ANNUAL REVIEWS

Annual Review of Medicine

Spectrum of Diabetic Neuropathy: New Insights in Diagnosis and Treatment

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Annu. Rev. Med. 2024. 75:293–306

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-043021-033114

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Keywords

diabetic neuropathy, diabetic peripheral neuropathy, autonomic neuropathy, cardiovascular autonomic neuropathy, gastroparesis, urogenital neuropathy

Abstract

Diabetic neuropathy is a highly prevalent complication of diabetes. It consists of a broad range of neuropathic conditions, such as distal symmetric polyneuropathy and various forms of autonomic neuropathies involving the cardiovascular, gastrointestinal, and urogenital systems. Prevention or diagnosis in early stages of disease is crucial to prevent symptomatic onset and progression, particularly in the absence of current disease-modifying therapies. In this review, we describe the four main types of diabetic neuropathy. We review current understanding with respect to diagnosis and treatment while highlighting knowledge gaps and future directions.

DN: diabetic neuropathy

DPN: diabetic peripheral neuropathy

CAN: cardiovascular autonomic neuropathy

DCCT: Diabetes Control and Complications Trial

EDIC: Epidemiology of Diabetes Interventions and Complications study

SDOH: social determinants of health

INTRODUCTION

As a clinical entity, diabetic neuropathy (DN) represents a spectrum of neuropathic conditions with clinical manifestations ranging from peripheral neuropathy to various forms of autonomic dysfunction, including cardiovascular, gastrointestinal, and urogenital. Despite advances in clinical care, it remains a highly common complication of diabetes, with an estimated lifetime prevalence of greater than 50% (1, 2). By 2045, 783 million adults are projected to be living with diabetes worldwide with up to 350 million developing DN and its comorbidities (3). Individuals with diabetic peripheral neuropathy (DPN) may experience severe pain, loss of sensation, impaired balance, falls, ulcers, and amputations, all leading to reduced quality of life. Cardiovascular autonomic neuropathy (CAN) is a dreaded complication, as it can exacerbate cardiovascular disease and contribute to heart failure and sudden cardiac death. DPN alone accounts for over $10 billon of annual healthcare costs and more than one-fourth of the total direct medical cost of diabetes (4).

EPIDEMIOLOGY

DN is a highly prevalent complication in both type 1 diabetes (T1D) and type 2 diabetes (T2D) (5). In the Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), the baseline prevalence rates of DPN and CAN in early T1D were low at 6% and 5% but increased to 33% and 44%, respectively, after 23 years of follow-up (6). Similar rates were reported in the European Insulin-Dependent Diabetes Mellitus Prospective Complications Study (EURODIAB IDDM) and in more contemporary cohort studies, such as the T1D Exchange Clinic Registry (7, 8). In T2D, the prevalence of DPN and CAN is likely higher. Based on the findings of several large cohort studies, the baseline prevalence of DPN in newly diagnosed or early T2D may be as high as 10–20% with progression to rates exceeding 50% after 10 or more years (1, 9–12). The prevalence of CAN in newly diagnosed or early T2D is approximately 9%, and subsequent rates are as high as 65% in individuals with longstanding T2D (13, 14). For youth with diabetes, the prevalence rates of DPN and CAN are surprisingly high; in the SEARCH for Diabetes in Youth cohort, reported rates of DPN were 8.5% and 17.7% while rates of CAN were 12% and 17% in youth with T1D and T2D, respectively (15, 16). Even prior to the onset of diabetes, DPN and CAN are prevalent among individuals with impaired glucose tolerance or prediabetes, with reported rates of 10–30% (1, 13, 17–19). Additionally, components of the metabolic syndrome and obesity are risk factors for DPN independent of glycemic status (20, 21).

Among the traditional risk factors, glycemia, age, dyslipidemia, obesity, and smoking consistently have been shown to be associated with DPN and CAN (1, 2, 6). In addition, social determinants of health (SDOH) are now recognized as risk factors for DN, and there is a need to better understand their relationship with complications risk and progression. For instance, a higher burden of DPN was reported in non-Hispanic Blacks compared to non-Hispanic Whites, even after adjustment for traditional risk factors (22). In youth and young adults with diabetes, a modeling analysis using longitudinal data from the SEARCH for Diabetes in Youth cohort implicated unmeasured race- and ethnicity-associated factors in predicted disparities in DPN in non-White versus White individuals (23). Preliminary data from the Flint Neuropathy Study with a predominantly Black, low-income population suggest that DPN is highly prevalent yet underrecognized (24). Prompt recognition is also crucial to facilitate appropriate monitoring and mitigation of risk for foot complications (1, 2). Recent data show that Black, Hispanic, and Native American patients admitted for foot infections associated with DPN have longer hospital stays and

increased risk of major amputations compared to White patients; attempts to address these inequities through early Medicaid expansion are associated with improvement in these disparities (25, 26). There is a need to better understand these associations and unidentified factors, particularly the ways in which systemic racism influences the various elements of SDOH, including an individual's socioeconomic status, physical environment, food environment, healthcare access, and social context (27). Further evidence linking SDOH with DN risk has been recently unveiled in two large contemporary T1D cohorts on both sides of the Atlantic. In the American T1D Exchange Clinic Registry cohort, lower education and higher rates of public insurance compared to private were associated with higher DPN prevalence (8). In the Scottish T1D Register cohort, social deprivation was a risk factor for DPN (28). These findings underscore the importance of understanding the role of SDOH in complications risk and better tailoring interventions to improve outcomes.

True gastrointestinal neuropathies secondary to diabetes (esophageal dysmotility, gastroparesis, constipation/diarrhea) have low prevalence in contemporary cohorts (1, 2).

Urological complications, including sexual dysfunction and lower urinary tract symptoms (LUTS), are highly prevalent in diabetes with an elevated risk of 50–200% in women and 25–300% in men (29). Risk factors for urinary incontinence (UI) in women with T1D in the DCCT/EDIC ancillary UroEDIC study were age, higher body mass index, and recent urinary tract infections (30), while for female sexual dysfunction (FSD), psychosocial factors such as depression and marital status were predominant (31). In women with T2D, prevalent UI is associated with age, diabetes duration, microvascular complications, and neuropathic pain (29, 32). Intensive glycemic control was not associated with decreased LUTS severity in men with T1D in UroEDIC (33), but was associated with decreased risk of erectile dysfunction (ED) (34).

LUTS: lower urinary tract symptoms

UI: urinary incontinence

FSD: female sexual dysfunction

ED: erectile dysfunction

DIAGNOSIS

Diabetic Peripheral Neuropathy

The diagnosis of DPN remains chiefly a clinical one with symptoms and signs reflective of the underlying damage to different types of nerve fibers (1, 2). The process resulting in the characteristic "stocking-and-glove" distribution begins at the tips of the toes and advances in a symmetrical, distal-to-proximal pattern (5). The neuropathy principally affects sensory nerves (1, 35). Small fiber damage manifests as neuropathic pain, which is characteristically burning, shooting, and electric shock–like. The pain is associated with tingling and prickling sensations (paresthesias) and dysesthesias, including exaggerated responses to painful stimuli (hyperalgesia) and pain evoked by contact with typically unpainful stimuli (allodynia) (1, 2, 5). Finally, more advanced, large fiber damage can result in numb, insensate feet, predisposing to the development of diabetic foot ulcerations with risk of infection and amputation, as well as reduced daily functioning and poor balance leading to falls and fractures (1, 2, 5).

Individuals who have had T1D for 5 years or longer and those with T2D should be assessed for DPN annually, as recommended by the American Diabetes Association (1). This is prudent given that many individuals are asymptomatic (5). Assessment should include a medical history targeted to the symptoms aforementioned and a combination of at least two examinations evaluating both small and large fiber function (**Figure 1**) (1, 35). Notably, while the 10g monofilament test alone allows for detection of more advanced DPN and risk for ulcerations, it does not reliably identify those individuals with early disease that would benefit most from therapeutic intervention to prevent progression (1, 2, 5). Thus, the clinician should not use it as the sole method for DPN diagnosis.

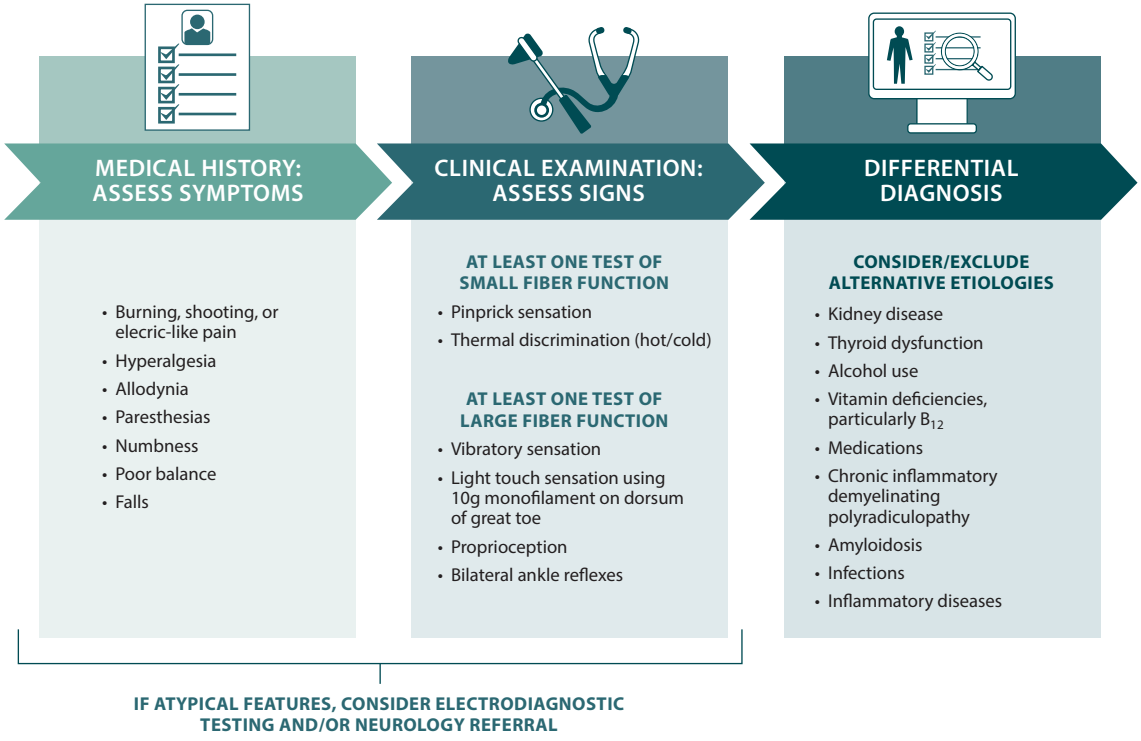

Figure 1

Approach to the diagnosis of diabetic peripheral neuropathy in the clinical setting.

Even when the clinical presentation is suggestive of DPN, maintaining a broad differential diagnosis is key to exclude other etiologies of neuropathy that may coexist in people with diabetes and may be reversible with appropriate treatment (1, 5, 36). These include neuropathies secondary to kidney disease, thyroid dysfunction, alcohol use, vitamin deficiencies (particularly B_{12}), medications, chronic inflammatory demyelinating polyradiculopathy, amyloidosis, infections, and inflammatory diseases (1, 2, 5). The diagnosis of DPN at the point of care has changed from the use of only electrodiagnostic studies through nerve conduction studies to new standard approaches capitalizing on symptoms and signs that can be documented in the office. That said, electrodiagnostic studies and/or neurology referral should be considered in presentations with atypical features (1, 35). As previously described, a combination of subjective and objective assessments allows for practical use in the clinical setting at the point of care as well as in larger epidemiological studies of DPN (2). However, more comprehensive and standardized outcome measures are needed for interventional trials, especially given that there are currently no approved disease-modifying therapies (2). Various validated clinical instruments have been used, which may combine questionnaires assessing symptoms with sensory and reflex examinations or consist solely of examinations (1, 2). Because small fiber loss typically precedes large fiber loss in DPN, and nerve conduction studies may be normal with only small fiber neuropathy, newer validated measures of small nerve fibers are important in recognition of early disease and in trials assessing therapeutic interventions (2, 36). Skin punch biopsy for assessment of intraepidermal nerve fiber density is the gold standard test for small fiber neuropathy, although widespread implementation at the point of care is challenging (2). Other emerging measures such as corneal confocal microscopy and

thermal quantitative sensory testing may be used in research but require expensive equipment and standardizations (2, 36).

HRV: heart rate variability

Cardiovascular Autonomic Neuropathy

CAN is a common complication of diabetes that leads to significant morbidity and increases all-cause and cardiovascular disease mortality, yet remains overlooked in clinical practice (1, 13). The diagnosis of CAN in its early stages is complicated by the fact that many affected individuals are asymptomatic (2). Common symptoms of advanced CAN occur upon standing and include weakness, lightheadedness, palpitations, and syncope (1, 35). Similarly, clinical signs of CAN, such as resting tachycardia, orthostatic hypotension, exercise intolerance, and abnormal blood pressure regulation (reverse dipping/nondipping), occur late in the disease course (1). In contrast, reduced heart rate variability (HRV) is observed in individuals with subclinical CAN and is considered the earliest clinical indicator of disease (1, 13). As with DPN, it is important to maintain a broad differential diagnosis and exclude alternative etiologies that may present with similar signs or symptoms as CAN (1, 35). These include anemia, thyroid disease, dehydration, adrenal insufficiency, substance use, and medication/supplement use (1).

There are multiple methods available for the diagnosis of CAN, including cardiovascular autonomic reflex tests, HRV studies in time and frequency domain, 24-h blood pressure profiles, baroreflex sensitivity testing, and cardiac sympathetic imaging including iodine-123 metaiodobenzylguanidine scintigraphy and carbon-11-labeled metahydroxyephedrine positron emission tomography; however, the majority of diagnostic methods may be used only in research settings (13). Cardiovascular autonomic reflex tests, which are the gold standard for CAN diagnosis, assess changes in blood pressure and heart rate during deep breathing, standing, and Valsalva maneuvers (1, 13). Although available in clinical care, their use is limited by burden, cost, and need for better understanding among clinicians of how to apply the results (2). Barriers to assessment of cardiovascular autonomic function in clinical practice include the lack of consensus within the field regarding clear outcome measures as well as the need for easily accessible tools for diagnosis (**Table 1**). Diagnosis in early disease requires detection of reduced HRV at the point of care (13). HRV indices derived from standard 10-sec 12-lead electrocardiography have proved feasible and reliable in larger, longitudinal cohorts (11, 37), and sensitive and specific cut-off values were recently validated (37); therefore, HRV indices now represent an easier-to-use tool for clinicians, particularly with the development of newer electrocardiogram recorders that can display these indices. Successful application of HRV measurement in the clinical setting will depend on the availability of these devices at the point of care.

Gastrointestinal Autonomic Neuropathy

Gastroparesis (gastrointestinal autonomic neuropathy) may present with symptoms of early satiety, fullness, bloating, vomiting, dyspepsia, and abdominal pain (1, 2). Individuals may experience unexpected glucose variability and hypoglycemia in the setting of a mismatch between food absorption and pharmacokinetics of antihyperglycemic medications (1). However, gastroparesis may be clinically silent in many, and symptoms have not necessarily correlated with its severity or findings on gastric emptying studies (1). Other conditions, such as gastric outlet obstruction or peptic ulcer disease, must be ruled out (1, 35). Contribution from medications, such as opioids and glucagon-like peptide-1 (GLP-1) receptor agonists, must be considered (1). The gold standard for diagnosis is scintigraphic gastric emptying studies, ideally at euglycemia to reduce the chance of false-positive results due to hyperglycemia (1). More recently, the carbon-13-octanoic acid or acetate breath test has been developed as a more feasible alternative (1, 2).

Table 1 Clinician-encountered barriers in assessing and treating diabetic neuropathy

Diabetic neuropathy	Barriers
Diabetic peripheral neuropathy	Knowledge gap among clinicians regarding methods to diagnose subclinical disease, need for more widespread implementation No disease-modifying therapy Current symptomatic treatment often inadequate Non-neuropathic etiologies of pain Health inequities; certain racial and socioeconomic groups disproportionately affected
Cardiovascular autonomic neuropathy	Asymptomatic in earlier stages Limited methods for diagnosis at point-of-care No widespread understanding of how to apply results of CARTs No disease-modifying therapy
Gastrointestinal autonomic neuropathy	Symptoms are nonspecific, do not correlate with severity of gastroparesis and gastric emptying studies Medication side effects (opioids, TCAs, anticholinergics, GLP-1 receptor agonists) and substance use (marijuana) may contribute to symptoms and signs given their direct effect on gastrointestinal motility Scintigraphic gastric emptying studies cumbersome
Urogenital autonomic neuropathy	No clinically available diagnostic tests of urogenital autonomic nerve function Medication side effects may contribute to symptoms BPH versus non-BPH LUTS Psychosocial factors

Abbreviations: BPH, benign prostatic hyperplasia; CARTs, cardiovascular autonomic reflex tests; GLP-1, glucagon-like peptide-1; LUTS, lower urinary tract symptoms; TCAs, tricyclic antidepressants.

Urogenital Neuropathy

Given the high prevalence of urogenital disturbances in diabetes and their significant impact on quality of life, it is crucial to assess individuals with diabetes for symptoms, particularly in the presence of other DNs and given that some individuals may not be forthcoming with respect to these symptoms (1). In women, targeted questioning should address the range of LUTS, including UI, bladder storage symptoms, sensory symptoms, and voiding/postmicturition symptoms (29). In men, the principal tool used in both clinical practice and research for assessment of LUTS is the American Urological Association Symptom Index (29). There can be significant clinical overlap between LUTS secondary to benign prostatic hyperplasia (BPH) and underlying bladder dysfunction due to diabetes; the relationship between the two is not well understood (29). With regard to sexual function, the most used outcome measures are the Female Sexual Function Index and International Index of Erectile Function (29, 38, 39). When diagnosing ED, the clinician should take care to exclude hypogonadism and consider other etiologies, including hypertension, hyperlipidemia, obesity, smoking, cardiovascular disease, medication use, and psychogenic factors (1).

TREATMENT

Diabetic Peripheral Neuropathy

BPH: benign prostatic hyperplasia

Despite advances in elucidating the pathogenesis of DPN, there are no current disease-modifying therapies. Developments in treatment have been challenging with many possible targets, and to date, various agents addressing those targets have failed to meaningfully alter or reverse the disease

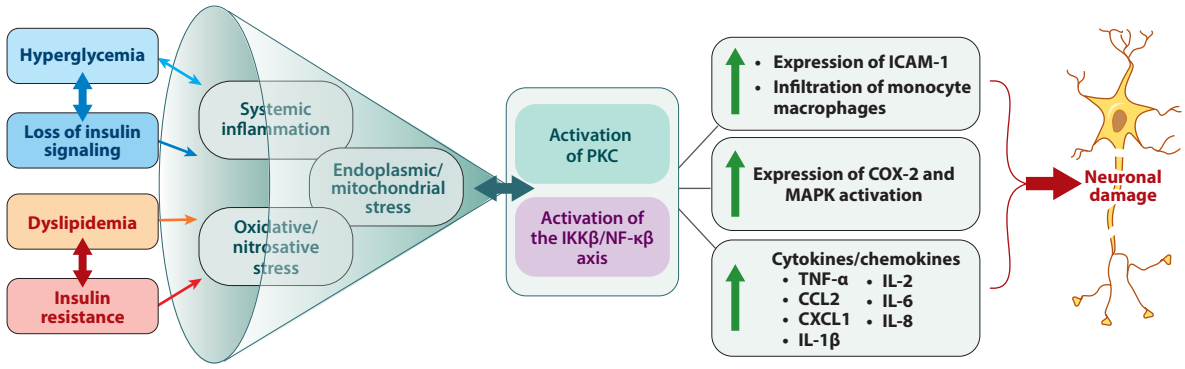

Figure 2

The role of chronic inflammation in diabetic peripheral neuropathy pathogenesis. Hyperglycemia, altered insulin signaling, and insulin resistance together with dysregulated lipid metabolism result in systemic inflammation, endoplasmic reticulum and mitochondrial stress, and ongoing cycles of oxidative/nitrosative stress. These lead to activation of multiple downstream kinases, including PKC, MAPK, and IKKβ, with activation of the NF-κβ family of redox-sensitive transcriptional regulators, in addition to induced expression of ICAM-1 and COX-2. There is also a cascade of proinflammatory cytokine and chemokine production, notably TNF-α, CCL2, CXCL1, IL-1β, IL-2, IL-6, and IL-8, which amplifies inflammatory responses, leading to cellular damage with consequent neuronal damage and loss. Abbreviations: CCL2, chemokine (C-C motif) ligand 2; COX-2, cyclooxygenase-2; CXCL1, chemokine (C-X-C motif) ligand 1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IKKβ, inhibitor of nuclear factor κB kinase subunit β; MAPK, mitogen-activated protein kinase; NF-κβ, nuclear factor κβ; PKC, protein kinase C; TNF-α, tumor necrosis factor-α.

course in human trials or proved too toxic in development (1, 2, 5). There has been an important shift away from a focus on glucose metabolism alone toward the role that metabolic and inflammatory factors play in DPN pathogenesis, with a need for development of potential treatments targeting these factors (2). The role of low-grade inflammation in the pathogenesis of DPN is well established, and the underlying cellular mechanisms have been identified (**Figure 2**) (40).

Given the current absence of disease-modifying therapies in DPN, prevention is paramount. While intensive glycemic control targeting euglycemia significantly reduces DPN incidence in T1D with a relative risk reduction of 78% (1, 41, 42), its effects in T2D are less pronounced with a relative risk reduction of 59% (9, 43), most likely in the setting of other contributing comorbidities and risk factors (1, 2). Lifestyle interventions have demonstrated success in preventing and perhaps even reversing DPN (1, 2, 44–47). These interventions have focused on exercise (aerobic and/or resistance training), dietary modification, or a combination of both. In one example, a lifestyle intervention featuring dietary recommendations and moderate-intensity exercise modeled on the Diabetes Prevention Program resulted in improved small fiber reinnervation as measured by intraepidermal nerve fiber density in participants with T2D or metabolic syndrome without clinical signs or symptoms of DPN (48). While the Diabetes Prevention Program used a low-calorie, low-fat diet, there is no established consensus on the optimal dietary plan, and others have advocated a Mediterranean diet (1). Finally, given the increased risk for impaired balance and falls, supervised exercise training has the potential to improve mobility, balance, and gait in older adults with DPN (49).

Current treatment of painful DPN primarily involves symptomatic therapies and remains very challenging (2, 5). Although numerous guidelines address the treatment of all-cause neuropathic pain, only a few trials have evaluated neuropathic pain in DPN alone (1, 5, 50). In clinical practice, it is important to consider alternative etiologies of pain, including nondiabetic neuropathic or non-neuropathic causes (1, 5, 36). Medication classes with evidence for effective pain

reduction in DPN include gabapentinoids, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants (TCAs), and sodium channel blockers (1, 2, 5). Due to similar effect sizes with minimal differences across classes, selection should be guided by tolerability, contraindications, and cost, but for most individuals with painful DPN, combining drugs from different classes is needed to achieve clinically relevant pain reduction (1, 2, 5).

A randomized, double-blind, head-to-head, crossover trial evaluated amitriptyline, pregabalin, and duloxetine for diabetic peripheral neuropathic pain (51). To mirror clinical practice, participants were started on monotherapy with one of the three agents, supplemented by a combination medication after 6 weeks if pain relief was suboptimal in three designed treatment pathways. All three monotherapies and pathways were similarly efficacious, and combination therapy was well tolerated, with improved analgesia in those participants who experienced suboptimal pain control with monotherapy (51). Unfortunately, less than one-third of individuals experience adequate pain relief with existing pharmacotherapies (52), which underscores the need for more effective modalities. Another pharmacological alternative is the topical 8% long-acting capsaicin patch, which is approved by the US Food and Drug Administration (FDA) for painful DPN with the benefit of fewer central adverse effects (2, 5).

Of note, opioids have a very weak level of evidence for pain control in people with painful DPN in short-term studies, and there are no long-term data on their efficacy (1, 2, 5). Unfortunately, despite this, their use remains unacceptably high in the community, resulting in high rates of complications, addiction, overdose, and death that are higher in people with diabetes even with short-term use (1, 2, 5). Thus, current guidelines strongly recommend against their use (1, 5, 53).

Nonpharmacological approaches, such as nutraceuticals or exercise, may also be effective for painful DPN (1, 2, 5). In addition, high-frequency spinal cord stimulation was also FDA-approved for painful DPN based on the results of a large, randomized trial that demonstrated significant pain relief and improved quality of life in people with painful DPN refractory to medical therapy (54). Additional studies are needed to test whether spinal cord stimulation and other technologies may also be effective as a disease-modifying approach for painful DPN.

DPN can have profound effects on an individual's quality of life and mental health. Optimal management likely includes provision of adequate behavioral and psychological support. While some data suggest benefit with exercise, cognitive-behavioral therapy, and mindfulness, further investigation is needed (55).

Cardiovascular Autonomic Neuropathy

For CAN, as for DPN, intensive glycemic control targeting euglycemia is most effective for prevention in T1D, as best evidenced by the 45% reduction in the risk of incident CAN during the DCCT and 31% reduction during the EDIC follow-up study (56, 57). In comparison, studies evaluating the effects of glycemic control on the risk of CAN in T2D are not consistent in their findings (1, 9, 13, 35). A multifactorial approach may be best, targeting additional risk factors and comorbidities. For example, in the Steno-2 cohort, a multifactorial intervention combining glycemic control with optimal pharmacological and lifestyle management of cardiovascular disease risk factors was associated with a 63% reduction in the risk of CAN (47). More recently, a study in Germany found that a 12-week period of high-intensity interval training improved CAN indices in a small group of overweight men with T2D (58). Larger, longitudinal studies are needed to characterize the ideal exercise type and duration as well as to establish the long-term sustainability of the effect (2).

There are no current disease-modifying treatments for CAN, despite advances in understanding of disease pathogenesis (1, 13). As with DPN, inflammatory targets are of interest. Many of the

inflammatory biomarkers thought to be involved in DPN pathogenesis were found to be inversely related to indices of HRV in T1D (59). Recently, levels of the inflammatory marker suPAR (soluble urokinase plasminogen activator receptor) were found to be negatively associated with measures of CAN in T1D (60). As such, suPAR's role as a potential biomarker and treatment target in CAN and possibly other autonomic neuropathies warrants further investigation.

Current CAN treatment is aimed at addressing symptoms. Orthostatic hypotension is particularly of concern and often requires a mixed approach using both behavioral and pharmacological interventions (1). Individuals should be counseled on adequate hydration, positional techniques, trigger avoidance, and counter-pressure maneuvers (1, 13, 35). Medications that may worsen hypotension, such as TCAs, phenothiazines, and diuretics, should be discontinued and avoided if possible (13). When needed, pharmacological treatments include use of sympathomimetics, including midodrine and droxidopa, or use of fludrocortisone in selected individuals who respond transiently or partially to nonpharmacological measures of volume repletion (1, 13, 35).

Gastrointestinal Autonomic Neuropathy

Initial management of gastroparesis consists of dietary modifications, such as eating multiple small meals and decreasing fat and fiber intake (1). When possible, drugs that slow gastric emptying should be stopped and avoided, including opioids, anticholinergics, TCAs, GLP-1 receptor agonists, pramlintide, and marijuana (1). Improved glucose variability through use of technologies including sensor-augmented pumps and semi-closed-loop insulin pumps can be used to avoid effects from extremes in glucose levels in either direction, in conjunction with attempts to optimize gastric motility (2). Management of severe gastroparesis requires pharmacological therapy. Although metoclopramide is FDA-approved for this indication, its use should be limited to 5 days or less given the risk for extrapyramidal symptoms (1).

Urogenital Neuropathy

Most data pertaining to the role of glycemic control in prevention of urological complications in diabetes come from the DCCT/EDIC ancillary UroEDIC study. With respect to LUTS in women with T1D, in the UroEDIC cohort at EDIC year 17, higher A1c was associated with incident UI, which was independent of age, body mass index, and DCCT treatment arm (61). In women with diabetes, there is a need for studies assessing the full range of LUTS (29). Lifestyle interventions alone have demonstrated benefit in symptom improvement (62, 63). Research is needed to better understand how diabetes contributes to the range of LUTS in women, in order to identify targets for treatment (29). Clinical trials assessing behavioral, pharmacological, and surgical treatments for UI in women with diabetes are needed, including the impact of standard diabetes treatment, standard UI treatment, and their combination (29).

In the UroEDIC cohort, intensive glycemic control did not decrease LUTS severity in men with T1D, although this may have been limited by the relatively young age of the cohort (33). It is important to recognize that LUTS as a syndrome in men may be produced by a myriad of different bladder-related etiologies, including diabetes and BPH (29). Future investigation must distinguish BPH-associated LUTS from non-BPH LUTS, in an effort to understand how diabetes influences BPH and LUTS phenotypes and tailor treatment accordingly (29).

In women with T1D in UroEDIC, depression and marital status were the only risk factors for FSD, notably not glycemic control; therefore, it is likely critical to address psychosocial factors in treatment (31). Additionally, as is also the case for men, multiple medications used to treat conditions comorbid with diabetes, including hypertension, hyperlipidemia, and depression, are associated with side effects of sexual dysfunction (29). Treatment for FSD in general includes

vaginal lubricants, low-dose hormone therapy, and psychological counseling; however, there is a need for clinical trials investigating the effects of nonpharmacological and pharmacological treatments for FSD specifically in women with diabetes (29, 64).

In the UroEDIC cohort, intensive glycemic control was associated with decreased risk of incident ED in men with T1D (34). A similar effect has not been shown in men with T2D (1). Lifestyle interventions are likely of benefit in preventing worsening erectile function but not improving it (29, 65). It is important to recognize that the etiology of ED is often multifactorial, and interventions should address concurrent vascular disease, hypertension, hyperlipidemia, smoking, obesity, depression, anxiety, and medication side effects (1). Pharmacological therapy includes phosphodiesterase type 5 inhibitors as first-line agents (1). Other potential treatments include transurethral prostaglandins, intracavernosal injections, vacuum devices, and penile prostheses in refractory cases (1). Overall, there is a need for clinical trials to assess treatments for ED in men with T1D and T2D, including the impact of standard diabetes treatment, standard ED treatment, and their combination (29).

Finally, in those with diabetes, the presence of CAN may predict risk for urological complications, particularly ED and LUTS in men and FSD and UI in women (66). Improvements in CAN detection at the point of care, discussed above, may serve to identify those individuals at risk and facilitate strategies for prevention and treatment.

CONCLUSION

In summary, DN is a prevailing complication in both T1D and T2D and encompasses a broad spectrum of clinical manifestations ranging from distal, symmetric polyneuropathy to autonomic neuropathies, including cardiovascular, gastrointestinal, and urogenital. While the diagnosis of DPN in clinical practice is established, challenges remain in the widespread implementation of methods for detection of subclinical disease. Furthermore, current symptomatic therapy for painful DPN is inadequate, and there is a critical need for disease-modifying agents, with a recent shift in the field to focus on metabolic and inflammatory targets. CAN is a deadly complication of diabetes, but individuals are asymptomatic in early disease, making diagnosis challenging. However, recent developments in diagnostic methods to be used at the point of care are promising. As with DPN, there is a need for disease-modifying agents that alter the natural history and reverse disease course. Although gastroparesis prevalence rates are comparatively low, morbidity and healthcare utilization remain high, making optimal diagnosis and management a priority. Bladder and sexual dysfunction are exceedingly common in both women and men with diabetes. Research is needed to uncover the underlying pathophysiology and investigate potential treatment targets. Finally, elucidating the role of SDOH in complications risk and progression will be essential to the development of tailored interventions.

DISCLOSURE STATEMENT

R.P.-B. reports receiving grant support from Lexicon Pharmaceuticals, Medtronic, and Novo Nordisk and consulting fees from Averitas Pharma, Lexicon, Nevro Inc, Novo Nordisk, and Procter and Gamble. B.R.D. and L.A. report no disclosures.

ACKNOWLEDGMENTS

R.P.-B. is supported by grants R01-DK-107956-01, U01 DK119083, and R01-DK126837-01A1, and by the JDRF Center of Excellence at the University of Michigan. L.A. is supported by the JDRF Center of Excellence at the University of Michigan.

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