

INTRODUCTION

Diabetic autonomic neuropathy affects many systems of our body namely cardio vascular, gastro intestinal, urogenital and sudo motor systems. This inturn results in many abnormalities varying from milder one like subclinical impaired heart rate variability(HRV),to severe one clinically manifesting as resting tachycardia, increased preponderance for various arrhythmias postural hypotension, altered bowel movement, decreased bladder contractility, erectile dysfunction (ED), lower urinary tract symptoms and sweating disorders.

Though autonomic neuropathy is less common than other complications, once occurs, it is rather debilitating and difficult to treat.

NATURAL HISTORY

Cardiac Autonomic Neuropathy (CAN) increases with duration of diabetes irrespective of diabetes type.

The natural history of autonomic neuropathy is not clear. Though the clinical features of overt autonomic neuropathy are not present at the time of diagnosis of diabetes, abnormalities in HRV or cardio vascular reflex test may be present early in its course. Framingham Heart Study shows changes in CAN i.e. a shift in sympathetic –parasympathetic balance showing sympathetic tone alteration in patients in prediabetic state. A similar observation was noted in many persons with impaired glucose tolerance. Many studies have shown that children with diabetes have higher average heart rate than those without diabetes. The reason remains unclear but may be due to autonomic dysfunction.

Resting tachycardia in children or adults may be due to anemia, thyroid dysfunction, underlying cardio vascular disease, obesity and poor fitness. So before arriving at a diagnosis of CAN. These conditions have to be excluded. A fixed heart rate that is not responsible to exercise, stress, hypoglycemia, sleep is due to cardiac denervation. Though subtle autonomic dysfunction is the cause for elevated heart rate in diabetes, hyperglycemia and myocardial dysfunction also can be the causes.

STUDIES

DCCT (Diabetes Control and Complication Trial) reveals intensive insulin therapy for type 1 diabetes, reduced the incidence of CAN by 53% compared with conventional treatment. EDIC study reveals CAN has progressed in both treatment groups, revealing metabolic memory decides it.

T1D treatment has to be initiated as soon as possible. In T2D impact of glycemc control on CAN is less conclusive.

In some studies like veterans affairs co operative study and Veterans Affairs Diabetes Trial(VADT), no difference was noted in both tight control and without control groups. Similarly,in a trail of Japanese patients with T2D, no significant difference was noted in CAN – Postural Hypotension, HRV. Several studies have shown association between CAN and glucose levels but the data relating to role of glucose variability causing CAN are limited. In one study CAN was not associated with glucose variability.

In many studies, CAN is associated with hypertension hyperlipidemia smoking and metabolic syndrome. Diabetes prevention program shows life style modification like diet and exercise are beneficial to prevent CAN.

PATHOGENESIS

The development of diabetic neuropathy results from complex interactions between degree of glycemc control,disease duration, age related neuronal involvement and other risk factors like blood pressure, lipids and weight. These factors facilitate autonomic neuronal dysfunction in a manner that starts distally and progress proximally.

Many studies have shown CAN complicating T1D, there is a compensatory increase in cardiac sympathetic tone as a response to subclinical peripheral denervation, Subsequently, sympathetic denervation ensues ie- begin at apex of the ventricles and progress towards base.

CLINICAL FEATURES

Autonomic neuropathy is asymptomatic in its early stages. This delays initiation of apt treatment. The advanced form of autonomic neuropathy is manifested by orthostasis, fixed tachycardia, severe diarrhea and impaired response to hypoglycemia.

CARDIO VASCULAR AUTONOMIC NEUROPATHY (TABLE 1)

1. Impaired Heart Rate Variability (HRV)- It is the earliest sign of CAN. It may not be associated with symptoms.
2. Resting Tachycardia and Exercise Intolerance – This may present in advanced cases and is due to reduced response in heart rate, BP and blunted increase in cardiac output in response to exercise. As already pointed out, Resting tachycardia has to be ruled out due to other causes. Resting tachycardia the fixed heart rate > 100 Beats /minute i.e- unresponsive to moderate exercise, stress or sleep point out more advanced disease.

Table 1: CV Autonomic Neuropathy

Impaired Rate Variability	Orthostatic Hypotension
Exercise Intolerance	While Standing.
Resting Tachycardia	Lightheadness
	Weakness
Abnormal BP Regulation	Faintness
Non Dipping	Dizziness
Reverse Dipping	Visual Impairment
	Syncope

Table 2: Gastrointestinal-Symptoms

Gastroparesis	Esophageal Dysfunction
Nausea	Heartburn
Bloating	Dysphagia for Solids
Loss of Appetite	
Early Satiety	Diabetic Diarrhea
Post Prandial Vomiting	Profuse and Watery Diarrhea
	Fecal Incontinence
	Constipation

3. **Silent Ischemia:** Many studies show association of CAN with silent ischemia in diabetes. A slow heart rate recovery after exercise is an indirect reflexion of CAN which was shown to be associated silent myocardial ischemia. The association of CAN and silent ischemia has important therapeutic implications, as reduced appreciation of ischemic pain hampers appropriate recognition of myocardial ischemia or infarction, thereby delaying apt therapy.

4. **Myocardial Dysfunction:** CAN is also associated with development of diabetic cardiomyopathy. Diastolic dysfunction i.e. impairment in left ventricle relaxation and passive filling is found to be the earliest manifestation of cardiomyopathy. In the natural presentation of CAN, isolated diastolic dysfunction may contribute to impaired exercise tolerance.

Some studies in T1D patients revealed LV dysfunction may precede or occur in the absence of coronary heart disease or hypertension often with normal ejection fraction. This was also confirmed in large cohort studies in patients who show increased LV mass with concentric remodelling assessed by cardiac magnetic resonance imaging independent of age, sex and other factors. The recent studies have shown T1D patients present with increased LV torsion as an early presentation of LV dysfunction.

5. **Abnormal Blood Pressure Regulation:** Normally, there is nocturnal dip of blood pressure due to predominance of vagal tone and decreased sympathetic tone. In CAN this is altered, resulting nocturnal sympathetic predominance during sleep, causing nocturnal hypertension due to non dipping and reverse dipping of blood pressure.

6. **Orthostatic Hypotension:** It is a fall in systolic or diastolic BP in response to position change from supine to standing. It occurs in diabetes as a result of efferent sympathetic vasomotor denervation causing reduced vasoconstriction of splanchnic and other peripheral vascular beds. It manifests late in CAN and indicates poor prognosis. Symptoms of postural hypertension are shown in Table 1.

Intractable lower limb edema is bothersome. It is a complication of peripheral sympathetic denervation

resulting in ulceration.

CAN and Chronic Kidney disease (CKD): The sympathetic activation in CAN plays a key roll in the pathogenesis of CKD, due to changes in glomerular hemodynamics and in circadian rhythm of BP and albuminuria. A high resting heart rate was also reported in overt nephropathy in T1D patients in another study –Atherosclerosis Risk in Communities (ARIC) Study as shown higher resting heart rate and lower HRV were associated with high risk of developing end stage renal disease.

The most serious consequences of CAN is its association with mortality risk

GASTRO INTESTINAL AUTONOMIC NEUROPATHY

- Esophageal dysfunction –symptoms shown in Table 2.
- Gastro peresis; It is due to delayed gastric emptying and is seen in 50% of long standing diabetic patients, The symptoms are many but non specific. Severe nausea and post prandial vomiting are present in advanced cases. It can complicate diabetes control and affects the quality of life.
- Diabetic diarrhea: it is intermittent in 20 % of DM patients. It is present in those with other forms of autonomic dysfunction. Profuse watery diarrhea esp at night is reported in T1D patients. It may alternate with constipation and its rather difficult to treat and rule out other causes of diarrhea like ingestion of lactose, non absorbable hexitol or drugs.
- Other feature: Diabetic patients may experience fecal incontinence due to poor sphincter tone or severe constipation.

UROGENITAL AUTONOMIC NEUROPATHY

- Bladder dysfunction; It occurs upto 50% of diabetic patients and symptoms are varied –shown in Table 3.
- Erectile dysfunction (ED); It is present in 30 to 75% of men with diabetes. Etiology is multifactorial viz autonomic neuropathy, vascular risk factors like Hypertension, Hyperlipidemia, Obesity, Endothelial dysfunction, Smoking, CVD, Drugs and Psychogenic causes.

Table 3: Urogenital-Symptoms

Bladder Dysfunction	Male Sexual Dysfunction	Female Sexual Dysfunction
Frequency	Erectile Dysfunction	Decreased Sexual Desire
Urgency, Nocturia	Decreased Libido	Increased Pain During Intercourse
Hesitancy, Dribbling	Abnormal Ejaculation	Decreased Sexual Arousal
Weak Stream		Inadequate Lubrication
Urinary Incontinence		
Urinary Retention		

OTHER MANIFESTATION OF AUTONOMIC NEUROPATHY

They are Sudomotor dysfunction like anhidrosis, heat intolerance, dry skin, and hyperhidrosis. Hypoglycemia unawareness is probably due to autonomic neuropathy.

DIAGNOSIS

1. Cardiovascular autonomic neuropathy(CAN)

I. Assess symptoms as shown in table 1

II. Cardiovascular autonomic reflex test(CART)- They are sensitive specific reproducible safe and gold standard tests as per Toronto Consensus Panel on diabetic neuropathy.

a. A change in RR interval with deep breathing is a test of sinus arrhythmia during quiet respiration denoting parasympathetic function.

b. RR response to standing inducing reflex tachycardia followed by bradycardia is due to vagal and baroreflex centered.

c. Valsalva ratio; It evaluates cardio vagal function in response to standard increase in intra thoracic pressure.

d. Orthostatic hypotension

e. BP response to vasalva maneuver and sustained isometric muscular strain – it is used in clinical research only.

f. Though no test is superior, the deep breathing test is the widely accepted test because of its high reproducibility, specificity and simplicity. Valsalva maneuver requires patients co-operation.

g. Beaware of increased intra thoracic, intra ocular and intra cranial pressure, as it may result in intra ocular hemorrhage or lens dislocation.

III. Heart rate variability (HRV) a decrease in HRV is the earliest indicator of CAN.

IV. Baroreflex sensitivity (BRS): It is useful to assess the capability to reflex increase in vagal activity and decrease in sympathetic activity due to sudden rise of BP. It is again used for research purpose. BRS detects sub clinical CAN even before other tests of CAN. It is an independent risk predictor of cardiac mortality in patients with heart failure, a recent MI or diabetes.

V. Imaging Techniques for CAN. Quantitative

scintigraphic assessment of sympathetic denervation of human heart is done with positron emission tomography by using many techniques. Though it is valuable test, it is not much applied due to cost constraint and sophisticated infrastructure and skilled personnel.

VI. Muscle sympathetic Nerve Activity (MSNA) – It is done by recording electrical activity of a skeletal muscle like peroneal, tibial, or radial at rest or in response to physiological excursions via micro electrodes placed on a fascicle of a distal sympathetic nerve to the skin or muscle and identification of sympathetic burst. Fully automated sympathetic neurogram provides good MSNA. It is not indicated as routine but used as a research tool.

VII. Head-up tilt-Table Testing(HUTT) – it is used to investigate CAN, a neutrally mediated – vaso vagal syncope. It records wide range of changes in the autonomic input to heart and in the RR intervals induced by rapid positional changes during the test. HUTT requires skilled personnel and so not used as a routine.

2. Gastro Intestinal Autonomic Neuropathy (Gastro paresis)

A. Symptoms – Diabetes bowel symptoms questionnaire is used in diabetic patients to quantify gastro intestinal symptoms. But its predictive value is poor. Objective measurements of gastric emptying are used to diagnose gastro paresis

B. Gastric emptying study: it is a sensitive test but affected by many factors like drugs smoking and blood glucose levels. The standardization of testing is vital. The use of this test is limited by poor correlation with symptoms and individual variability. A barium meal or upper endoscopy are recommended to rule out mucosal obstruction. Scintigraphy is a gold standard test for measurement of gastric emptying. It also helps to find the intra gastric distribution of meal. It is frequently abnormal in diabetic patients. Scintigraphy has its own limitation as it involves radiation expense and standardization. Breath test is safe and inexpensive and correlates with scintigraphy result. Ultra sonography is another diagnostic non invasive method.

Magnetic resonance Imaging(MRI) is useful to

measure gastric emptying and motility with excellent reproducibility. But it is limited for research. Other investigations are surface electro gastrography,monometry are all used to assess gastric, intestinal motility,but reserved for research purpose.

3. **Erectile Dysfunction: Clinical assessment :** Assess the patients with ED by eliciting sexual, medical history, drug use like tranquilizers, antidepressants, anti hypertensives psychic and organic factors.It aids to assess the nature of erectile problem and to differentiate from other sexual problems like penile curvature or pre mature ejaculation. Elicit history from the partner also and it will help to show other causes like vaginal dryness, dysparunia. International index of erectile function and sexual encounter profile are helpful to assess severity of ED.

Lab investigations: Routine lab test like A1c, Fasting blood glucose and lipid profile are done. Testosterone level is also done to rule out primary or hypo gonadotropic hypogonadism esp in patients not responding to phosphodiesterase type 5 inhibitors (PDE-5). The other useful tests are evaluation of nocturnal penile tumescence,penile Doppler ultra sound, bulbocavernosus reflex,dorsal sensory nerve conduction of the penis, amplitude and latency of penile sympathetic skin response, pudendal nerve somatosensory evoked potentials, assessment of prostaglandin E1 (PGE1) effect on erection, psychological evaluation, and urodynamic studies.

4. **Bladder Dysfunction:**

- a. Clinical assessment – lower urinary tract symptoms (LUTS) can be assessed by eliciting history of nocturia, frequency, urgency, weak urinary stream, intermittency, straining and sensation of incomplete emptying.The American urological association symptom index can assess the severity-scores range from 0 to 35.0 to 7- none, 8 to 19 –mild, 20 to 35 –severe.

Checking perineal sensation, sphincter tone and bulbocavernous reflex can recognize peripheral neuropathy in diabetes.Uro gynecological evaluation is required to exclude pelvic organ prolapsed or other pelvic disorder.

- b. Lab investigations: as diabetic patients are at increased risk of bacterial cystitis, microscopic urine analysis and culture are essential to assess the patients complaining of LUTS.

Do a total count as polymorpho leucocytes function is altered in LUTS.

- c. **Urodynamic Study-** It is indicated if initial management is unsuccessful or there is doubt about the diagnosis.It includes cytometry, uroflow study etc., urodynamic findings associated with

autonomic dysfunction reveal impaired bladder sensation, increased cystometric capacity, decreased detrusor contractility and increased post voidal residual urine.

5. **Sudomotor Dysfunction**

Though there are several methods like quantitative sudomotor axon reflex test, it has own limitation Recently sudoscan + is a non invasive device that uses reverse iontophoresis and chrono amperametry to test for sudomotor dysfunction.It is an easier technique.

6. **Micro Vascular Function Assessment: Laser Doppler (LD)** is useful to assess micro vascular blood flow and endothelial function.

7. **Treatment:**

- a. Glycemic intensive control in T1D patients has shown reversal of CAN or delayal of progression of CAN,as shown in DCCT and EDIC. They all indicate, it is advisable to initiate treatment of T1D intensively as early as possible. But in T2D the effects of glycemic control is less clear.

- b. Stratification of multiple risk factors – cardiovascular risk intervention targeting glucose, BP, Lipids Smoking etc., reduced the progression or development of CAN in diabetic patients.

- c. Other treatment – Anti oxidants have not shown any benefit.

- d. **Symptomatic Treatment –**

1. **Orthostatic hypo tension**

- A. **Life Style Measures.**

- Avoid sudden changes in body positions from lying to sitting then sitting to standing and sub sequently standing to walking
- Avoid drugs that precipitate hypotension-tricyclic antidepressants, pheno thiazines, diuretics.
- Eat small but frequent meals
- Avoid stressful activity.
- Elevate the Head end of the bed to 1.5 feet at night.
- Use stockings over legs and inflatable band on abdomen.
- Avoid physical manoeuvres like leg crossing, squatting, have fluid and salt unless contra indicated.

- B. **Drugs-**

1. Midodrine is a alpha 1 adreno receptor agonist, approved by FDA. Dose 2.5 to 10 mg tid – qid, first dose to be taken before arising.

2. Avoid taking several hours before lying posture.

3. Adverse effects –Piloerection. pruritus, parasthesia supine hypertension, urinary retention.

4. Fludrocortisone- It is a synthetic mineralo corticoid of long duration of action inducing plasma expansion. It increases sensitivity of blood vessels to catecholamines. The drug effects are not immediate. It may take 1 to 2 weeks to act. Dose; Begin with 0.05 mg at bed time titrate it gradually to a maximum of 0.2 mg per day. High doses may have side effects- supine hypertension, hypokalemia, hypomagnesimia, congestive heart failure and peripheral edema, Be cautious in congestive heart failure to avoid fluid over load.
5. Erythropoietin - It improves Standing BP in patients with orthostatic hypertension. It acts by increasing red cell mass central blood volume, correcting the anemia, altering blood viscosity regulating neuro humoral effect of vascular wall and tone. Be cautious of cardio vascular effects.
6. Somatostatin analogues – It regulates post prandial BP fall and orthostatic hypertension in patients with autonomic failure. It acts by influencing splanchnic vessels by inhibiting release of vasoactive gastro intestinal peptides. It enhances cardiac output and increase in forearm and splanchnic vascular resistance. Dose; 25 to 200 mcg per day subcutaneously tds. Long acting depot 20 to 30 mg IM once monthly. Adverse effects- severe hypertension
7. Caffeine citrate- It is a methyl Xanthene derivative it has a pressor effect by blocking vasodilating adenosine receptors. It improves orthostatic hypotension and reduces post prandial hypotension- Dose- 100 to 250 mg orally tds. It is taken as tablet or caffeinated drinks. Tachyphylaxis may occur due to prolonged use.

GASTROPARESIS

- A. Diet changes- Eat multiple small meals and reduce dietary fat and fibre.
- B. Drugs-1) Metoclorpropamide – yet to be approved by FDA.
It is an anti emetic. It stimulates acetyl choline release in myentric plexus and is a dopamine agonist. Be cautious of its adverse effects lik extra pyramidal symptoms.
Do not use more than 5 days. It is not advised on long term basis. It is reserved for severe cases not responding to other treatment.
2. Domperidone – Not FDA approved- It is a dopamine receptor antagonist. It is an anti emetic. It is a prokinetic stimulating gastric motility-both liquid and solid phase gastric emptying. Its role is controversarial due to its adverse effects.
3. Erythromycin- It increases gastric emptying. It stimulates motilin receptors in the gut. Oral or iv
4. Onabotulinumtoxin A (BOTULINUM TOXIN TYPE A); It is for severe diabetic gastroparesis, not

responding to dietary modifications and high dose prokinetic drugs.

- C. Other non drug therapy 1) Gastric Pacing (stimulation) – it has shown improvement in nausea and vomiting in patients with gastric peresis
Surgery- Feeding jejunostomy bypassing an atonic stomach and radical approach by resection of large part of stomach by Roux- en -Y loop.

DIABETIC DIARRHEA- DRUGS

1. Metronidazole 500mg qid for 3 weeks
2. Ampicillin or tetracycline 250 mg tds or qid for 2 weeks
3. Amoxicillin(875 mg) / clavulanate bd for 2 weeks.
4. Cholestyramine
5. Octatide- it enhances gastric emptying and delays small bowl to large bowl transit. It is useful if other treatment is not beneficial.

ERECTILE DYSFUNCTION

Drugs: Phosphodiesterase -5 inhibitors (PDE-5) are helpful ex., Sildenafil Tadalafil Vardenafil. Be cautious in prescribing for patients taking nitrates. Frequent side effects are head ache, flushing.

Non drug therapy: Intra cavernosal injection – success rate 90%, vacuum devices, penileimplants, inflatable prosthesis –show mild to moderate benefit.

BLADDER DYSFUNCTION

Bethanechol- parasymphathomemetic agent helps.

Bladder training like scheduled voiding, credes method –suprapubic compression by self to evacuate urinary bladder to avoid retention.

CONCLUSION

Autonomic neuropathies complicate diabetes commonly with varied manifestations and high morbidity. The exact pathophysiology is yet to be understood. We are still behind the therapeutic approach. Glycemic control is effective esp in T1D patients. Life style modification may be helpful in some T2D Patients or pre diabetics. Though there are so many modalities of treatment, we can only offer symptomatic relief to many patients with severe autonomic neuropathy.

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