it within 6 hours of bedtime. Norepinephrine pro-drug Droxidopa is orally given, and it has recently received US Food and Drug Administration approval.

### Gastrointestinal System

Gastroesophageal reflux disease (GERD), gastroparesis, and diabetic diarrhea are the commonest gastrointestinal (GI) manifestations of DAN. The autonomic neuropathy

decreases the pressure of the lower esophageal sphincter (LES), impaired clearance function of the tubular esophagus and hyperglycemia increases transient relaxations of LES. As a result, patient complains of heartburn and regurgitation. The GERD may also lead to laryngitis, chronic cough, and even bronchospasm. Control of hyperglycemia and use of prokinetic agents are advocated.

Gastric emptying time is delayed in up to 50% of cases. Gastroparesis diabetorum is the term used to indicate altered GI motility. Food residue is retained in the stomach as a result of dysmotility. It may manifest as nausea, pain in abdomen, loss of appetite, early satiety, postprandial vomiting, and bloating. A gastric splash may be elicitable on clinical examination. It may also be associated with bezoar and bacterial overgrowth in the stomach and small intestines. It is prudent to rule out the obstructing lesion in stomach or intestine by endoscopy. The delayed gastric emptying time may be studied by scintigraphy.

Gastroparesis may impair glycemic control by mismatching plasma glucose and insulin levels. Diarrhea manifest as profuse, watery stools, usually nocturnal, lasting for a few days alternating with constipation. Reduced motility, reduced receptor-mediated fluid absorption, pancreatic insufficiency, and bacterial overgrowth contribute to diabetic diarrhea.

Fecal incontinence due to incompetence of anal sphincter is another manifestation of diabetic neuropathy. Chronic severe constipation is also common. Studies have implicated hyperglycemia as a cause of GI dysmotility. Control of hyperglycemia, use of prokinetic agents, some simple physical measures like small frequent meals and avoiding supine position immediately after food are advocated.

### Genitourinary System

The urinary bladder is innervated by autonomic and somatic nerves. Diabetic autonomic neuropathy causes bladder dysfunction, retrograde ejaculation, erectile dysfunction, and dyspareunia due to lack of lubrication. Erectile dysfunction is associated with cardiovascular disease.

Bladder dysfunction may manifest initially as decrease in feeling the sensation of full bladder due to loss of autonomic afferent innervations. It results in frequent urination, while involvement of efferent fibers results in incomplete emptying. It leads to frequent urinary tract infections, dribbling due to overflow—incontinence. About 7 to 10% of cases may develop atonic bladder, necessitating regular catheterization.<sup>4</sup>

### Management

The patient may initially be subjected to urine analysis and sonography to see the postvoidal residual volume. It is necessary to carry out complete urodynamic testing. The medications that impair detrusor activity like anticholinergic

agents, tricyclic antidepressants, and calcium-channel blockers may be changed. Bladder training with strict voluntary micturition schedule, coupled with Crede maneuver, is advised. Intermittent catheterization may be needed.

Such problems are further contributed by smoking, alcohol, anxiety, and depression which need attention. Sexual dysfunctions in males include erectile dysfunction, retrograde ejaculation, and impotence. Sexual functions are affected in diabetic females too. Anxiety and depression play a role in sexual functions. Management should be tailored to individual needs. Phosphodiesterase inhibitors are used as first-line therapy in erectile dysfunction. However, they are contraindicated in the presence of heart disease which is being treated with nitrates.

### Sudomotor System

Thermoregulation and sweat function are under the control of peripheral sympathetic cholinergic system. There is a loss of sweat function in glove and stocking area with compensatory proximal hyperhidrosis. Peripheral autonomic dysfunction manifests as sweating abnormalities, change in skin texture, loss of nails, itching, callous formation, edema, and foot ulceration. Quantitative sudomotor axon reflex testing may be used to detect denervation.

### Other Changes

Pupillary abnormalities may cause failure in dark adaptation and difficulty in night driving. Peripheral neuropathy along with autonomic neuropathy is the main cause of diabetic arthropathy.

A prospective study in type I diabetes mellitus (T1 DM) with a 14-year follow-up has shown increasing hypoglycemic episodes due to autonomic neuropathy, resulting in decreased glucagon and epinephrine response to falling sugar levels. It is also termed as hypoglycemia-associated autonomic failure. Hypoglycemia unawareness is a major risk factor for strokes in diabetics independent of CAN. Surgeon and anesthesiologist have to be aware of DAN in diabetic patients undergoing any surgery. The American Diabetic Association recommends screening for DAN in T2 DM patients at the time of diagnosis and 5 years after the diagnosis of T1 DM.

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