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REVIEW ARTICLE

Spectrum of diabetic neuropathies

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Abstract
The diabetic state results in neuropathy. The main causative mechanism is hyperglycemia, although microvascular involvement, hypertriglyceridemia, as well as genetic and immune mechanisms may be contributory. There is a growing spectrum of types of diabetic neuropathies that differ based on the type of fibers involved (e.g. myelinated, unmyelinated, autonomic, somatic), distribution of nerves involved, and mechanisms of neuropathy. The most common type is distal sensory neuropathy (DSN), which affects the distal ends of large myelinated fibers, more often sensory than motor, and is often asymptomatic. The next-most common is distal small fiber neuropathy (DSFN), which largely affects the unmyelinated fibers and carries the phenotype of burning feet syndrome. Diabetic autonomic neuropathy (DAN) occurs when widespread involvement of autonomic unmyelinated fibers occurs, and patients can be incapacitated with orthostatic hypotension as well as neurogenic bladder and bowel involvement. Radiculoplexus diabetic neuropathy causes proximal weakness and pain, usually in the lower extremity, and has a combination of immune, inflammatory, and vascular mechanisms. The nerve roots and plexus are involved. These patients present with proximal weakness of a subacute onset, often with severe pain and some autonomic failure. Finally, rapid and sustained reduction of blood glucose can result in treatment-induced diabetic neuropathy (TIND), which largely affects the sensory and autonomic fibers. This occurs if HbA1c is rapidly reduced within 3 months, and the likelihood is proportional to the original A1c and the size of the reduction.

Keywords Diabetes · Neuropathy · Autonomic · Radiculoplexus · Treatment-induced neuropathy

Introduction

Diabetic neuropathy is disease of the peripheral nerves secondary to the diabetic state. The wide spectrum of neuropathies represents the complex interplay of the involvement of different tissues (large and small vessels) and different fiber types (large and small nerve fibers). There is also the complex involvement of mechanisms ranging from hyperglycemia to ischemia with the additional potential contribution of hyperlipidemia, obesity, and age [1, 2]. Table 1 describes the classification of diabetic neuropathies, and Table 2 shows the topics covered in this review, which is an expanded version of the presentation at the 34th Annual Japan Society of Diabetic Complications.

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Epidemiology and pathogenesis

The most thorough study conducted thus far was a cross-sectional followed by a longitudinal study of the incidence and prevalence of diabetic neuropathy: the Rochester Epidemiology study by Peter Dyck [3]. The study was unique in that the population was stable, and the study utilized a well-established database and sophisticated evaluation that included assessments of the neurologic history and examinations as well as nerve electrophysiology and autonomic testing. The minimal criteria for the diagnosis of neuropathy were set based on the clinical features and simple electrophysiologic and autonomic testing results [4]. The authors reported that 66% of type 1 patients had some form of neuropathy, and among type 2 patients, 59% had neuropathy [3]. However, overall, two-thirds of diabetic patients had objective evidence of some type of neuropathy, although only about 20% had symptoms. This study

Table 1 Classification of diabetic neuropathies

Symmetric diabetic neuropathies
1. Distal sensory neuropathy due to diabetes or impaired glucose tolerance (IGT)
2. Distal small fiber neuropathy (DSFN)
3. Diabetic autonomic neuropathy (DAN)
4. Diabetic autoimmune autonomic ganglionopathy (DAAG)
5. Treatment-induced neuropathy of diabetes (TIND)
Asymmetric or focal diabetic neuropathies
1. Cranial mononeuropathies
2. Limb and truncal mononeuropathies
3. Radiculoplexus neuropathy (brachial or lumbosacral)

Table 2 Diabetic neuropathies covered in the current review

1	Common distal sensory neuropathy (DSN)
2	Distal small fiber neuropathy (DSFN)
3	Diabetic autonomic neuropathy (DAN)
4	Diabetic autoimmune autonomic ganglionopathy (DAAG)
5	Neuropathy of impaired glucose tolerance (IGT)
6	Lumbosacral radiculoplexus neuropathy (LSRPN)
7	Treatment-induced neuropathy of diabetes (TIND)

is unique in the detailed evaluations that were done that allowed for the detailed classification of different types of neuropathy as well as their severity and rate of progression. The methodology for the longitudinal evaluation of diabetic neuropathy was also described [5]. The minimal criteria using nerve conduction and a reduced heartbeat response to deep breathing detected diabetic polyneuropathy in approximately twice as many patients as a clinical examination and quantitative sensory testing. Using a composite score comprising the results of a clinical examination and nerve conduction studies as well as cardiovagal testing, the average diabetic patient in the epidemiologic study demonstrated a worsening of symptoms at more than double the rate of that seen in the matched controls [5].

Regarding the autonomic function, the loss of cardiovagal function precedes adrenergic failure, as manifested in orthostatic hypotension or other tests of the adrenergic function. In the Rochester Diabetic Study, Dyck et al. [6] reported a prevalence of 13.9% based on an impaired heart rate response to deep breathing. Approximately half of patients have some clinical manifestations of neuropathy, and about 1 in 10 of these patients show clinical autonomic neuropathy [3]. Among laboratory tests, the detection of a nerve conduction abnormality on two or more nerve and autonomic function tests (a decreased heartbeat response to deep breathing and the Valsalva ratio) and the composite autonomic scoring scale (CASS) were the most sensitive and objective and were particularly suitable for the detection of subclinical neuropathy [4].

In a study of the Rochester cohort, we evaluated autonomic symptoms using a validated instrument, the autonomic symptom profile, and the evaluation of the sudomotor, cardiovagal, and adrenergic functions [7]. We examined 231 diabetic patients (Type 1, $n=83$; Type 2, $n=148$) and 246 healthy controls, matched by age and gender. Autonomic neuropathy, defined as a CASS score ≥ 5, occurred in 14% ($n=33$ [$n=9$ Type 1 diabetic, $n=24$ Type 2 diabetic patients]). However, milder impairment (CASS of 1 in at least 2 domains of ≥ 2 in one domain) was present in 54% of type 1 and 73% of type 2 diabetics. OH was present in 8.4% of type 1 and 7.4% of type 2 diabetics [7].

The phenotype of diabetic neuropathies reflects the pathogenetic mechanisms of diabetic neuropathy. The most cogent mechanism is the duration and severity of hyperglycemia. In a longitudinal population-based study [5, 8], the duration and severity of hyperglycemia were associated with the incidence and severity of neuropathy. The DCCT study on 1441 patients with type 1 diabetes was a prospective study comparing tight versus conventional glycemic control over 10 years. By year 3, the tight control limb showed a significant reduction in all three complications of neuropathy, retinopathy, and nephropathy. The development of clinical neuropathy was reduced by 60% [9]. Apart from hyperglycemia, other variables that might have contributed included hyperlipidemia (especially hypertriglyceridemia), hypertension, and smoking [10]. Vascular disease, both macrovascular and microvascular [8], is regularly present and linked to the severity of neuropathy. The inflammatory immune response is an important contributor to some varieties of diabetic neuropathy [2].

Classification of diabetic neuropathies

The existence of multiple mechanisms of diabetes, which include hyperglycemia, vasculopathy, inflammation, and immune response, results in a number of different types of neuropathy. For convenience, these are classified as symmetric or asymmetric diabetic neuropathies (Table 1). Distal sensory neuropathy is a length-dependent, primarily sensory neuropathy that is attributed to hyperglycemia (Table 3), and its effects largely fall on large sensory fibers. Distal small fiber neuropathy (DSFN) follows a similar pattern, although the effects of the disease fall on the small nerve fibers, primarily unmyelinated somatic and autonomic fibers. In diabetic autonomic neuropathy (DAN), there is widespread involvement of autonomic fibers. Diabetic autonomic ganglionopathy is a rare entity involving antibodies targeting the autonomic ganglia. Treatment-induced neuropathy of diabetes (TIND) follows a too-rapid reduction

Table 3 The comparison of major diabetic neuropathies

Variable	DSN	DSFN	DAN	LS Radiculoplexus neuropathy	TIND
Onset	Insidious	Gradual	Usually gradual	Subacute	Acute
Fiber type	LF > SF involvement	Distal small fiber	Widespread autonomic	All types; regional	UF, somatic and autonomic
Main clinical features	Mostly asymptomatic or distal numbness	Distal burning sensation	Many including: OH; CAN; gastroparesis neurogenic bladder and ED	Proximal weakness with pain and autonomic failure	Symmetric length-dependent painful and autonomic neuropathy
Physiology	Length-dependent axonal neuropathy	Distal sweat loss; IEFD ↓	Widespread autonomic failure	EMG of axonal > demyelinating radiculoplexus n	Sensory loss SF > LF; Autonomic failure
Pathology	Axon > myelin loss; microvascular change	IEFD ↓	Widespread axonal loss in autonomic systems	Axon > myelin loss; microvasculitis; round cell infiltration	UF loss in IEFD and autonomic

DSF distal sensory neuropathy, *DSFN* distal small fiber neuropathy, *DAN* diabetic autonomic neuropathy, *LS* lumbosacral, *TIND* treatment-induced neuropathy of diabetes, *LF* large fiber, *SF* small fiber, *OH* orthostatic hypotension, *UF* unmyelinated fiber, *CAN* cardiac autonomic neuropathy, *ED* erectile dysfunction, *EMG* electromyography, *IEFD* intraepidermal fiber density

in hyperglycemia, as manifested by a rapid decrease in the HbA1c, and results in acute small > large fiber neuropathy. The asymmetric neuropathies involve vascular pathology, coupled with inflammatory-immune reaction in radiculoplexus neuropathy.

This review follows the format of the lecture, and the seven diabetic neuropathies listed in Table 2 will be covered in greater detail.

Distal sensory neuropathy

The most common phenotype is distal sensory neuropathy (Table 3). Neuropathy is usually present after about 10 years of the diabetic state. Early on, patients with neuropathy are asymptomatic, and the majority of patients will have no neuropathy or subclinical neuropathy [3]. When symptoms develop, sensory deficits manifest as a loss of vibratory perception, hypesthesia, or positive symptoms of paresthesias. Pain is usually absent but can develop. Motor involvement is inconspicuous clinically but is usually present, at least electrophysiologically [11, 12]. The symptoms are relatively symmetric, as is sensory impairment. The Achilles tendon reflex is often reduced. When sensory deficits, which are mediated by large myelinated fibers, are over-represented, the term large-fiber-type neuropathy is suggested.

The evolution of clinical distal sensory neuropathy was well demonstrated in a natural history study [3]. In the first 10 years of diabetes, the majority of patients have no neuropathy. After 10 and 20 years of diabetes, there is an increasing proportion with mild neuropathy and a modest number with clinical neuropathy. However, even then, the majority have either no neuropathy or only subclinical neuropathy [3]. Proprioceptive and vibratory perception are particularly impaired. As the earliest laboratory abnormalities, the impairment of the cardiovagal (Table 1) and distal postganglionic sudomotor functions occur with similar frequency [13].

There is an early phase of neuropathy, lasting about 5 years, when the changes tend to be more reversible; in this phase, the changes might be responsive to course-modifying therapy. In a prospective study, Dyck et al. [5] found that the rate of change in the large and small fiber function was relatively predictable. Cardiovagal testing showed a change of 1 bpm per year in HRDB and NIS + 7 changes at 0.85 points, whereas the controls changed by 0.34 points per year.

Pathology of diabetic sensory neuropathy The underlying pathology of distal sensory neuropathy is summarized here. The pathology of other phenotypes are described under their respective titles. The pathology is complex, involving axons [14], Schwann cells [15, 16], large and small vessels [16–19] as well as a variable but usually modest degree of inflammatory changes [20, 21]. The peripheral nerve myelinated fiber density is reduced in diabetic sensory neuropathy, and there is a progressive increase in fiber loss over the duration of diabetes [19]. Apart from the loss of axons, it has been suggested that a key manifestation of axonopathy is the degeneration of terminal arbors of peripheral nerves, resulting in a loss of epidermal nerve fibers and inappropriate termination of nerve endings [16]. In a thorough study of patients with diabetic distal sensory neuropathy and control nerves obtained at an autopsy, the density and distribution of myelinated fibers were quantified from the nerve roots to the distal peripheral nerve [17]. While there was a uniform fiber loss at distal sites, the distribution at the proximal sites showed

a pattern of multifocal fiber loss, which is characteristic of vasculopathy [17]. Direct evidence of microvasculpathy was also shown [22–24] in epineurial arterioles. Inflammatory changes may be important in the evolving phase of the disease and constitute a mechanism for intervention. Changes involving inflammatory molecules (inflammatory cytokines, adhesion molecules, chemokines) and pathways (nuclear factor kappa B, JUN N-terminal kinase) may be implicated in the development and progression phase of diabetic neuropathy [20].

Diabetic DSFN

A distal burning sensation can occur with patients with diabetic distal sensory neuropathy. However, there is a subset of patients who have distal burning pain with normal or near-normal nerve conduction studies of large myelinated fibers (Table 3). Patients complain of prickling, stabbing, or burning sensations of the toe pads or balls of their feet. Distal small fiber neuropathy is a subset of small fiber neuropathy for which diagnostic criteria have been established [25]. DSFN can be idiopathic but also occurs in some diabetic patients, where the involvement of small nerve fibers precedes that of large myelinated fibers. The fiber type involved is mainly unmyelinated fibers, both somatic afferent and sympathetic efferent. With the advent of the quantitative sudomotor axon reflex test (QSART), it has become possible to demonstrate failure of transmission of the sympathetic sudomotor fibers. The relevant findings on the QSART are the absence of or marked reduction in the axon-reflex-mediated sweat response, confined to the foot. The thermoregulatory sweat test shows anhidrosis confined to the toes and adjacent foot [26]. Stewart et al. [27] demonstrated that the thermoregulatory sweat test was positive in 80% of patients with DSFN. In a review of 125 patients with DSFN [26], the QSART was abnormal in 74% of cases. The most common cause was idiopathic (73%) and diabetes (10%). Patients had an essentially normal adrenergic function, and there was no marked difference between the patients with normal nerve conduction studies and those with minor abnormalities.

The intraepidermal nerve fiber (IENF) density has a high sensitivity for detecting somatic C-fiber pathology in DSFN. In previous studies in patients with DSFN, the IENF densities in calf skin were reduced below the lower limit of normal in about 80% of patients [28]. Skin biopsies, which evaluate somatic C fibers, provide information unavailable on a sural nerve biopsy, which evaluates the nerve fibers of the sensory nerve trunk. Support for this comes from a study of patients with DSFN subjected to both a sural nerve biopsy and skin biopsies, where unmyelinated fiber loss was detectable in the skin but the sural nerve morphometry was normal [29]. This has become accepted as a test for small fiber neuropathy [30]. Following pioneering work and the establishment of a normative dataset [31], such studies have been duplicated and validated in multiple laboratories, and an international normative dataset is available [32].

The relationship between the QSART and the IENF density has been studied. Thaisetthawatkul et al. (2013) [33] performed the QSART, quantitative sensory testing, and a skin biopsy on the same 101 patients with small fiber neuropathy, primarily DSFN. They found that the QSART had high sensitivity and specificity (82% and 89%), while the IENF density had a low sensitivity (67%) but high specificity (91%), and quantitative sensory testing had a high sensitivity (88%) but low specificity (50%). These authors suggested that a diagnosis of DSFN should be made in cases with abnormalities on two of these three tests. The QSART should thus be considered complementary to sensory testing [34]. In a prospective study of patients with distal and generalized small fiber neuropathy, the patients underwent full autonomic function testing, including a QSART, and received a skin biopsy with measurement of skin norepinephrine levels as well as the IENF density in diabetic DSFN, POTS, autoimmune autonomic neuropathy, and idiopathic neuropathy [35]. As expected, variable agreement was found between somatic C, sudomotor C, and the adrenergic function. These findings suggest that the tests are complementary.

DAN

Autonomic fibers are involved concurrently with somatic large and small nerve fibers. Early involvement of the cardiovagal function occurs, followed by that of the distal sudomotor fibers [13] and then by widespread involvement of the autonomic pathways. The details of DAN are summarized below (Table 3).

- *Cardiac autonomic neuropathy* usually refers to cardiovagal autonomic neuropathy. This is clinically evaluated by a combination of the heart rate response to deep breathing and the Valsalva ratio. Cardiac autonomic neuropathy is usually the earliest abnormality in autonomic testing (see Prevalence). The prevalence of abnormalities in autonomic function tests is reportedly greater in type 1 than in type 2 diabetes. There is good general agreement that patients with CAN have a higher mortality than those without CAN.

  In addition to cardiovagal impairment, diabetic patients can also develop cardiac adrenergic denervation. Cardiac postganglionic sympathetic adrenergic innervation can be evaluated by single-photon emission computed tomography (SPECT) or positron emission tomography (PET) using radiopharmaceuticals, such as ^{123}Imetaiodobenzylguanidine (^{123}I-MIBG) and ^{11}C-hydroxyephedrine (^{11}C-HED). Denervation is

demonstrable in both type 1 and type 2 diabetes in the majority of patients, regardless of cardiovagal impairment [36]. The pattern of sympathetic disturbances is heterogeneous, with a predominant effect in the distal left ventricular region [37]. Adrenergic denervation can be present in patients with an intact cardiovagal function [37]. Adrenergic innervation can be heterogenous, being significantly increased in the proximal segments of severe DAN despite deficiency in distal retention, with the potential for hyperinnervation and arrthymogenesis [37]. Of interest is that some patients with improved glycemic control appeared to have regression of adrenergic denervation [38].

- *Orthostatic hypotension* (OH) is common in DAN, occurring in 25–50% of such patients [7, 39]. In diabetic OH, there is failure in both the vagal and adrenergic limbs of the baroreflex [40]. Pathologically, there is degeneration of sympathetic pre- and postganglionic fibers, including those supplying the splanchnic mesenteric bed [41, 42], which is a large-volume bed that increases in volume by 200–300% after a carbohydrate-heavy meal [43]. This increase results in venous pooling and major orthostatic stress, which is responsible for post-prandial OH [43].

  Denervation supersensitivity can occur with postganglionic adrenergic denervation, occurring in about 25% of patients with diabetic neuropathy [42]. It results in an exaggerated pressor response to directly acting adrenergic agonists, such as midodrine or droxidopa. Indeed, Palma et al. [44] found an inverse relationship between supine plasma norepinephrine and the BP increase following droxidopa, a directly acting α-agonist.
- *Gastrointestinal diabetic autonomic neuropathy* can involve the entire gastrointestinal tract from esophagus to rectum. A major issue is gastroparesis [45]. Gastric motor abnormalities are common, occurring in about 47% of diabetic patients in the DCCT–EDIC study, often without clinical manifestations [46]. It results in nausea, early satiety, postprandial bloating, belching, and diffuse epigastric pain. Weight loss can occur with severe gastroparesis. There is a relatively poor concordance between symptoms and gastroparesis. For instance, almost 60% of patients attending a diabetes clinic had such symptoms, but < 10% were found to have gastroparesis, whereas up to 25% of brittle diabetic patients had gastroparesis [45, 47]. The scintigraphic measurement of the gastric-emptying time is helpful for diagnosing gastroparesis [45]. Diabetic gastroparesis is multifactorial, with contributions from hyperglycemia, extrinsic (vagal) denervation, and intrinsic neural denervation [45]. Intrinsic changes include reductions in the levels of neuronal nitric oxide synthase and the numbers of interstitial cells of Cajal [45].

The most prominent symptom of intestinal neuropathy is diabetic diarrhea. Diabetic diarrhea can be sudden, explosive, paroxysmal, nocturnal, uncontrollable, and often embarrassing [48]. It surprisingly does not generally lead to severe malnutrition and tends to be self-limiting. Although several mechanisms have been postulated to be operative in the pathophysiology of this condition, diarrhea is essentially unexplained. Most patients have generalized autonomic neuropathy, which usually precedes diarrhea. Several mechanisms involving autonomic neuropathy, bacterial overgrowth, and pancreatic exocrine insufficiency as well as intestinal mucosal ischemia have been postulated as pathogenic factors [48]. Radiological transit studies have demonstrated both increased and decreased transit times in these patients [49]. Using the breath hydrogen test, it has been shown that the small-bowel transit in diabetic patients with autonomic neuropathy was significantly slower than transit time in uncomplicated patients [50, 51].

Constipation is the most prominent colonic manifestation of gastrointestinal neuropathy in diabetes [52]. This may be due to extensive denervation of the colon, since denervation of the lower intestinal tract in experimental animals resulted in obstipation [53]. Constipation may worsen or be induced with medications, especially opioids.

Thermoregulatory abnormalities are the rule in the diabetic autonomic neuropathies. They range from distal anhidrosis in distal sensory neuropathy and DSFN to regional anhidrosis in radiculoplexus neuropathy to widespread—even global—anhidrosis [54]. Patients with widespread anhidrosis are at risk of heat illness. On exposure to heat, they can become flushed, weak, and dizzy and are at risk of heat stroke. Patients with distal anhidrosis may experience compensatory truncal hyperhidrosis [55]. Sudden gustatory sweating at the forehead, face, scalp, neck, and sometimes even shoulders and chest often occurs when patients chew tasty food [56].

- *Neurogenic bladder* The prevalence of diabetic cystopathy increases with the duration of diabetes and is usually a part of generalized autonomic failure [57]. Parasympathetic failure occurs first, manifesting as a poor detrusor muscle tone and clinically as an increased bladder capacity, reduced perception of bladder fullness, and reduced urine flow [58]. Paradoxically, there is urgency, and overflow incontinence can manifest, along with secondary infections. A residual urine volume in excess of 100 ml is abnormal and can be demonstrated by ultrasonography [59]. A formal study can be performed with cystometry and uroflowmetry. On cystometry, the diabetic bladder is typically atonic and has an increased capacity and increased residual urine volume. On uroflowmetry, there is a reduced peak flow from the usual value of about 30 ml/s to lower values, such as 10 ml/second [60].

- *Erectile dysfunction*, defined as the inability to achieve and/or maintain an erection for satisfactory intercourse [61], is well recognized in diabetic men [62] and is quite common, often being the first manifestation of autonomic failure. It is initially partial and becomes complete over a period of 1–2 years [63]. Erectile dysfunction is due initially to parasympathetic failure, resulting in failure to maintain an erection [48]. This is followed by sympathetic denervation that results in failure to ejaculate or sometimes in retrograde ejaculation [64]. Aside from denervation, impairment of the endothelium-mediated relaxation of the penile smooth muscle and nitric oxide levels and release are involved [65]. Also involved are macro- and microvascular disease, as well as impairment of the somatic sensation. Female sexual dysfunction in diabetics is less well studied, although abnormalities are present and are perhaps as common in women as in men [66]. Problems in women include depression, decreased libido, impaired lubrication, dyspareunia, and problems with orgasm [66, 67].
- *Pupillary involvement* The pupil diameter and behavior have been of some limited value in evaluating the autonomic function. These include infrared recordings of the dark-adapted pupil diameter [68], light reflex amplitude, light reflex latency, velocity, and redilation time [55, 68] as well as the pupil cycle time [69]. The pupil cycle time refers to the frequency of oscillations of the pupil in response to a light stimulus and is an index of the parasympathetic function [69]. This frequency is reduced in cases of diabetic autonomic neuropathy [69]. The test might be of value in patients who cannot undergo cardiovagal testing because of arrhythmia.

Natural history of DAN and mortality

In the natural history of early diabetic neuropathy over a 2-year period, the autonomic test findings deteriorated as follows [5] for type 1 and type 2 diabetes: HR_{DB}, 2.05 bpm ($P = 0.005$) and 1.56 bpm ($P < 0.001$), respectively. Clinical or laboratory evidence of autonomic neuropathy is usually not evident at the inception of the diabetic state and is usually absent for the first 10 years. After 10–15 years of diabetes, about 30% of insulin-treated diabetic patients develop measurable signs of autonomic neuropathy [70]. Clinical autonomic failure is less common, occurring in about 5% of the diabetic population, but the frequency is extremely variable, reflecting the referral and selection bias of study populations. The symptoms increase with the duration and severity of peripheral neuropathy and increasing age [70, 71].

There have been numerous reports that DAN not only causes significant morbidity but also increases the mortality rate. A meta-analysis of 15 studies with a baseline assessment of the cardiovascular autonomic function and mortality follow-up supported an association between cardiac autonomic neuropathy and the increased risk of mortality [72]. Impaired cardiac pain perception accounting for silent myocardial ischemia and prolonged exercise tolerance after ischemia onset also seems to be associated with cardiac autonomic neuropathy [73]. In a 10-year follow-up study [74], an increased mortality of 40% in patients was found with cardiovagal DAN vs. 10% in those without DAN. Multiple mechanisms have been proposed and include arrhythmogenesis related to QT lengthening due to diabetes [70, 75] as well as hyperadrenergic islands in proximal denervated heart [37].

Diabetic autoimmune autonomic neuropathies

While inflammatory-immune mechanisms might be involved in diabetic neuropathy, there is a subset of diabetic neuropathies where autoimmune mechanisms appear to be the major mechanism underlying neuropathy. Diabetic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and diabetic autoimmune autonomic ganglionopathy (AAG) are major examples.

CIDP is characterized by diffuse weakness, electrophysiologic evidence of widespread conduction slowing, and increased CSF protein [76]. Diabetic patients can develop a syndrome mimicking CIDP clinically and electrophysiologically [77]. CIDP has been reported to be present in increased numbers in diabetics [78]. However, epidemiologic studies of the incidence and prevalence have not demonstrated such an association [79]. This issue is important because of the responsiveness of CIDP to immunotherapy, including intravenous gamma globulin (IVIG) [80]. In a recently completed randomized clinical trial, patients designated as diabetic CIDP did not respond to IVIG [81]. However, it is likely that many of the cases diagnosed as diabetic CIDP are not truly CIDP, so these findings should not dissuade physicians from using immunotherapy in cases that meet both the clinical and electrophysiologic criteria for CIDP.

Autoimmune autonomic ganglionopathy (AAG) is a rare autonomic disorder typically characterized by the subacute onset of generalized autonomic failure with orthostatic hypotension and cholinergic neuropathy (Adie's pupils, gastroparesis, neurogenic bladder, widespread anhidrosis) and associated with acetylcholine receptor A3 ganglionic receptor (ganglionic antibody; [82]). This antibody is increased in some diabetic patients, and the occasional case of AAG has been reported in a diabetic patient [82]. Whether AAG in diabetics is truly diabetic AAG or merely coincidental is unclear at present.

Diabetic radiculoplexus neuropathy

Although this entity has been recognized for some time [83–85], many recent insights have come from systematic studies by Dyck et al., who studied hundreds of patients; provided an update on the phenotype, nerve pathology, electrophysiology, and epidemiology; and described their experience with the management (Table 3).

Among diabetic neuropathies, this entity has several special characteristics. It has a subacute onset of nerve plexus involvement with significant muscle weakness and pain as well as microvascular disease which is associated with an inflammatory-immune mechanism. Although both brachial [86, 87] and lumbosacral plexopathy have been reported, our focus will be on lumbosacral radiculoplexopathy [88, 89].

The entity is acute or subacute in onset, with muscle weakness and pain that is usually deep and dull, in the thigh, and associated with significant weight loss [88, 90]. The affected muscles are weak and usually proximal, and there is hypo- or areflexia [91, 92]. The lesion is unilateral or asymmetric in the majority of cases. This results in proximal selective or asymmetric weakness of the lower extremity [90]. The whole process is monophasic with at least some recovery over 3–18 months [90, 93]. This entity is more common than CIDP, and although it can occur independent of diabetes, is significantly associated with the diabetic state [94]. Electromyographically shows active denervation of the affected muscles, increased femoral nerve latency, and denervation of the paraspinal muscles [91, 95]. Patients may respond to immunotherapy with prednisone, plasma exchange, intravenous gamma globulin, and intravenous methylprednisolone [92]. Intravenous methylprednisolone is recommended as the preferred agent in patients with significant pain, since pain improvement is often dramatic [92, 96].

A nerve biopsy of the sural or more proximal nerve fascicles shows a combination of axonal loss and demyelination [8]. A histopathologic examination provided strong evidence for ischemic injury (axonal degeneration, multifocal fiber loss, focal perineurial necrosis and thickening, injury neuroma, neovascularization, and swollen fibers with accumulated organelles), which we attribute to microscopic vasculitis (epineurial vascular and perivascular inflammation, vessel wall necrosis, and evidence of previous bleeding). Segmental demyelination was significantly associated with multifocal fiber loss [8]. In a study of inflammatory mediators of this entity in 19 disease patients compared with 20 control patients, we found a significant increase in the number of ICAM-1-positive vessels in disease patients compared with controls ($P < 0.01$). The TNF-α expression was seen in Schwann cells and some macrophages of DLRPN nerves, whereas the IL-6 expression was minimal. The NF-κB immunoreactivity was greater in the vessels and endoneurial cells of DLRPN nerves than in the controls ($P < 0.001$). Our findings suggest the up-regulation of inflammatory mediators in target cells at different disease stages and that these mediators may be sequentially involved in an immune-mediated inflammatory process.

Widespread autonomic failure was usually present [90]. This was quantified using the CASS, which determined the combined sudomotor, adrenergic, and cardiovagal autonomic deficit, correcting for the confounding effects of age and gender. The CASS was 7.8 out of a maximum of 10 with the similar involvement of sudomotor, adrenergic and cardiovagal domains [90]. Since autonomic failure is pre-existent, it is unclear how much additional autonomic failure radiculoplexus neuropathy confers on the patient. Results to date suggest that autonomic failure is mainly due to radiculoplexus neuropathy, since widespread autonomic failure occurs in both diabetic and non-diabetic radiculoplexus neuropathy cases [97].

TIND

Acute, small fiber, painful neuropathy can occur with the rapid correction of hyperglycemia, usually with insulin and was previously designated as “insulin neuritis” [98–100]. Recent studies by Gibbons and Freeman [101, 102] provide an updated description of the entity as well as its relationship to glycemic control, physiology, pathology, and natural history. A study of 16 subjects with TIND described acute small fiber somatic and autonomic neuropathy that developed following the institution of tight glycemic control (Table 3). All patients developed painful neuropathy within 8 weeks of achieving tight glycemic control. Autonomic failure involving both cardiovagal and adrenergic failure with orthostatic hypotension occurred in a few subjects, and all eight patients who had a skin biopsy showed a loss of intraepidermal fibers. The retinopathy steadily worsened. However, after 18 months of glycemic control, there was substantial improvement in the pain, autonomic symptoms, and autonomic deficits as well as the IENFD. Greater improvement occurred in cases of type 1 than in type 2 diabetes.

That study was followed by a larger study of 104 patients with TIND [102] who developed this acute small fiber neuropathy among 954 diabetic patients evaluated for small fiber neuropathy. This entity together with worsening retinopathy developed within 8 weeks of improvement in glycemic control. This larger study better quantified the risk of development of TIND. There was a strong correlation between the size of the decrease in HbA1c, the severity of neuropathic pain, cardiovagal failure, and adrenergic failure. The authors found a clear relationship between the magnitude of the A1c reduction within this time window and the risk of developing TIND.

The mechanism underlying TIND is unclear. One proposed mechanism involves arteriovenous shunting and the proliferation of new vessels [100]. An alternative hypothesis is that since these nerves are ischemic and hypoxic, they have a disproportionate dependence on inefficient anaerobic metabolism. These fibers survive because of high glucose stores. However, under conditions of the rapid reduction in the blood glucose levels, there is an energy crisis, and unmyelinated fibers (with a large surface area-to-size ratio) are particularly susceptible, causing small fiber neuropathy [103].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics policy This article does not contain any studies with human or animal subjects performed by any of the authors.

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