

Diabetic autonomic neuropathy: a clinical update

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Abstract

Diabetic autonomic neuropathy is an under-recognised complication of diabetes and the prediabetic state. A wide range of manifestations can be seen due to involvement of cardiovascular, gastrointestinal, genitourinary, sudomotor and neuroendocrine systems. Cardiac autonomic neuropathy is the most dreaded complication carrying significant mortality and morbidity.

Early detection and control of diabetes and other cardiovascular risk factors is the key to treat and prevent progression of autonomic neuropathy. Recently, a new entity of treatment-induced neuropathy (TIND) of diabetes mellitus causing autonomic neuropathy is being increasingly recognised.

Keywords: diabetic autonomic neuropathy, cardiac autonomic neuropathy, treatment-induced neuropathy

Financial and Competing Interests: No conflict of interests declared

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Introduction

The incidence and prevalence of diabetes mellitus (DM) is increasing all over the world, with an estimated 425 million people suffering from DM.¹ Peripheral neuropathy and autonomic neuropathy are complications of uncontrolled DM. Dysautonomia can manifest as generalised autonomic neuropathy, prediabetic state causing autonomic neuropathy and treatment-induced neuropathy (TIND). Dysautonomia may also occur during and after hypoglycemia.² In this review we have tried to bring the reader up to date with recent advances in the management of this challenging complication of DM.

Diabetic autonomic neuropathy (DAN) has been defined as a disorder of the autonomic nervous system in the setting of DM or metabolic derangements of prediabetes after exclusion of other causes.^{3–5} Autonomic neuropathy is often missed unless it is overtly symptomatic. In all diabetic patients one should elicit history of dysautonomia and confirm it by physical examination, as it is associated with increased mortality. Autonomic neuropathy can be cardiac autonomic neuropathy (CAN), sudomotor neuropathy, gastrointestinal autonomic neuropathy, and urogenital autonomic neuropathy.

Pathophysiology

The exact pathophysiology of diabetic neuropathy is unclear. Hyperglycaemia and dyslipidemia are known to affect nerve axons, dorsal root ganglia and Schwann cells. Multiple mechanisms have been invoked in causing nerve injury and death including polyol pathway activation, oxidative stress,

protein kinase C (PKC) activation and advanced glycation end-products (AGEs) formation. Hyperglycaemia and vascular risk factors activate these noxious pathways which cause injury to microvascular endothelium, nerve support cells and axons.⁶ Recently, however, the focus has been on dyslipidemia and elevated triacylglycerols as a source of non-esterified fatty acid (NEFA) in type 2 DM. NEFA are catabolised by beta oxidation leading to accumulation of acetyl CoA and its conversion to toxic acylcarnitine which contributes to nerve injury. The oxidation of low-density lipoproteins (LDLs) can induce reactive oxygen species generation and activate receptors for advanced glycation end products, oxidised LDLs and TLR4 exacerbating nerve injury. There is increasing evidence that altered sphingolipid metabolism in type 2 diabetes results in formation of atypical neurotoxic deoxysphingolipids which also contribute to nerve damage.⁷ This pathophysiology is common for all forms of diabetic neuropathy.

Cardiovascular autonomic neuropathy

Symptoms and risk factors

Cardiovascular autonomic neuropathy is defined as impairment of autonomic control of the cardiovascular system.^{3–5} CAN should be suspected in a diabetic/prediabetic patients when they have resting tachycardia, postural tachycardia, reduced heart rate variability, bradycardia, decreased exercise tolerance, orthostatic hypotension, supine hypertension, or intra/post-op cardiovascular instability. Patients at greater risk of CAN are those with increasing age, uncontrolled DM, cardiovascular risk factors, diabetic complications and those

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who smoke.⁸ Inflammation and oxidative stress are predictors of deterioration of CAN.^{9,10} Inflammatory biomarkers have been independently associated with more impaired cardiac autonomic reflex tests suggesting the role of inflammation in pathogenesis of CAN.^{10,11} CAN has possibly some underlying genetic predisposition in view of the association of CAN with genes encoding a few microRNAs i.e. MIR 146a, MIR 27a, MIR 499. MicroRNAs are regulators of gene expression at post-transcriptional level which are involved in many pathways that are dysregulated in diabetes.^{12,13} Low levels of vitamin B12 and vitamin D have been associated with CAN.^{14,15}

Diagnosis of CAN

The diagnosis of CAN is based on symptoms which occur more on standing and include lightheadedness, weakness, palpitation, fainting and syncope. They can be assessed using a Compass 31 questionnaire¹⁶ which has reasonable sensitivity and specificity. Cardiovascular signs like tachycardia, orthostatic hypotension, reverse dipping and non-dipping on ambulatory blood pressure monitoring may point towards CAN.⁹

The 2017 American Diabetes Association (ADA) recommendations:¹⁷

- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular and neuropathic complications.
- In the presence of symptoms or signs of CAN, tests excluding other comorbidities or drug effects should be performed.
- Consider assessing symptoms and signs of CAN in patients of hypoglycaemia unawareness.

Cardiovascular autonomic reflex testing (CARTs) are the gold standard in autonomic testing for establishing the diagnosis of CAN as stated in the Toronto Consensus document.^{4,18} They include tests of predominantly parasympathetic function which include heart rate variability to deep breathing, heart rate response to standing and heart rate response to Valsalva manoeuvre. Tests of predominant sympathetic adrenergic function are beat-to-beat blood pressure response to Valsalva manoeuvre, and the systolic and diastolic blood pressure changes in response to tilt table or active standing. Tests of sympathetic cholinergic function are quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat testing and sympathetic skin response (SSR).^{18–20} The diagnosis and staging of cardiovascular autonomic neuropathy require these tests. Early or possible CAN requires one abnormal cardiovagal test; definite or confirmed CAN requires two abnormal cardiovagal tests and severe or advanced CAN requires the additional presence of orthostatic hypotension (Table 1).^{4,9}

Subtle degrees of CAN can be detected by iodine-123 meta-iodobenzylguanidine (MIBG) scan or 11C-hydroxyephedrine scintigraphy of the heart. In addition, small nerve-fibre function using neurometer, neuropad plaster patch, sudoscan may be used as a surrogate marker for CAN.^{7,9} Skin biopsy has been used in confirming small fibre neuropathy by

evaluating intraepidermal nerve fibre density (IENFD). It has good test characteristics for diagnosing neuropathy (AUC = 0.76) and for small fibre neuropathy (AUC = 0.82).⁷ Corneal confocal microscopy (CCM) which measures corneal small-fibre innervation may also be used to diagnose CAN with a sensitivity of 86%–100% and specificity of 56%–78%.^{7,19,20} Optical coherence tomography (OCT) measuring retinal nerve fibre layer may be useful in detecting early diabetic peripheral neuropathy (DPN). Both are reliable, repeatable, non-invasive methods that hold promise in early detection of DPN.⁷

Management of CAN

CAN is the commonest and most studied form of DAN. The preventive and pathogenetic treatment of CAN is similar for other forms of DAN and diabetic sensorimotor polyneuropathy reiterates the common pathophysiology that all forms of diabetic neuropathy share.

Prevention of CAN

Several observational studies have demonstrated that glucose control is essential for prevention of neuropathy in type 1 & 2 diabetes. However, the various Diabetes Control and Complications Trial / Epidemiology of Diabetes Intervention and Complication (DCCT/EDIC) studies have demonstrated that intensive glycaemic control prevents or delays DPN and CAN in type 1 diabetes. The effect of glycaemic control on DPN or CAN are less conclusive for type 2 diabetes. ACCORD, the largest type 2 diabetes trial, reported significant DPN reduction after five years' follow-up.²¹ No effects were observed with other large trials although the United Kingdom Prospective Diabetes Study reported a modest risk reduction with intensive treatment after 15 years of follow-up. The presence of multiple comorbidities in these patients might have attenuated the effect of glucose control.^{8,22} The DCCT/EDIC study demonstrated that intensive glucose control reduced the risk of developing DPN and CAN in patients with type 1 diabetes followed for more than 23 years. During this study 33% patients developed DPN and 44% developed CAN.

The 2017 ADA recommendations for preventive treatment are:¹⁷

- Optimise glucose control as early as possible to prevent or delay the development of CAN in people with type 1 diabetes.
- Consider a multifactorial approach targeting glycaemia among other risk factors to prevent CAN in people with type 2 diabetes.
- Consider lifestyle modifications to improve CAN in patients with prediabetes.

Pathogenetic and pharmacological treatment of CAN

This involves targeting underlying pathophysiological mechanisms to improve neuronal function. Some of these therapies have shown efficacy in RCTs, but not translated into clinically meaningful results. Alpha-lipoic acid, epalrestat and benfotiamine are used in some countries to target

Table 1 Diagnostic tests of diabetic autonomic neuropathy**Cardiovascular autonomic testing****Tests of predominantly parasympathetic function**

- Heart rate variability to deep breathing (i.e. supine position with the subject breathing at a fixed rate of five breaths per minute during a six-minute period): Analysed by the heart rate variability and the expiratory to inspiratory ratio
- Heart rate response to standing (the 30:15 ratio)
- Heart rate response to Valsalva manoeuvre (the Valsalva ratio)

Sympathetic system evaluation

- Blood pressure response to a Valsalva manoeuvre (drop in phase 2, the phase 4 overshoot)
- The systolic and diastolic blood pressure change in response to tilt table testing or active standing
- Handgrip dynamometer

Tests of sympathetic cholinergic function

- Quantitative sudomotor axon reflex testing (QSART)
- Thermoregulatory sweat testing (TST)
- Sympathetic skin response (SSR)

Direct assessment of cardiac autonomic integrity by scintigraphic imaging**Gastrointestinal autonomic testing**

- Gastric emptying scintigraphy
- Isotope-based breath test
- Anorectal manometry for evaluating sphincter tone

Urologic autonomic function testing

- Post-void residual urine
- Urodynamic studies
- Measurement of nocturnal penile tumescence
- Measurement of penile and brachial blood pressure with Doppler probes and
- calculation of the penile-brachial pressure index (<0.7 suggests penile vascular disease)

Pupillary autonomic function testing

- Pupillometry

these pathophysiological mechanisms. There are currently no FDA-approved disease modifying treatments for CAN. Lifestyle measures, like weight loss and exercise, may be of some benefit in view of obesity being an important risk factor as well hyperglycaemia.^{7,9} All the above holds true for all forms of diabetic neuropathy. The SGLT2i group of antidiabetic drugs may have a beneficial modulatory effect on cardiovascular autonomic function.²³

Symptomatic treatment of CAN

Treatment of symptomatic patients with orthostatic hypotension (OH) requires stopping drugs that worsen OH, volume correction and strength training.⁹ Pharmacological therapy has included fludrocortisone (0.1–0.4 mg), midodrine, an alpha adrenoceptor agonist, in doses of 2.5 mg to 5 mg twice a day. Droxidopa, an orally administered norepinephrine prodrug, is used for neurogenic OH; however, its role in CAN-associated OH is not well established.²⁴ Octreotide 50 µg three times a day subcutaneously may be helpful in patients with postprandial hypotension. Fludrocortisone and midodrine should be used carefully because of the risk of supine hypertension.

Gastrointestinal autonomic neuropathy

The major gastrointestinal manifestations include gastroesophageal reflux disease (GERD), gastroparesis, diabetic diarrhoea, faecal incontinence, gallbladder atony and enlargement. All these manifestations are managed symptomatically. The ADA recommends evaluating for gastroparesis in people with diabetic neuropathy, retinopathy and/or nephropathy by assessing for symptoms of unexpected glycaemic variability, early satiety, bloating, nausea, and vomiting. Treatment of diabetic gastroparesis involves taking small, frequent meals, preferably semiliquid along with prokinetic agents, preferably metoclopramide or itopride. A low-fibre and low-fat diet is advisable. It is necessary to avoid carbonated drinks and chewing gum. Patients with diabetic gastroparesis should discontinue the use of incretin drugs (GLP1 analogues and DPP4 inhibitors). Patients with small intestinal bacterial overgrowth syndrome should be given antibiotic therapy i.e. metronidazole and rifaximin and a diet with restricted products with high fermentation potential. For diabetic diarrhoea, avoiding metformin and using loperamide on an 'as and when required' basis is recommended. Treatment of GERD involves use of proton pump inhibitors and prokinetic agents along with non-pharmacological methods.^{2,25}

Genitourinary autonomic neuropathy

Diabetic genitourinary neuropathy-related manifestations result in bladder dysfunction, erectile dysfunction, retrograde ejaculation, and dyspareunia. Symptoms may be present in 50% of individuals with diabetes in varying combination. All these manifestations are treated symptomatically. Diabetic bladder dysfunction should initially be evaluated by a post-void residual urine ultrasound and further evaluated by complete urodynamic testing if necessary. The initial treatment consists of removing medications that impair detrusor activity (anticholinergics, tricyclic antidepressants, and calcium channel antagonists) or agents that increase urethral sphincter tone. Treatment comprises a strict voluntary urination schedule, frequently coupled with the Credeé maneuver.² Phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil are first-line therapies for erectile dysfunction in diabetes.

Peripheral sudomotor and vasomotor neuropathy

The peripheral sympathetic cholinergic system regulates sweat function and thermoregulation. Peripheral autonomic nerve dysfunction causes change in skin texture, oedema, venous prominence, loss of nails, dryness, sweating abnormality of feet. It contributes to foot ulceration and Charcot arthropathy. QSART and SSR can be used to detect sympathetic denervation.^{19,20}


Small-fibre neuropathy can be assessed using skin biopsy as nerve conduction velocity studies are able to demonstrate mainly large-fibre neuropathy.²⁶ The assessment of sweat gland nerve-fibre density can be used as a marker of sudomotor neuropathy.²⁷ Therapy involves meticulous foot care.

Treatment induced neuropathy of diabetes (TIND)

This entity has been described in recent times and has been found to occur in patients where rapid glycaemic control is achieved in the presence of high pre-treatment HbA1c.

It has been described in both type 1 & 2 DM and with insulin or oral hypoglycaemic agents. Dysautonomia and neuralgia are the cardinal features of TIND. These symptoms are more severe than seen in generalised DPN. Dysautonomia does improve over time, especially in type 1 DM. Nephropathy and retinopathy are known to increase concomitantly. The underlying pathophysiology is not known.²

Conclusions

DAN, though common, remains underdiagnosed, thus contributing to the morbidity of DM and may not be reversible. The ADA therefore recommends screening for DAN at the time of diagnosis of type 2 DM and five years after the diagnosis of type 1 DM. Screening should include a history eliciting symptoms of poor exercise tolerance, orthostatic symptoms, fainting, diarrhoea, GERD, erectile dysfunction, voiding symptoms, skin changes, hypoglycaemia unawareness, and physical examination for signs of autonomic dysfunction. Tests of heart rate variability may be indicated. If initial screening is negative, a history and physical examination for signs of autonomic dysfunction should be repeated annually. The identification of subclinical DAN is useful for risk stratification and for individualisation of glycaemic, lipid and blood targets.⁹ 

References

- 1 Feldman EL, Callaghan BC, Pop-Busui R et al. Diabetic neuropathy. *Nat Rev Dis Primers* 2019; 5: 42.
- 2 Freeman R. Autonomic Peripheral Neuropathy. *Continuum (Minneapolis)* 2020; 26: 58–71.
- 3 Tesfaye S, Boulton AJ, Dyck PJ et al. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33: 2285–93.
- 4 Spallone V, Ziegler D, Freeman R et al. Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011; 27: 639–53.
- 5 Bernardi L, Spallone V, Stevens M et al. Toronto Consensus Panel on Diabetic Neuropathy. Methods of investigation for cardiac autonomic dysfunction in human research studies. *Diabetes Metab Res Rev* 2011; 27: 654–64.
- 6 Feldmann EL, Nave KA, Jenett TS et al. New Horizons in diabetic neuropathy: mechanisms, bioenergetics and pain. *Neuron* 2017; 93: 1296–313.
- 7 Callaghan BC, Gallagher G, Fridman V et al. Diabetic Neuropathy: what does the future hold? *Diabetologia* 2020; 63: 891–97.
- 8 Braffet BH, Gubitosi-Klug RA, Albers JW et al and the DCCT/EDIC research group: Risk factors for Diabetic Peripheral Neuropathy and Cardiovascular Autonomic Neuropathy in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes* 2020; 69: 1000–10.
- 9 Spallone V. Update on the Impact, Diagnosis and Management of Cardiovascular Autonomic Neuropathy in Diabetes: What Is Defined, What Is New, and What Is Unmet. *Diabetes Metab J* 2019; 43: 3–30.
- 10 Heng Yang, Sloan G, Yingchun Ye et al. New Perspective in Diabetic Neuropathy: From the Periphery to the Brain, a Call for Early Detection, and Precision Medicine *Front Endocrinol (Lausanne)* 2019, 10: 929.
- 11 Herder C, Schamarek I, Nowotny B et al. German Diabetes Study Group. Inflammatory markers are associated with cardiac autonomic dysfunction in recent-onset type 2 diabetes. *Heart* 2017; 103: 63–74
- 12 Ciccacci C, Morganti R, Di Fusco D et al. Common polymorphisms in MIR146a, MIR128a and MIR27a genes contribute to neuropathy susceptibility in type 2 diabetes. *Acta Diabetol* 2014; 51: 663–71.

- 13 Ciccacci C, Latini A, Greco C et al. Association between a MIR499A polymorphism and diabetic neuropathy in type 2 diabetes. *J Diabetes Complications* 2018; 32: 11–17.
- 14 Hansen CS, Jensen JS, Ridderstrale M et al. Vitamin B12 deficiency is associated with cardiovascular autonomic neuropathy in patients with type 2 diabetes. *J Diabetes Complications* 2017; 31: 202–8.
- 15 Maser RE, Lenhard MJ, Pohl RT. Vitamin D insufficiency is associated with reduced parasympathetic nerve fiber function in type 2 diabetes. *Endocr Pract* 2015; 21: 174–81.
- 16 Sletten DM, Suarez GA, Low PA et al. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clin Proc* 2012; 87: 1196–201.
- 17 Pop-Busui R, Boulton AJM, Feldman EL et al. Diabetic Neuropathy: A Position Statement of American Diabetic Association. *Diabetes Care* 2017; 40: 136–54.
- 18 England JD, Gronseth GS, Franklin G et al. American Academy of Neurology. Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009; 72: 177–84.
- 19 Azmi S, Petropoulos IN, Ferdousi M et al. An update on the diagnosis and treatment of diabetic somatic and autonomic neuropathy. *F1000Res.* 2019; 8: F1000 Faculty Rev-186. doi:10.12688/f1000research.17118.1
- 20 Azmi S, Ferdousi M, Kalteniece A et al. Diagnosing and managing diabetic somatic and autonomic neuropathy. *Ther Adv Endocrinol Metab* 2019; 10: 1–10.
- 21 Pop-Busui R, Evans GW, Gerstein HC et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; 33: 1578–84.
- 22 Ang L, Jaiswal M, Martin C et al. Glucose Control and Diabetic Neuropathy: Lessons from Recent Large Clinical Trials. *Curr Diab Rep* 2014; 14: 528.
- 23 Jordan J, Tank J, Heusser K et al. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. *J Am Soc Hypertens* 2017; 11: 604–12.
- 24 Issacson S, Shill HA, Vernino S et al. Safety and Durability of Effect with Long-Term, Open-Label Droxidopa Treatment in Patients with Symptomatic Neurogenic Orthostatic Hypotension. *J Parkinsons Dis* 2016; 6: 751.
- 25 Kuźnik E, Dudkowiak R, Adamiec R et al. Diabetic autonomic neuropathy of the gastrointestinal tract. *Gastroenterol* 2020; 15: 89–93.
- 26 Luo KR, Chao CC, Chen YT et al. Quantitation of sudomotor innervation in skin biopsies of patients with diabetic neuropathy. *J Neuropathol Exp Neurol* 2011; 70: 930–38.
- 27 Gibbons CH, Illigens BM, Wang N et al. Quantification of sweat gland innervation: a clinical-pathologic correlation. *Neurology* 2009; 72: 1479–86.