Diabetic autonomic neuropathy

An oft neglected entity

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Autonomic neuropathy is a common complication of diabetes that can manifest in a range of different organ systems. It represents a major source of morbidity, mortality and healthcare use.

Key points

- **Diabetic autonomic neuropathy (DAN) is common and important but generally under-recognised.**
- **DAN is not a single entity, but an 'umbrella term' with broad clinical implications reflecting the diffuse and integral involvement of the autonomic nervous system with major body organ systems.**
- **Cardiac autonomic neuropathy is a particularly serious manifestation that may be associated with silent myocardial infarction and represents a major risk for cardiovascular (CV) mortality.**
- **Simple inexpensive tests of cardiac autonomic function are markedly underused.**
- **Gastric autonomic neuropathy is not only associated with upper gastrointestinal symptoms but also has impacts on postprandial blood glucose control.**
- **Erectile dysfunction, another manifestation of autonomic neuropathy, is common in men with diabetes and a marker of disordered CV function.**

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Diabetic autonomic neuropathy: common, poorly understood and underestimated in severity

Because the autonomic nervous system innervates every organ in the body, diabetic autonomic neuropathy (DAN) has diverse and often nonspecific manifestations. These range from silent myocardial infarction (MI), cardiomyopathy, ischaemic strokes and orthostatic hypotension on one hand to gastroparesis, diarrhoea, erectile dysfunction (ED) and urinary retention on the other. Although the prevalence of DAN remains uncertain due to lack of standardisation in definition, diagnostic criteria, study populations and methodologies adopted, even by conservative estimates it is likely to be as high as 40% of the diabetic population (type 1 or 2 diabetes).[1]

In this article we focus on three systems in which DAN manifests: cardiac autonomic neuropathy (CAN), gastrointestinal autonomic neuropathy (GAN) and ED.

A summary of features of other major systems in which DAN is involved is provided in the Table.

Pathogenesis of diabetic autonomic neuropathy

The pathogenesis of DAN remains poorly understood but is thought to be multifactorial.[2] Proposed mechanisms include:

- hyperglycaemia – by a direct effect on the autonomic nerves (involving the polyol pathway)
- advanced glycation end-products (AGE) – the interaction between AGE and its receptor (RAGE) may have a direct impact
- proinflammatory mechanisms
- 'stress' on endoplasmic reticulum – increased nitric oxide and accumulation of peroxynitrite may cause endothelial and neuronal damage (nitrosative stress)
- immunological mechanisms – for example, autoantibodies to autonomic nerve structures in patients with type 1 diabetes, lymphocytic infiltration, circulating immune complexes and activated T-cells.

Table. Lower GI, bladder, sudomotor and pupillary dysfunction in diabetes: signs, symptoms and diagnostic tests

System	Symptoms and signs	Tests	Comments
Lower GI	• Diarrhoea • Incontinence • Constipation	Tests of anorectal motor and sensory function are in clinical use	Small intestinal motility has been measured in research studies with manometry and scintigraphic techniques
Bladder	• Urinary incontinence • Retention • Difficulty in initiating micturation reflex • UTI	• Validated questionnaires • Urodynamic testing	Diabetic cystopathy may occur in up to 80% of patients with type 1 diabetes Urinary incontinence is strongly associated with type 1 but not type 2 diabetes
Sudomotor (sweat)	• Dry skin • Itching • Foot ulcers	• TST • QSART • Silicone impressions • Indicator plaster	Combining tests improves sensitivity and specificity
Pupillary	• Visual difficulty • Light insensitivity • Argyll-Robertson pupil	Tests of pupillary function	Tests are currently used only in research studies and not in clinical practice

Abbreviations: DAN = diabetic autonomic neuropathy; GI = gastrointestinal; QSART = quantitative sudomotor axon reflex test; TST = thermoregulatory sweat test; UTI = urinary tract infection.

Cardiac autonomic neuropathy: the most lethal manifestation

CAN encompasses neuropathic damage of autonomic nerves supplying the heart and the systemic vasculature. A meta-analysis indicated a relative mortality risk of 3.45 (95% confidence interval, 2.66 to 4.47) in patients with diabetes and symptomatic CAN compared with those without CAN.[3] CAN is linked to MI ('silent MI'; Figure 1).[4] It is often overlooked during the assessment of patients, even in those with known coexisting cardiovascular disease (CVD); however, it probably has a greater impact than traditional CVD risk factors (hypertension, hyperlipidaemia) on CVD mortality, even in patients who are 'asymptomatic'.

The consequences of CAN include MI, cardiomyopathy, and orthostatic and postprandial hypotension. Orthostatic hypotension is defined as a fall of ≥30 mmHg in systolic blood pressure or ≥10 mmHg in diastolic blood pressure within two minutes of standing and symptoms include dizziness, syncope and visual impairment. Postprandial hypotension is defined as a fall of ≥20 mmHg in systolic blood pressure within two hours of a meal. Approaches to the diagnosis and management of orthostatic (postural) hypotension are described elsewhere.[5]

The presence of CAN increases the already greater perioperative and intraoperative risk in patients with diabetes and has implications in those undergoing anaesthesia. The haemodynamic response to induction and tracheal intubation is disturbed in patients with CAN and they are at a higher risk for hypothermia and CV instability intraoperatively.[6]

Diabetic autonomic neuropathy and hypoglycaemia

The normal counter-regulatory response to hypoglycaemia includes inhibition of insulin and release of glucagon and adrenaline. These responses may be impaired in patients with diabetes and established autonomic neuropathy so that they are at high risk of 'severe' hypoglycaemia (low blood glucose level that requires assistance from another person to manage). Patients with self-reported hypoglycaemia have more than a threefold increased risk of five-year mortality.[7]

Traditionally, autonomic neuropathy has not been considered critical to the development of hypoglycaemia unawareness (inability to detect sympathoadrenal symptoms and a consequent increased risk of neurological manifestations),[8] but this is probably incorrect.[2] Autonomic neuropathy may increase the propensity for cardiac arrhythmias with hypoglycaemia. These issues are important. Although recent large-scale trials of intensive glucose control (ACCORD, ADVANCE, VADT and the UKPDS 10-year follow-up) have established the benefits of intensive blood glucose control on the prevention of microvascular complications in type 2 diabetes, improvement in CV outcomes may be expected in only a subset – i.e. younger patients with recent diagnosis and without CV complications ('good metabolic legacy' effect).[9-12] Accordingly, in older patients with a long duration of diabetes and established CVD, intensive glucose control increases the risk of hypoglycaemia and could potentially increase CV mortality. Hence, an aim of treatment should be to optimise glycaemic control without inducing hypoglycaemia.[13]

Testing for cardiac autonomic neuropathy

Simple, inexpensive and noninvasive cardiovascular autonomic reflex tests developed by Ewing and Clarke in the 1980s are safe and standardised with good reproducibility.[14] These five simple tests require access only to an ECG machine and a sphygmomanometer that assess responses of R-R interval and blood pressure to the Valsalva manoeuvre,

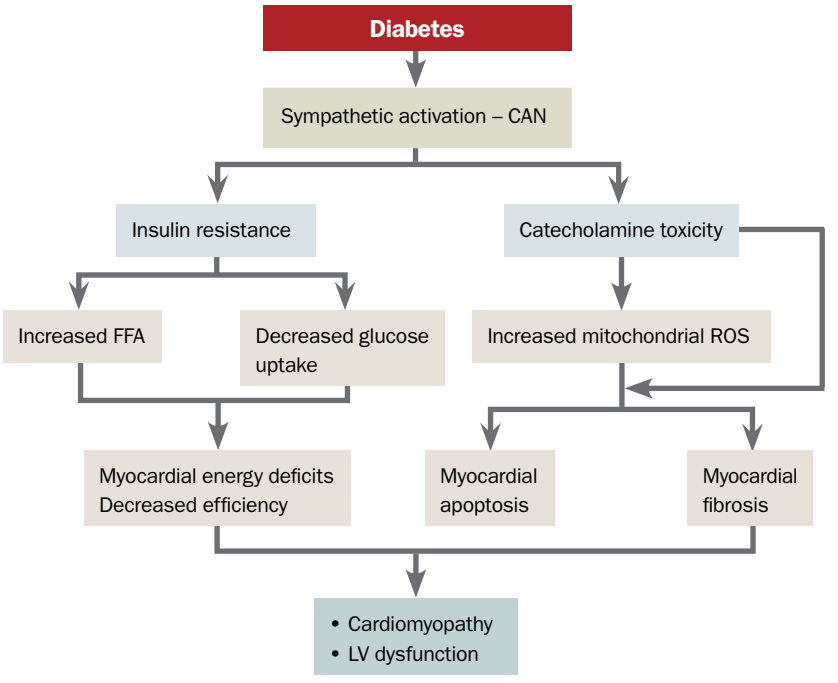

Figure 1. Proposed link between cardiac autonomic neuropathy and myocardial infarction.

Reproduced with permission from Pop-Busui R. J Cardiovasc Transl Res 2012; 5: 463-478.[4]

Abbreviations: CAN = cardiac autonomic neuropathy; FFA = free fatty acids; LV = left ventricular; ROS = reactive oxygen species.

deep breathing and posture change (Box). Unfortunately, these are not used as widely as they should be. They can be performed by medical practitioners, as well as trained nursing staff, outside of specialised centres.

Gastointestinal autonomic neuropathy: quality of life and postprandial blood glucose effects

Gastroparesis, defined as delayed gastric emptying in the absence of mechanical obstruction, is the most important manifestation of GAN and is evident in 30 to 50% of patients with long-standing diabetes in an outpatient setting. Although gastroparesis is associated with symptoms such as nausea and postprandial fullness, such symptoms do not usually correlate closely with the gastric emptying rate.[15]

The rate of gastric emptying is critically important to the postprandial blood glucose level. The 60-minute blood glucose measurement (a strong predictor of the development of type 2 diabetes) following a 75 g oral glucose tolerance test is directly proportional to the rate of gastric emptying in people with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and type 2 diabetes.[16-18] The 2-hour blood glucose measurement is dependent on insulin sensitivity, and in people with diabetes, it correlates positively with the rate of gastric emptying, which is not the case in those with NGT.[18] Gastric emptying is also influenced by the blood glucose levels: acute hyperglycaemia (even within the upper limit of normal postprandial blood glucose range – i.e. about 8 mmol/L) slows gastric emptying,[19] whereas insulin-induced hypoglycaemia accelerates it.[20]

These findings have practical clinical applications. In patients with type 2 diabetes who are not on insulin, slowing gastric emptying may diminish postprandial glycaemia. Short-acting glucagon-like peptide-1 receptor agonists, such as exenatide twice daily and lixisenatide, slow gastric emptying, which is the dominant mechanism by which they improve postprandial glycaemia. In contrast, in patients with type 1 diabetes and those with type 2 diabetes who are treated with insulin, nutrient delivery needs to be matched to the mealtime exogenous insulin. In these patients, abnormally delayed gastric emptying could result in postprandial hypoglycaemia (also called 'gastric hypoglycaemia') and strategies that accelerate gastric emptying such as use of a prokinetic drug, or the use of relatively slower acting exogenous insulin may be required.[21]

We suggest the following simplified approach to a patient with suspected gastroparesis:

- Take a detailed history, paying special attention to medication history and smoking status.
- Exclude mucosal lesions and organic obstruction by upper gastrointestinal (GI) endoscopy.

Cardiovascular autonomic reflex tests (CARTs)

Who to refer for CARTs*

- Patients with type 1 diabetes at five years of diagnosis
- Patients with type 2 diabetes at diagnosis
- Patients with diabetes with unexplained tachycardia, orthostatic hypotension, poor exercise tolerance or evidence of autonomic neuropathy affecting other systems

How to evaluate parasympathetic activity

R-R interval (heart rate) response to:

- deep breathing
- Valsalva manoeuvre†
- postural change

How to evaluate sympathetic activity

Blood pressure response to:

- Valsalva manoeuvre†
- postural change

How to diagnose cardiac autonomic neuropathy (CAN)

- Possible or early CAN: one abnormal test result
- Definite CAN: two or more abnormal R-R interval changes
- Severe, advanced CAN: two or more abnormal R-R interval changes plus orthostatic hypotension

* Based on the recommendations of the Toronto Diabetic Neuropathy Expert Group (2010).

† The Valsalva manoeuvre is contraindicated in patients with proliferative retinopathy.

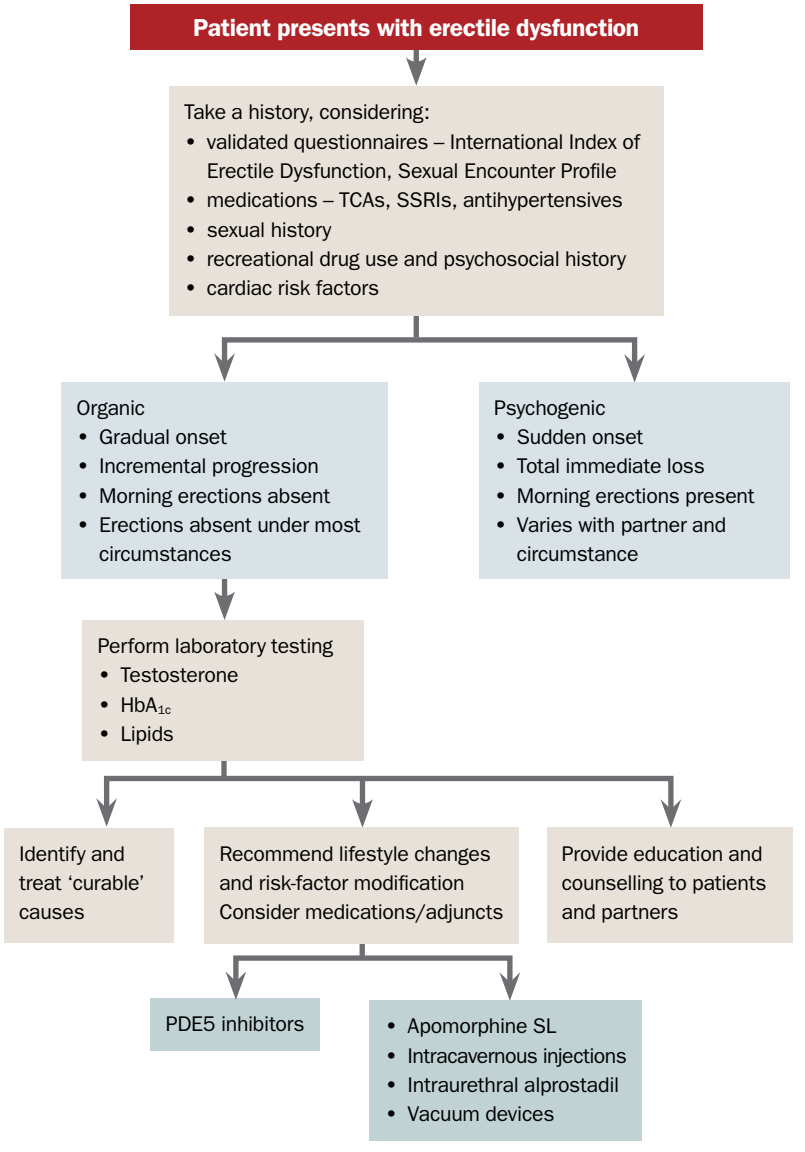

Figure 2. Approach to the management of erectile dysfunction.

Modified from Kempler, et al. Diabetes Metab Res Rev 2011; 27: 665-677.[21]

Abbreviation: HbA_{1c} = haemoglobin A_{1c}; PDE5 = phosphodiesterase type 5; SL = sublingual; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

- Measure gastric emptying. Scintigraphy is the gold-standard technique but the noninvasive ^{13}C-octanoic acid or acetate breath test is an acceptable second choice. Blood glucose should be monitored during the test.
- If symptoms are bothersome, initiate treatment with a prokinetic drug such as domperidone or metoclopramide.
- Optimise the patient's glycaemic control.
- Appreciate that gastric emptying has a significant role in the postprandial blood glucose level.

Erectile dysfunction: a marker of impaired cardiovascular health

ED is defined as the 'persistent inability to achieve or maintain an erection sufficient to permit satisfactory sexual intercourse'.[21] As with other manifestations of autonomic neuropathy, the reported prevalence varies widely (from 35 to 90%) in men with diabetes, reflecting variations in methodologies and study populations. Cross-sectional surveys indicate a fourfold increase in ED in men with diabetes compared with men in the community.[22] In addition, ED appears to be as common in relatively younger men with diabetes (age range 40 to 60 years) as older men without diabetes (age range 70 to 80 years).[22] Although ED is common in patients with diabetes, psychogenic factors must be excluded as, not infrequently, autonomic and psychological dysfunction coexist.

Importantly, ED is now well recognised as an 'independent' predictor of coronary artery disease, of comparable importance to traditional CVD risk factors such as hypertension, active smoking status or positive family history.[23,24] ED predicts both CVD development and mortality; new onset or progressive deterioration in ED should alert the medical practitioner to possible worsening ischaemic heart disease.[21] An approach to the management of ED is given in Figure 2.

Conclusion

Autonomic neuropathy is a common complication of diabetes and represents a major source of morbidity, mortality and healthcare use. CAN, in particular, is associated with an increased risk of sudden death. Simple inexpensive, CV autonomic reflex tests should be part of routine assessment of patients with type 1 or type 2 diabetes. Diabetic gastroparesis impairs quality of life and may be associated with GI symptoms and poor glycaemic control. Understanding the relationship between glycaemia and gastric emptying is important, particularly as antidiabetic agents targeting gastric emptying are now used widely. ED is not only common and can have a substantial impact on quality of life, but it is also a marker of impaired CV health. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS. None.

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