INTRODUCTION
Diabetic autonomic neuropathy (DAN) is the most neglected, yet one of the most serious complications of diabetes. It is a form of peripheral neuropathy due to damage to parasympathetic and/or sympathetic nerves in people with diabetes, excluding other causes of neuropathy. It is manifested by dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal [GI], genitourinary, sudomotor, or ocular).

The importance of this diabetic complication is best illustrated by the fact that the mortality rate in patients with Cardiac autonomic neuropathy (CAN) is 5-6 times higher in the period of 5-6 years than the mortality in patients with diabetes but without CAN in the same period. Longitudinal studies have shown that the 5-year mortality rates of people with CAN are 16%-50% in patients with type 1 and type 2 diabetes, most often due to sudden cardiac death. A meta-analysis of 15 studies reports a relative risk of mortality of 3.45 in patients with CAN. It is known that CAN significantly increases the risk of life-threatening arrhythmias and sudden death with the contribution from other risk factors such as hypoglycemia, drug side effects, hypokalemia, hypotension, ischemia etc.

EPIDEMIOLOGY
Prevalence rates of DAN from several different studies exhibit a dramatic variability from as low as 7.7% for newly diagnosed patients with type 1 diabetes, when strict criteria to define CAN were used, to as high as 90% in potential recipients of pancreas transplant. The prevalence varies from 20% to 73% in patients with type 2 diabetes. The great diversity of data is a result of inconsistencies in the criteria used for the diagnosis of CAN as well as major differences in the groups of patients selected in research, particularly with respect to risk factors (e.g., patient age, sex, duration of diabetes).

After extensive analysis of published reports, the Consensus Panel on Diabetic Neuropathy has concluded that the prevalence of confirmed cardiovascular autonomic neuropathy (CAN) in an unselected group of patients with both type 1 and type 2 diabetes is about 20%, but can be up to 65% with increasing age and diabetes duration.

CLINICAL MANIFESTATIONS
During the course of DAN, asymptomatic (subclinical) and symptomatic phases can be recognized. Using simple cardiovascular tests, DAN can be detected early during the asymptomatic phase of the disease. Vagus nerve (the longest of the autonomic nerves) accounts for 75% of all parasympathetic activity and DAN, being a length dependent disease, manifests first in longer nerves. That’s why even early effects of DAN are widespread in the form of decreased parasympathetic activity and sympathetic predominance. The sympathetic dominance lasts until the late stage of the disease when sympathetic denervation takes place. It is this phase when symptoms of DAN are apparent.

The symptoms and signs of DAN vary widely and depend on the affected organ.

Metabolic
1. Hypoglycemia unawareness
2. Hypoglycemia associated autonomic failure

Cardiovascular system (CAN)
1. Loss of circadian rhythm of blood pressure (‘non-dipping’)
2. Resting tachycardia
3. Exercise intolerance
4. Intra-operative cardiovascular lability
5. ‘Silent ischemia’ and ‘painless’ myocardial infarction
6. Diabetic cardiomyopathy
7. Arrhythmias, sudden cardiac arrest
8. Orthostatic hypotension

Gastrointestinal system
1. Dysfunction of the esophagus
2. Gastroparesis
3. Change in gut motility (constipation, diarrhea)
4. Anorectal dysfunction (fecal incontinence)

Genitourinary system
1. Neurogenic bladder (diabetic cystopathy)
2. Erectile dysfunction
3. Retrograde ejaculation
4. Female sexual dysfunction (e.g., loss of vaginal lubrication)

Respiratory system
1. Central dysregulation of breathing
2. Reduced bronchial reactivity
Table 1: Differential Diagnosis: Diabetic autonomic neuropathy

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary neuropathies</td>
<td></td>
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<tr>
<td>Metabolic diseases (amyloidosis, chronic liver and kidney disease)</td>
<td></td>
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<tr>
<td>Endocrine diseases (panhypopituitarism, pheochromocytoma)</td>
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<tr>
<td>Inflammatory diseases (Chagas’ disease, HIV, botulism, leprosy, Guillain-Barre syndrome)</td>
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<tr>
<td>Cardiovascular disease (syncope, idiopathic orthostatic hypotension, POTS)</td>
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<tr>
<td>Chronic dysautonomies (Shy-Drager syndrome, autonomic dysfunction in Parkinson disease)</td>
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<td>Toxic(heavy metals, alcohol, chemotherapy-vincristine, cisplatin, paclitaxel)</td>
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<tr>
<td>Paraneoplastic neuropathy</td>
<td></td>
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<tr>
<td>Drugs (Vasodilators, sympathetic blockers, diuretic induced hypovolemia, insulin therapy)</td>
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**Sudomotor**

1. Hyperhydrosis of upper limbs
2. Gustatory sweating
3. Anhidrosis of lower limbs, dry skin
4. Heat intolerance
5. Changes in skin blood flow (warm skin, varicose veins, peripheral edema)

**Pupillomotor**

1. Pupil dysfunction (decreased diameter of dark adapted pupil)
2. Argyll-Robertson pupil

**DIAGNOSIS**

The diagnosis of diabetic autonomic neuropathy is one of exclusion, and many other causes of autonomic dysfunction should first be ruled out (Table 1). It should also be borne in mind that even about 10% of symptomatic DAN patients in general have another cause of neuropathy other than diabetes.

The clinician should take a careful history, asking about diabetes, cancer, drug use, alcohol use, HIV exposure, and family history of familial amyloidosis.

Patients should be asked whether they have traveled to South America, where they might have been exposed to Trypanosoma cruzi, the cause of Chagas disease. Serologic testing for antibodies to this organism may be valuable.

Testing the norepinephrine response to standing may help identify the cause of idiopathic orthostatic hypotension. Basal values and the response to standing are normal in diabetic autonomic neuropathy; whereas are severely reduced in multiple system atrophy or idiopathic orthostatic hypotension and impaired in Shy-Drager syndrome.

**AUTONOMIC NERVOUS SYSTEM TESTING**

To confirm the diagnosis of DAN, a series of tests (depending on the organic system to be tested) can be used. Cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of DAN due to its association with a variety of adverse outcomes including cardiovascular deaths. Also because of noninvasiveness, sensitivity, specificity and standardization, a standard ‘battery’ of cardiovascular tests (Table 2) is used as gold standard.[10]

CAN could be graded regarding the results of the testing as follows:

- Presence of one abnormal finding indicates a possible CAN
- Atleast two abnormal findings are required to confirm the diagnosis of CAN
- Presence of orthostatic hypotension in addition to other abnormal findings indicates Advanced CAN[10]

**Other Methods**

Among other methods used to confirm the diagnosis of DAN are Baroreflex sensitivity measures, Quantitative sudomotor axon reflex test (QSART), Muscle sympathetic nerve activity, Dynamic pupillometry and more rarely, direct scintigraphic analysis of cardiac sympathetic fibers using SPECT or PET scans.[7,11,12] As the mentioned tests are often very demanding, the standard battery of CAN tests is considered a surrogate for confirmation of DAN in general.

**SPECIFIC INVESTIGATIONS**

If CAN testing is abnormal, specific investigations (Table 3) depending on symptoms and organ involvement can be carried out.[10]

**PREVENTION**

Successful prevention of diabetic autonomic neuropathy lies in the strategy of intensive glycemic control and treating risk factors mainly. Risk factors are age, duration of diabetes, glycemic control, microvascular complications (polyneuropathy, retinopathy, nephropathy) and other factors such as hypertension, dyslipidemia, smoking, obesity and alcohol consumption.

The results of the Diabetes Control and Complication Trial (DCCT) showed that tight glycemic control resulted in 50% reduction of the incidence of CAN during 6.5-year follow up. This protective effect persisted for 14 years after the end of the study despite the disappearance of HbA1c differences that were reached between the groups during the randomized phase.[13]

There has been a number of agents designed to improve the underlying pathophysiology of the disorder rather than for symptomatic relief. Of the proposed mechanisms that underlie the diabetes induced damage to peripheral nerve, two are linked to ‘oxidative stress’. These include advanced glycosylation end product (AGEs) and the accumulation of sorbitol. There have been no clinical
Aldose reductase inhibitors (ARI) have been used in trials over the past 30 years, which demonstrated improvements in sensory and motor conduction velocity (CV) compared to placebo in some RCTs [25]. Subsequent large, multicenter studies of other ARIs, including tolrestat, ponalrestat, epalrestat, zenarestat, and ranirestat, did not demonstrate a convincing clinical efficacy.

Recombinant human nerve growth factor (rhNGF) has been the subject of several trials. A phase II trial of rhNGF over six months showed preliminary evidence of efficacy in patients with diabetic neuropathy [26].

C-peptide replacement therapy in patients with type 1 diabetes with short-term use had early beneficial effects on sensory nerve conduction studies and some measure of sensory function [27].

Dietary supplementation with myoinositol over 6 months...
improve NCSs in rats, but no definitive clinical or electrophysiologic benefits were seen in human trials.[28]

Others vitamine like thiamine, B12, and pantothenic acid, were ineffective when performed as controlled clinical trials.[29]

As all diabetic microvascular complications share a common pathogenic mechanism and same risk factors; diabetic nephropathy, retinopathy and polyneuropathy are considered clinical predictors for DAN. Screening and management aimed at these complications play a pivotal role in DAN prevention as well.[15,16]

Steno-2 study in patients with type 2 diabetes and microalbuminuria has shown that intensive pharmacological treatment of hypertension, hyperlipidemia and microalbuminuria together with lifestyle changes significantly diminishes not only the risk of DAN, but the risk of cardiovascular disease as well and reduces overall diabetic patient mortality.[14]

Use of antioxidants[20] and ACE inhibitors[21] along with management of risk factors, hyperglycemia reduce the odds ratio for autonomic neuropathy to 0.32.

It has been shown in DIGAMI study that mortality is a function of loss of beat-to-beat variability with myocardial infarction which can be reduced by 33% with acute administration of insulin.[22]

Kendall and coworkers[23] reported that successful pancreatic transplantation improves epinephrine response and normalizes hypoglycemia symptom recognition in patients with longstanding diabetes and established autonomic neuropathy.


SCREENING
According to the American Neurological Society guidelines, screening for autonomic dysfunction should be carried out immediately after the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Patients at a greater risk because of poor glycemic control, cardiovascular risk factors and with the presence of other micro- and macrovascular complications of diabetes should be tested in particular. Clinician should repeat testing yearly if CAN testing comes normal.[1,11,17]

Every patient who is about to begin any kind of intense physical activity except for vigorous walk and any patient that is going to have a surgery in general anesthesia should also be tested as well.[18]

TREATMENT
Basic measures
If the symptoms of DAN are already present, patients need to be advised about simple behavioral measures and lifestyle changes that can alleviate the symptoms[19]:

*Orthostatic hypotension

Getting up in gradual stages; perform physical counter-maneuvers (leg crossing, stooping, squatting); wearing elastic stockings reaching to the waist; increasing fluid and salt intake; reducing the dosage or excluding medications that may precipitate orthostatic hypotension e.g. thiazides, beta blockers, phenothiazines, tricyclic antidepressants etc; raising the head of the bed by 10-20° (stimulation of renin-angiotensin-aldosterone system).

• Gastroparesis
Multiple, small meals; staying upright for half an hour after each meal; if necessary semi-liquid or liquid food; low fat/fiber diet; omission of drugs that slow gastric emptying (e.g., calcium channel blockers, GLP-1 analogs, tricyclic antidepressants)

Modify insulin dosage & timing (Even when mild, gastroparesis interferes with nutrient delivery to the small bowel, disrupting the relationship between glucose absorption and exogenous insulin administration. This may result in wide swings of glucose levels, unexpected episodes of postprandial hypoglycemia, and apparent “brittle diabetes.”).

• Constipation
Rule out other causes such as hypothyroidism, drug effects e.g. amitriptyline or calcium channel blockers and colonic carcinoma by fecal occult blood test.

Increased fluid intake; regular exercise; increased intake of foods rich in fiber

• Diarrhea
Restriction of gluten and lactose in the diet

• Loss of hypoglycemic signs
Often self-control; recognition of some unusual symptoms (e.g., tingling in the hands or feet); higher target plasma glucose level

• Bladder dysfunction
Patients are instructed to palpate their bladder and to try to urinate when it is full. If they are unable to start urination, they should massage or press the abdomen just above the pubic bone (Credé maneuver) to start the flow.

• Sexual dysfunction
Avoidance of alcohol and smoking, cease taking medications known to cause erectile dysfunction e.g. beta-blockers, thiazides, phenothiazines, tricyclic antidepressants, spironolactone, fibrates, marijuana etc.

• Anhidrosis of lower limbs & gustatory sweating
Foot care, Avoid particular inciting food if present in case of gustatory sweating.

Symptomatic treatment: Pharmacological therapy
In cases of advanced, symptomatic DAN, it is sometimes...
necessary to use drugs which should be prescribed by specialists depending on the affected organ. Unfortunately, there are currently no generally accepted guidelines for the treatment of DAN.[19]

- **Orthostatic hypotension**
  Central α-2 agonist- clonidine (0.1-0.5 mg bedtime); mineralocorticoid – 9 alpha-fludrocortisone (0.5-2 mg/day); somatostatin analog-octreotide.

- **Gastroparesis**
  Antiemetics – metoclopramide, domperidone(10 mg 30-60 mins before meals and bedtime); levosulpiride(25 mg thrice daily); gastric electrical stimulation

- **Constipation**
  Osmotic laxatives – lactulose; motility or secretion stimulating laxatives – magnesiumsulfate, sodium sulfate
  Prokinetics (dopamine antagonists) – metoclopramide

- **Diarrhea**
  Broad-spectrum antibiotics –ampicillin; Metronidazole (250 mg thrice a day for atleast 3 weeks); synthetic opioids –loperamide (2 mg 4 times a day); α-2 agonist-clonidine (0.1 mg twice or thrice a day); somatostatin analog–octreotide (50 microgm thrice a day)

- **Bladder dysfunction**
  Mechanical methods (intermittent self-catheterization);
  Anticholinergics (in detrusor hyperreflexia); parasympathomimetics (in reduced contractility of the detrusor)-Bethanechol 10 mg four times a day
  α-1blocker- Doxazosin(1-2 mg 2-3 times a day) relaxes sphincter

- **Sexual dysfunction**
  5-phosphodiesterase inhibitors- Sildenafil (50 mg 1 hr before sexual activity,once only per day); intracavernous injection of vasodilator; transurethral application of prostaglandins
  Penile implants; vacuum devices (in vascular cause of erectile dysfunction)
  Vaginal lubricants in females

- **Hyperhidrosis and gustatory sweating**
  Anticholinergics; agonist of α-2 receptors – clonidine.

**CONCLUSION**

Diabetic autonomic neuropathy is a common and serious complication of diabetes, presenting most commonly as exercise intolerance, silent myocardial ischemia, orthostatic hypotension, impaired intestinal motility, bladder and erectile dysfunction, sweating disturbances and hypoglycemia unawareness. The consequences of DAN significantly affect the survival of diabetic patients and are associated with increased mortality from malignant arrhythmias and sudden cardiac death. DAN is unfortunately often recognized too late. Thanks to a standard battery of cardiovascular autonomic tests used as gold standard screening tests in diabetic patients, especially in those who have additional risk factors such as poorly controlled glycemia, vascular risk factors, other microvascular complications; DAN can be detected early. Strict blood glucose control is still the only major therapy that allows delaying, halting or slowing the progression of DAN. Symptomatic treatment consistof simple measures and lifestyle modifications and in severe cases, pharmacological treatment.

**REFERENCES**

13. Martin CL, Albers JW, Pop-Busui R. Neuropathy and


