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REVIEWS AND COMMENTARIES

Diabetic neuropathy in children and youth: New and emerging risk factors

Gulcin Akinci | Masha G. Savelieff | Gary Gallagher | Brian C. Callaghan | Eva L. Feldman

Department of Neurology, University of Michigan Medicine, Ann Arbor, Michigan, USA

Correspondence
Eva L. Feldman, University of Michigan, 109 Zina Pitcher Place, 5017 AAT-BSRB, Ann Arbor, MI 48109, USA.
Email: efeldman@umich.edu

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Abstract

Pediatric neuropathy attributed to metabolic dysfunction is a well-known complication in children and youth with type 1 diabetes. Moreover, the rise of obesity and in particular of type 2 diabetes may cause an uptick in pediatric neuropathy incidence. However, despite the anticipated increase in neuropathy incidence, pathogenic insights and strategies to prevent or manage neuropathy in the setting of diabetes and obesity in children and youth remain unknown. Data from adult studies and available youth cohort studies are providing an initial understanding of potential diagnostic, management, and preventative measures in early life. This review discusses the current state of knowledge emanating from these efforts, with particular emphasis on the prevalence, clinical presentation, diagnostic approaches and considerations, and risk factors of neuropathy in type 1 and type 2 diabetes in children and youth. Also highlighted are current management strategies and recommendations for neuropathy in children and youth with diabetes. This knowledge, along with continued and sustained emphasis on identifying and eliminating modifiable risk factors, completing randomized controlled trials to assess effectiveness of strategies like weight loss and exercise, and enhancing awareness to support early detection and prevention, are pertinent to addressing the rising incidence of neuropathy associated with diabetes and obesity in children and youth.

KEYWORDS
children, diabetes complications, neuropathy, risk factors, youth

1 | INTRODUCTION

Peripheral neuropathy is a heterogeneous group of diseases characterized by peripheral nerve damage. Associated signs and symptoms include sensory loss, paresthesia, and pain.[1-3] Numerous inherited and acquired causes of peripheral neuropathy manifest in children and youth.[2-4] Inherited forms include Charcot-Marie-Tooth disease and inherited metabolic disorders, such as Fabry disease, Leigh syndrome, and metachromatic leukodystrophy.[4-6] Acquired neuropathy can occur with diabetes, infectious disease, toxin exposure, vasculitis, compression/trauma, vitamin deficiencies, and immune-mediated disorders.[2,7-10]

While peripheral neuropathy in children and youth is primarily due to hereditary causes,[2,8] diabetes is increasingly reported as the cause of neuropathy in children and youth.[11-15] Type 1 diabetes (T1D) accounts for about 98% of all diabetes cases younger than 10 years and 87% of all diabetes cases in adolescents (aged 10–19 years).[16] As the prevalence of T1D and type 2 diabetes (T2D) is rising among this demographic,[17-23] the incidence of pediatric diabetic neuropathy (DN) is also increasing. Moreover, the lifetime exposure to diabetes is longer in subjects diagnosed in early life.[9] Given that diabetes complications emerge with disease longevity, the increasing diabetes rates in children and youth is alarming since many will be at risk of diabetes

complications in early adulthood.[14] Longstanding, poorly controlled diabetes is a well-established DN risk factor.[24,25] Recent data, however, implicate risk factors beyond hyperglycemia for childhood onset DN.[14,26]

Two recent studies, SEARCH for Diabetes in Youth (SEARCH) and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY), have enhanced our understanding of risk factors and management of pediatric T2D. In 2001, SEARCH reported a diabetes prevalence of 6% in the US pediatric population,[19,27,28] and follow-up assessments from 2002 to 2009 reflected increases in T1D and T2D prevalence, with a steeper 30% increase in T2D.[18,19,28] Early signs of diabetic complications, including DN and cardiovascular autonomic neuropathy (CAN), were evaluated in a smaller SEARCH cohort, the first US study to systematically determine the prevalence and predictors of DN.[18,27-29] TODAY, which ended in 2011,[22] compared outcomes following different treatments for youths with T2D (n = 699) with a disease duration ≤2 years and body mass index (BMI) ≥85th percentile at diagnosis.[30,31] Preliminary findings from the TODAY2 long-term observational study tracking T2D progression, comorbidities, and complications as participants transition to young adulthood demonstrated high DN prevalence.[22] These recent large studies are a testament to the rising prevalence of youth-onset T2D and the need to identify risk factors and therapeutic management options.

This review presents the current state of knowledge on the prevalence, clinical presentations, and traditional and emerging DN risk factors in children and youth with both T1D and T2D. Pediatric T1D is the significantly more prevalent diabetes type and many excellent reviews have been published on the subject.[14,15] Herein, we place a significant focus on the less prevalent T2D, due to its steeper rise in incidence compared to T1D and as an emergent health issue and cause of DN in children and youth. Given the public health importance of the increasing childhood diabetes prevalence and high DN burden, identifying emerging risk factors is crucial for developing vigilant screening, early detection, and eliminating modifiable risk factors.

1.1 | DN prevalence in children and youth

Prevalence studies in children and youth are limited and hard to generalize to general populations with diabetes due to variability in the tests used to diagnose neuropathy across studies. Many children and youth also have subclinical neuropathy, which is not diagnosed unless sensitive tests and/or detailed neurological examinations are performed.[26,32,33]

Neuropathy is present in T1D, with a prevalence ranging from 3 to 62%. In the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, clinical history and neurological exams identified neuropathy in only 3% of patients with T1D ≤18 years old (n = 400), but prevalence was higher for young adults with longer disease duration.[34] The multicenter EURODIAB IDDM Complications Study[35] (3,250 subjects with T1D) reported DN in 19% of subjects aged 15 to 29, as assessed by symptoms and reflex loss, vibration perception threshold (VPT), and autonomic dysfunction, with increased prevalence with older age and longer diabetes duration. In contrast, a population-based longitudinal Danish study reported a DN prevalence of 62% in 339 subjects with T1D aged 12–27 years using VPT.[36] Additionally, in 73 subjects with a mean age of 13.6 years with T1D duration ≥5 years, only 4% reported neuropathy symptoms, yet 36% had an abnormal neurological exam, 57% had nerve conduction abnormalities, 51% had abnormal VPT, and 26% had abnormal tactile perception thresholds.[32] Using nerve conduction studies (NCS) as a confirmatory tool, screening 151 youths with T1D by neurological examination and a modified version of MNSI identified DN in 11% of the subjects.[37] Other studies have confirmed a high prevalence of abnormal nerve conductions in children and adolescents with variable T1D duration and metabolic control.[33,38-44] DN signs are also reported with shorter diabetes duration; an Australian study reported abnormal VPT and thermal perception threshold (TPT) tests in 14% of youth aged 11 to 17 years (n = 819) with only 2 to 5 years T1D duration.[45]

For T2D, the first documentations of DN in children and youth came from single case reports and small case series, which implicated susceptibility to DN.[46,47] A population-based longitudinal Australian study of youths with T1D (n = 1,433; median T1D duration 6.8 years) and T2D (n = 68; median T2D duration 1.3 years) showed similar rates of peripheral (27% T1D; 21% T2D) and autonomic neuropathy (AN) (61% T1D; 57% T2D) using VPT, TPT, and pupillometry.[48] Strikingly, neuropathy, determined using the Michigan Neuropathy Screening Instrument (MNSI), was more common in T2D (22%; n = 258) versus T1D (7%; n = 1,734) in the SEARCH cohort among subjects with similar diabetes duration.[12,49] Similarly, a Canadian population of 1,011 subjects with T1D (mean age 8.9 years, 53.2% male; of note, the subject number was mislabeled in the original article), 342 subjects with T2D (mean age 13.5 years, 37.8% male), and 1,710 controls without diabetes exhibited shorter neuropathy-free survival for youths with T2D versus T1D.[50] Preliminary analysis of TODAY2 showed high rates of macro- and microvascular complications, with DN in 28–33% of subjects by year 12 and increased prevalence in males.[22]

CAN, an independent predictor of cardiovascular mortality,[51-54] is also highly prevalent among adolescents with T1D and T2D. A systematic analysis of 19 studies comprising 3,943 subjects with T1D ≤24 years of age reported subclinical CAN prevalence ranging from 16 to 75%, depending on the outcomes reported.[55] Methodical evaluation of CAN in SEARCH also showed early signs of autonomic dysfunction in youth[56] at prevalence rates of 12 and 17% in participants with T1D (18 ± 4 years old) and T2D (22 ± 4 years old), respectively.[13] The prevalence of cardiac autonomic dysfunction was 8% in a cohort with T2D from the TODAY study (397 participants; mean age 20.7 ± 2.5 years; diabetes duration 7.7 years; 64.7% females; BMI 36.6 kg/m^2).[57]

1.2 | DN clinical presentations

Distal symmetric polyneuropathy (DSP) is the most common DN presentation.[58] Although the terms "diabetic neuropathy" and

"peripheral neuropathy" are frequently used to refer to DSP, DN is a family of several neuropathy types,[58,59] including mononeuropathies and radiculopathies, which are rare in childhood.[47,60,61] DSP can be classified as: (a) primarily small fiber neuropathy, defined as impairment of small unmyelinated or thinly myelinated axons, which carry pain and temperature information, (b) large fiber neuropathy, defined as impairment of myelinated fibers, which relay vibratory and proprioceptive information, or (c) a mixed polyneuropathy where both fiber types are involved with corresponding loss of all sensory modalities. DSP is a mixed polyneuropathy, which usually starts as small fiber neuropathy[62,63] and progresses to a large fiber neuropathy in a length-dependent "stocking-glove" pattern, that is, starts in the feet and slowly spreads distally-to-proximally. Most children and youth with early DSP are asymptomatic or have mild symptoms. Classically, DSP presents with spontaneous and stimulus-evoked distal extremity pain, sensory impairments like paresthesias, altered temperature sensations, neuropathic itch, burning, tingling, or deep aching. Symptoms generally worsen at night. Although DSP is primarily a sensory neuropathy, there may be later distal motor nerve involvement, typically detected by weakness of the extension. However, motor unit number estimation (MUNE), an electromyography metric, can detect motor unit loss at earlier disease stages. Significantly, lower MUNE is reported in asymptomatic children with T1D,[64] but profound early muscle weakness warrants a differential diagnosis for other causes, for example, Charcot-Marie-Tooth disease.[65]

Diabetes is a common cause of AN,[66,67] which may affect both sympathetic and parasympathetic fibers. Overt AN is rare in children, but autonomic dysfunction signs can be detected a few years after diabetes diagnosis.[68-71] AN most commonly presents with impaired gastric emptying and brittle diabetes, as well as vomiting, diarrhea, constipation, and fecal incontinence. Brittle diabetes is a term used to describe difficult to treat diabetes, which is characterized by severe glycemic instability and unexpected hypoglycemic episodes.[72-74] AN also causes neurogenic bladder. However, all these above-stated AN symptoms are rare in children and youth.[75,76]

CAN is a serious diabetes complication, which presents with a wide range of symptoms, including exercise intolerance, heart palpitations, orthostatic tachycardia syndrome, postural hypotension, lightheadedness, silent myocardial infarctions, and sudden death.[67] CAN may relate to impaired hypoglycemia awareness, a serious condition associated with severe hypoglycemic episodes[77,78] and neuroglycopenia,[78] by altering the counter regulatory catecholamine response to hypoglycemia and diminishing autonomic alarming symptoms. This phenomenon becomes more severe when the glucagon response is lost. Although recent studies provided evidence of impaired glucagon response, already in the early phases of T1D,[79] glucagon response to hypoglycemia is generally completely lost in many patients with longstanding T1D.[80] Also, repeating hypoglycemic episodes in T1D may lead to a phenomenon called "hypoglycemia-associated autonomic failure," which can contribute to defective glucose counter-regulation. In children and youth with T1D or T2D, CAN is associated with arterial stiffness, a well-documented risk factor, which predicts future cardiovascular events.[56,57,81] Early CAN may be asymptomatic, but can be detected by reduced heart rate variability (HRV),[82,83] which can develop after a mean diabetes duration of 8 years in children and youth.[13]

1.3 | DN diagnosis in children and youth

DN diagnoses are based on symptoms and signs. A careful differential diagnosis is essential,[84] since potential treatable and reversible neuropathies, such as vitamin B12 deficiency or inflammatory neuropathies, can be present in young diabetes patients and should be considered.[59,85] Unique presentations should alert physicians to the possibility of neuropathies other than DN, for example, acute or subacute presentations, upper limb involvement, severe painful or asymmetrical neuropathy, cranial nerve involvement, family history, and presence of distinct hereditary neuropathy characteristics.

1.3.1 | Symptoms

DN is rarely reported in pediatric practice, likely due to subclinical presentation,[26,32,33] and children and youth may not voluntarily report DN symptoms. Early DN symptoms are usually related to small fiber involvement.[58,86] Several scoring systems exist to screen and evaluate neuropathic symptoms, though most are validated for adults.[87-89] A study in a small cohort developed self-reported measures for youth and found that they may suffer from unique DN symptoms.[90] Pain and dysesthesias are the most common presentation,[58,90,91] but patients should also be questioned for hyperalgesia and allodynia. Symptoms like gait imbalance, and weakness may arise with large fiber involvement.

1.3.2 | Neurological examination

Neurological exams assess small and large fiber functions. Small fiber function is evaluated by pinprick and temperature sensation, while large fiber function is usually evaluated by VPT and proprioception.[58,59] Motor function should be examined, with specific attention to great toe extension. More profound weakness should prompt consideration of alternative etiologies.[59,92] Reflexes, with attention to ankle reflexes, should be checked. DN may cause bounding pulses; dorsal pedal and posterior tibial pulses should be checked to rule out impaired peripheral circulation.[16]

1.3.3 | MNSI

MNSI is an easy, accurate, and widely used screening tool to detect DN,[93,94] including in children and youth.[12,37] MNSI has high specificity (95%) and sensitivity (80%) to detect DN in adults.[93,94] Although the tool has not been formally validated in children, several groups has used the original or modified versions to detect DN in pediatric

populations.[12,37] The two main parts include a questionnaire of key DN symptoms, and a focused neurological examination with foot inspection, great toe VPT, and ankle reflexes. MNSI can further be combined with other additional tests, TPT or pinprick sensation, to evaluate small fiber function.

1.3.4 | Quantitative sensory testing (QST)

QST relies on a patient's response and cooperation to quantitate levels of sensorial involvement.[95,96] Monofilament testing applies a predefined force using a 10-g Semmes-Weinstein nylon filament to evaluate light-touch perception and assess foot ulcer development risk.[97] Monofilament testing characteristics vary in sensitivity (19–73%) and specificity (64–87%).[32,98] VPT evaluates large myelinated fiber function,[99,100] most commonly in clinical practice using a 128 Hz tuning fork,[59] which has high specificity but low sensitivity.[98,101] The Rydel-Seiffer graduated 64 Hz tuning fork may provide a quantitative VPT measurement.[102] The use of graduated fork has been shown to be reliable in adults,[103] but its sensitivity and specificity in children may be poor.[101,104] Alternative VPT-measuring devices are also available, for example, biothesiometer, neurothesiometer,[105,106] and pocket-sized Vibratip™.[107] Although finer monofilaments and electronic devices, like biothesiometers, are more sensitive,[32,101,106] additional research is needed to determine their utility in clinical pediatric practice. The sensitivity and specificity of biothesiometry to detect DN was reported as 82 and 75% in children and adolescents with T1D.[106] However, the reproducibility of VPT was low in children.[108] TPT detects small fiber dysfunction[109]; however, the lack of standardized testing procedures and reference values limits its clinical use in children and youth.[98,110,111]

1.3.5 | NCS

NCS are the accepted gold standard for objectively detecting and quantifying early changes in DN, but they are time-consuming and expensive.[42,44,92,112-115] NCS detect DN-induced reductions in sensory nerve action potential (SNAP) amplitudes accompanied with mild slowing of motor conduction velocities.[116] Age, sex, height, weight, and surface temperature are important parameters for interpreting results.[117] Current algorithms suggest that if sural sensory and peroneal motor NCS in one distal lower extremity are normal, no further NCS are needed.[118,119] Abnormal test parameters in at least two separate nerves are generally sought to confirm DN.[87,120] NCS are rarely used in children and youth to diagnose DN, but are helpful to exclude inherited or inflammatory neuropathies. NCS assess large fibers, thus readings can be normal in patients with early DN, when small fibers are primarily affected. Nevertheless, NCS abnormalities in one or more nerves can be detected in children.[37,101,104] Also, some children would poorly tolerate the technique because of the discomfort caused. Despite having been used in the DCCT study, the use of NCSs to monitor the progression of DN is still limited in pediatric age.[121]

1.3.6 | Autonomic function testing

Symptoms and signs of diabetic AN, such as resting tachycardia, reduced exercise tolerance, and gastroparesis, should be investigated.[55,58,122] CAN may be asymptomatic in earlier diabetes stages in pediatric patients, but can be detected by reduced HRV.[13,59,123] Orthostatic hypotension can be documented in more advanced CAN. Age- and race/ethnic-dependent variations in HRV should be accounted for while interpreting test results.[124-127] Several approaches can identify CAN, including evaluation of HRV and blood pressure changes following various maneuvers, such as deep breathing, standing, and Valsalva maneuver,[122,128] but cardiovascular reflex tests are the gold standard.[122128] Other autonomic dysfunction tests include the thermoregulatory sweat test, quantitative sudomotor axon reflex test, sympathetic skin response test, pupillometry, and gastric emptying scintigraphy.[129-133] Like NCS, these techniques are uncommonly used for CAN testing in children and youth due to limitations, for example, sophisticated, time consuming, expensive, specific equipment requirements, and usually assess rare DN presentations in childhood.

1.3.7 | Skin biopsy

Immunohistochemical analysis of skin punch biopsies provides a sensitive, reproducible, quantitative measure of small unmyelinated sensory fiber neuropathy by counting intraepidermal nerve fiber density (IENFD).[134] It is usually well tolerated in neuropathy research, but is seldom used in children and youth as it is considered invasive and pediatric reference values are lacking.[63,135]

1.4 | DN risk factors in children and youth

Beyond hyperglycemia, several risk factors for DN in children and youth with diabetes have emerged in recent years. These risk factors are further discussed below, and likely interconnect in a multifactorial manner to promote DN development (Figure 1).

1.4.1 | Traditional risk factors

The role of hyperglycemia in DN has been examined by several large, well-designed clinical studies. The Pittsburgh EDC study showed a significant association between baseline HbA1c and DN in subjects with childhood-onset T1D,[34] and that long-term HbA1c improvement correlated with lower DN incidence.[136] EURODIAB demonstrated that DN prevalence increased in parallel with elevated HbA1c,[24] and the Diabetes Control and Complications Trial (DCCT) found that good glycemic control prevents or delays DN development and progression in T1D.[121] Several additional studies in children and youth with T1D confirmed an increased DN risk with poor glycemic control and longer disease duration.[42,115,137-141]

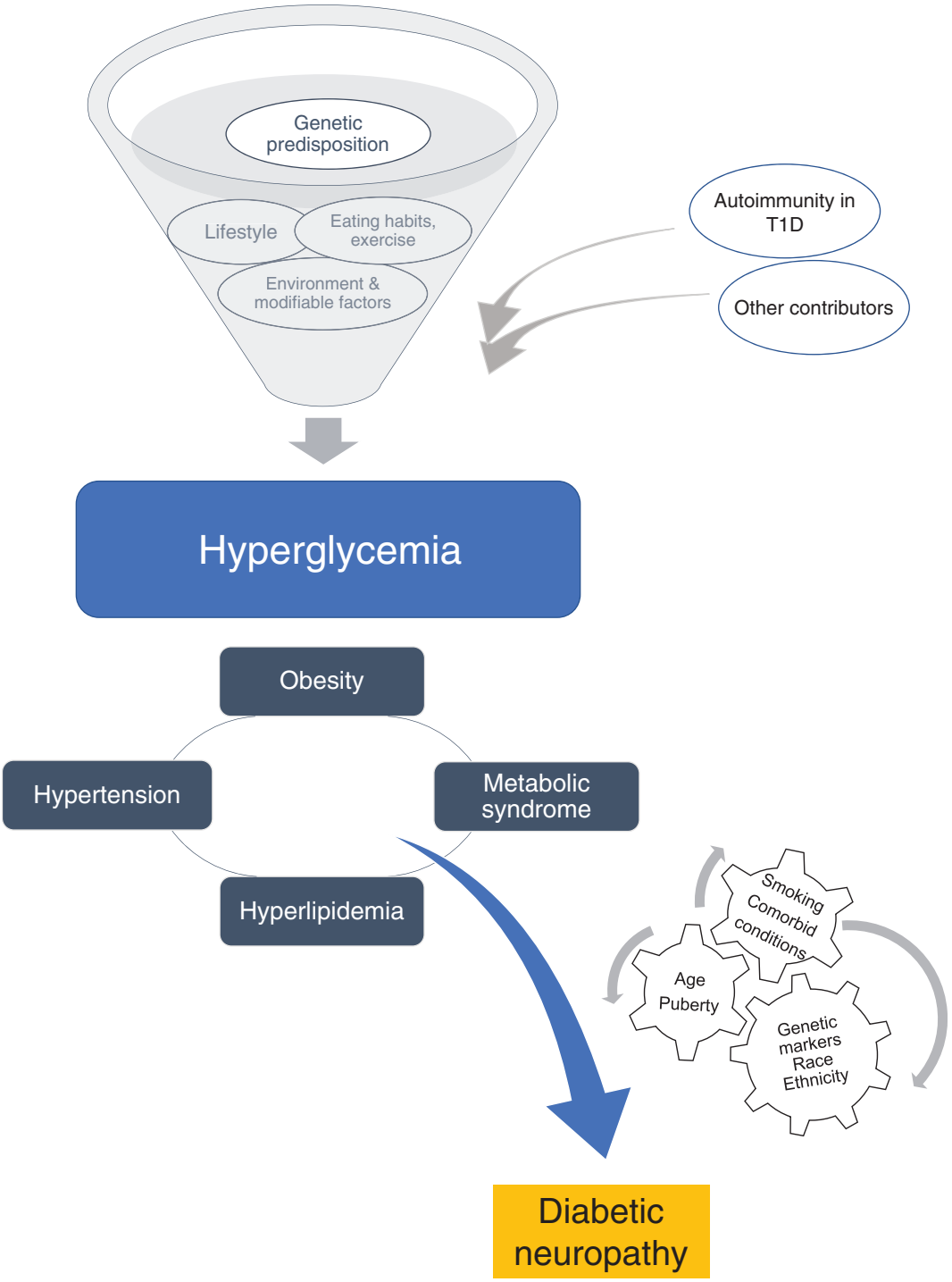

FIGURE 1 Risk factors underlying DN in children and youth. DN development in pediatric populations is likely due to complex, multifactorial factors that interconnect to drive nerve damage. Traditionally, hyperglycemia is the main DN risk factor, and the duration of diabetes and poor glycemic control are two major drivers of nerve damage. In addition to these well known risk factors, emerging data suggest multifactorial etiology. Diet, lifestyle, and genetic predisposition can all contribute to the onset of metabolic syndrome and associated features, including obesity, hyperlipidemia, hypertension, and hyperglycemia. In parallel, age, puberty, genetics, race, ethnicity, smoking, and other comorbid conditions further compound DN risk

Overall, the evidence suggests that well-controlled glucose delays DN development and progression in T1D.[142] In contrast, in T2D, the impact of improved glycemic control on DN progression is moderate in adults,[143] and few studies have been conducted in children and youths.[92] Disease duration associates with higher DN prevalence in T2D.[50] SEARCH demonstrated a significant relationship between DN and diabetes duration in children and adolescents with T1D and T2D.[12] In a recent Asian Indian study in children/youths with T2D,

DN prevalence by VPT increased from 3% (n = 165) with a diabetes duration <5 years to 49.2% (n = 61) with a duration >15 years.[144] Further research is needed to better understand the evolution and DN risk factors in youth with T2D, though recent studies are highlighting novel findings (see "Emerging risk factors").

Hyperglycemia is a well-documented risk factor for CAN development and progression, as clearly shown in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) long-term follow-up of the T1D DCCT cohort.[145] Glycemic control and CAN were also significantly correlated in EURODIAB.[146] The effect of glycemic control on CAN in T2D is less clear[13,147]; more research is required.

1.4.2 | Emerging risk factors

Obesity and dyslipidemia: Recent studies support additional risk factors for DN beyond hyperglycemia.[148] Our meta-analysis of interventional studies found that good glycemic control delays DN progression in adults with T1D, but much less so in adults with T2D.[143] Indeed, in clinical adult populations, we[142,149-154] and others[155-158] have shown that the metabolic syndrome (MetS), independent of glycemic status, raises the risk of developing DN.[159] MetS is an array of metabolic impairments, which include obesity (larger waist circumference), dyslipidemia (an abnormal lipid profile, e.g., adult characteristics are triglycerides ≥150 mg/dL; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL males, <50 mg/dL females), elevated fasting glucose (≥100 mg/dL), and hypertension (systolic ≥130 or diastolic ≥85 mmHg).[160]

Defining MetS is more challenging in children and adolescents due to intra-individual variation over time.[161] However, available studies in childhood cohorts reveal a similar correlation between obesity and dyslipidemia with increased DN risk. EURODIAB followed youths and young adult enrollees with T1D for 8 years to identify incident DN risk factors other than glycemia. They observed that elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, BMI, and hypertension, correlated with DN risk, after adjusting for HbA1c and diabetes duration.[24] SEARCH found that obesity, increased triglycerides, LDL-C, diastolic blood pressure, and decreased HDL-C were DN risk factors in youths with T1D, but that poor glycemic control over time was also a DN risk, even after adjusting for several parameters.[12] In contrast, lower HDL-C correlated with higher DN risk in youths with T2D, independent of glucose regulation. SEARCH found similar effects of dyslipidemia on CAN, with elevated triglycerides increasing DN development in youths with T1D and T2D.[13] Higher BMI and central adiposity, after adjusting for HbA1c, likewise predicted CAN, measured by HRV, at follow-up in participants with T1D (n = 253, aged 8–30 years).[162]

A few small scale studies have shown the association of obesity and neuropathy in children with impaired fasting glucose or insulin resistance without clinical diabetes. NCS on adolescents with obesity and impaired glucose tolerance (n = 15), insulin resistance (n = 31), and normal glucose tolerance (n = 23) versus age- and sex-matched controls without obesity (n = 32) revealed significant differences in medial plantar mean SNAPs, although most parameters did not differ across groups.[163] Another study of adolescents with obesity with (n = 27) and without insulin resistance (n = 33) in Turkey found medial and sural SNAP abnormalities versus controls (n = 30), along with slowed medial and peroneal nerve conduction velocities (NCVs).[164] Recently, BMI was found to be associated with cardiac autonomic dysfunction in the TODAY study.[57]

Comorbid microvascular complications: Several studies indicate that DN is linked to the presence of microvascular complications. In Pittsburg EDC patients with T1D, DN correlated with nephropathy, retinopathy, and cardiovascular disease (CVD) in univariate analysis.[34] EURODIAB also found that CVD and albumin excretion rate correlated with a raised cumulative risk of DN incidence.[35] A systematic review further reported associations of AN with nephropathy and retinopathy in several studies after adjusting for covariates.[55]

Genetic markers: Genetic susceptibility to DN has been recently reviewed in T1D[26] and T2D[26,165]; thus, only salient points related to diabetes pathophysiology[166] and new directions are highlighted here. Highly relevant are single-nucleotide polymorphisms (SNPs), either injurious or protective, in genes related to metabolism (aldose reductase [*AKR1B1*] involved in the polyol pathway, adolescent study),[167] cholesterol transport (apolipoprotein E [*APOE*], adult study),[168] mitochondrial uncoupling (*UCP2*, *UCP3*, adult study),[169] and oxidative stress defense (superoxide dismutase [*SOD2*, *SOD3*, children and younger adult study]),[170] catalase (*CAT*, younger adult study),[171] glutathione peroxidase-1 (*GPX1*, adult study).[172] Mutations in vascular endothelial growth factor (*VEGF*, adult studies) may be relevant to the ischemic nature of nerve damage, and correlate with DN[173,174] and diabetic foot ulcers,[175] although associations may be population-dependent.[176] CAN has been linked to genes regulating DNA methylation (DNA methyltransferase 1 [*DNMT1*, younger female adult study],[177] which also causes hereditary sensory neuropathy) and antioxidants (glutathione S-transferase [*GST*, adolescent study],[178] *GPX4*, younger adult study)[179] polymorphisms.

To date, we know of a single GWAS for DN from the Action to Control Cardiovascular Risk in Diabetes (ACCORD; n = 4,384 DN, n = 784 controls, adult study) trial, which identified 28 SNPs on chromosome 2q24 that were validated in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D, adult study) cohort.[180] Multiple analyses of the Genetics of Diabetes Audit and Research Tayside (GoDARTS, adult study) cohort identified clusters on 8p21.3 (next to *GFRA2*),[181] 1p35.1 (*ZSCAN20-TLR12P*), and 8p23.1 (next to *HMGB1P46*) related to neuropathic pain,[182] and a *MAPK14* SNP on 6p21.31 related to diabetic foot ulcers.[183]

We conducted the first genome-wide DNA methylation analysis of human sural nerve biopsies from DN patients (adult study),[184] identifying profound differences in regulation of genes involved in neuron development and axon guidance, glycerophospholipid metabolism, and cell signaling in patients with progressive versus nonprogressive DN. A genome-wide DNA methylation study of patient-derived diabetic foot ulcer fibroblasts found differences related to angiogenesis and extracellular matrix assembly.[185] Overall, GWAS and genome-wide DNA methylation studies will more comprehensively characterize genetic susceptibility to DN and CAN. Although the vast majority

of studies have been conducted in adults, identified SNPs or as yet unidentified SNPs may also predispose children and youth to DN or CAN, and studies are need to evaluate this possibility.

Race and ethnicity: From 2002 to 2015, SEARCH determined that T1D and T2D incidence increased more in racial/ethnic minorities compared to whites in the US.[17] Racial and ethnic disparities are likewise reported in T1D treatments and outcomes.[205] SEARCH revealed no difference in DN prevalence in participants with T1D (p = 0.65) and T2D (p = 0.77), by self-reported race/ethnicity,[12] although significant effects of race/ethnicity on CAN were noted in youths with T2D (p = 0.001), which was more prevalent in non-Hispanic whites (27%) and Hispanics (29%), but not in youths with T1D (p = 0.63; 8–14% prevalence).[13] This partly agrees with an earlier study, which found a CAN prevalence of 29% by HRV, but no racial differences in children and adolescents with T1D, using their classification of white or black.[186] Thus, the influence of race/ethnicity on DN and CAN risk is incompletely understood due to lack of evidence, and larger studies are needed to evaluate this relationship and to address health care inequalities.

Puberty: Several studies have evaluated the effect of puberty on DN and CAN incidence. Using VPT to measure DN signs, threshold differences between children with T1D (n = 55) versus controls (n = 34) were greatest postpubertal, after accounting for sex and age.[187] Late puberty is also reported to independently raise the risk of peripheral sensory dysfunction (n = 92, mean age 14.2 years),[140] although no effect of puberty was noted on CAN in T1D (n = 110, aged 6–18 years) in multivariate analysis.[188] This contrasts with a T1D study (n = 73, aged 3–18 years, mean age 12.1 years) that found critical effects of puberty on CAN using the more sensitive HRV outcome measure.[82] Hence, puberty represents a time pediatric physicians should be especially vigilant for DN and CAN in children with T1D. In children with T2D, diabetes onset occurs in the postpubertal period.

Eating disorders (EDs) and disordered eating (DE): Eating disorders are usually associated with poor glycemic control[189] and increased risk for acute and chronic diabetes complications.[190] In its most extreme form, diabetes patients omit taking their glucose-controlling medication in order to lose weight, a condition colloquially termed "diabulimia." SEARCH determined the presence of DE in 21.2% of subjects with T1D (2,156 participants; 50.0% female, mean 17.7 years old) and 50.3% of those with T2D (149 participants; 64.4 % female, mean 21.8 years old).[191] Since poorly controlled glycemia is a DN risk factor in T1D and T2D,[143] patients with ED and DE can be at risk for developing DN as a result of uncontrolled glycemic and related factors. The association of ED with clinical DN has been reported in small clinical series.[192] Among 208 young women with T1D aged between 16 and 25, Steel et al.[193] reported six neuropathies associated with EDs. Of those, four patients with anorexia nervosa had acute painful polyneuropathy. The development of pain was not associated with any significant change in HbA1c but coincided with ED onset, and pain remission was observed after subjects regained weight. Although these case series are interesting, they do not rule out the contribution from other aspects, such as deficient nutritional factors.[194] Diabetes patients suffering from EDs and DE require particular attention for early DN symptoms or signs, as well as any other complications.

Smoking: Smoking has repeatedly been linked to DN in multiple studies. The Pittsburg EDC study found smoking correlated with DN in participants with T1D ≥18 years,[34] and in EURODIAB, smoking was linked to cumulative DN incidence in T1D, independent of diabetes duration or HbA1c.[35] SEARCH similarly pointed to smoking as a DN risk factor in subjects with both T1D and T2D,[12] and a focused smoking analysis in SEARCH found that tobacco use in youth with T1D and T2D correlated with longer diabetes duration, older age, poorer glycemic regulation, and MetS.[195]

2 | MANAGING DN IN CHILDREN AND YOUTH

Earlier identification and intervention is optimal since DN may be improved or even reversed at subclinical stages with appropriate interventions.[11,91,196] The American Diabetes Association currently recommends performing an annual comprehensive foot exam in youth with T1D, starting 5 years after diagnosis, at the start of puberty, or at age ≥10 years, whichever is earlier.[16,59,197] Screening is recommended at diagnosis and then annually in youth with T2D.[92] Comprehensive foot examinations should include inspection, palpation of dorsalis pedis and posterior tibial pulses, assessing either temperature or pinprick sensation, and determination of proprioception, vibration sensation, monofilament sensation, and patellar and Achilles reflexes.[16,197] The importance of frequent foot inspection should be discussed with patients at diagnosis and each visit.[198]

2.1 | Managing glycemia

2.1.1 | Type 1 diabetes

Achieving glycemic control is the primary mainstream goal for managing DN.[11] Long-term impairment of glycemic control is the strongest predictor of DN development in T1D. Several clinical studies, most in adults, found robust associations between poor glycemic control and DN development. The DCCT is a landmark study showing the benefit of intensive glycemic control to improve DN related outcomes in subjects with T1D.[25,121] NCS showed slower NCVs at 5 years in conventionally versus intensively treated DCCT youth with T1D (195 of 1,441).[121] The EDIC study, a follow-up of DCCT, demonstrated the effect of early intensive glycemic control, also called metabolic memory effect).[199-201] Although both standard and intensive glycemic control groups had comparable HbA1c levels (around 8%) one year after treatment initiation as per EDIC protocol, subjects within the former intensive group had lower DN incidence at year 8 and years 13–14.[202,203] Mean HbA1c was recently identified as the most significant risk factor for DN after over 23 years of follow-up in the EDIC cohort.[204] Poorly controlled long-term diabetes has been demonstrated as a significant risk factor for CAN development in children

and youth with T1D.[13,162,205] DCCT demonstrated that intensive glycemic regulation reduced DN and CAN risk.[25,206,207] On the other hand, there is little evidence that well controlled glycemia improves neuropathic pain in T1D, but rapid and large glycemic drops can occasionally precipitate a dramatic worsening of pain.[208,209] Recently, glucose variability was proposed to accelerate DN development and progression, but well-designed studies are needed in children and youth.[210,211]

2.1.2 | Type 2 diabetes

Despite well-established evidence in T1D that intensive glycemic control reduces DN risk, the effect of glycemic control is less clear in T2D, even in adulthood.[143] The benefit of glycemic control on DN development and progression has not been widely investigated in children and youth with T2D; a few adult studies suggest improvement[212,213] but most report weak or no effect.[143,214-217] Data from the TODAY study showed the association of HbA_{1c} with CAN in subjects with youth onset T2D.[57] The SEARCH study found a significant relationship between DN and diabetes duration in children and adolescents with T2D.[12] Similarly, an Asian Indian study reported higher DN prevalence with increasing diabetes duration in children and youths with T2D.[144]

2.2 | Managing metabolic and other risk factors

Obesity and dyslipidemia are emerging adult DN and CAN risk factors, particularly in T2D,[149-158,218] which is mirrored in pediatric studies.[12,13,24,162-164,219,220] Youths and their guardians should be counseled on nutrition, weight loss, and exercise as a means to shed excess weight and improve insulin resistance.[92,221] Adult studies found exercise improved IENFD, even without significant weight loss,[222-224] and a small randomized controlled trial found aerobic exercise improved NCS parameters and VPT after 4 years in adults with T1D and T2D.[225] Nevertheless, the effect of managing weight on DN is not well-established in T1D, but since excess weight is an emerging issue in youth with T1D,[197,226] dietary counseling with exercise should be integrated. Several diabetes medications (e.g., metformin, SGLT2 inhibitors, GLP-1 agonists) potentially reduce weight,[92,227-231] but their impact on DN is not conclusive yet,[232-235] and only metformin and liraglutide are currently FDA-approved for pediatric patients.[236,237] Moreover, orlistat is FDA-approved for weight loss in pediatric patients with obesity aged 12 years and older,[238,239] independent of diabetes status, but its effect on neuropathy is unknown. Metformin use may be associated with B12 deficiency and worsening of neuropathy symptoms,[240,241] and increased lower extremity amputation rates were reported for canagliflozin,[242] an SGLT2 inhibitor. Lipid control may potentially prevent DN development, but evidence is limited.[243] Future well-designed studies must establish the effect of exercise, diet, weight loss, and lipid lowering strategies on DN in children, youth, and adults. Although several studies suggest angiotensin-converting enzyme inhibitors improve DN,[244-250] evidence is limited and hypertension should be treated appropriately for individuals. Smoking and alcohol use are DN risk factors,[11,12,34,35,65] and youths should be counseled to avoid smoking (including e-cigarettes) and alcohol use.

2.3 | Managing painful neuropathy

Compared to adults, painful DN is rare in children and youth.[251-254] Calcium channel a2δ ligands (gabapentin, pregabalin), serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants are the most widely used medications for painful DN in adults.[255-258] These medications are used to treat various presentations of neuropathic pain in children, but clinical studies devoted to painful DN are not available[259-264] and no drugs are licensed specifically for painful DN in childhood and youth.[254]

2.4 | Managing CAN

Morbidity and mortality is higher in CAN patients,[122] who require a vigilant cardiovascular risk elimination strategy. Patients with diabetes and CAN undergoing surgery require perioperative caution, since CAN is linked to arrhythmia risk and hemodynamic dysbalance.[265] Cardiac status should also be carefully reviewed in patients with CAN before advising exercise program participation, and patients with orthostatic hypotension may require specialized personalized care.[59] Managing hypoglycemia awareness and brittle diabetes is outside the scope of this review, but the role of autonomic dysfunction should be considered.[58,266]

3 | FUTURE DIRECTIONS

Our understanding of DN in pediatric patients has improved, but remains suboptimal, particularly for pediatric T2D because most findings are based on studies of pediatric patients with T1D, which fundamentally differs in pathophysiology and hence in potential management approaches. The second reason for this less than optimal situation is that much of our understanding is based on drawing parallels to studies of adults with T2D. Therefore, we have substantial knowledge gaps, which will require further research to fill. For instance, screening at all ages, even in younger children, using standardized and sensitive tools shown to be sensitive and specific in pediatric populations, will be needed to both refine the prevalence data in pediatric populations with T1D and T2D and identify evidence-based age brackets for screening in the American Diabetes Association pediatric guidelines. Furthermore, as childhood T2D prevalence continues to mount, we must better understand DN in the T2D context. Importantly, this means defining the magnitude of the problem, not only of childhood obesity, for which statistics are available,[267] but also on the childhood prevalence of prediabetes, a

risk factor for developing frank diabetes, of which relatively little is known. We further must investigate the role of obesity, other MetS components, and additional potential risk factors (genetic susceptibility, race/ethnicity, lifestyle habits, physical activity level) on DN development and progression in children and youth with normoglycemia and prediabetes as well as diabetes. More sensitive screening methods are imperative to detect subclinical DN when it is most feasible to slow DN progression or halt development. To date, there is no curative DN treatment and good glycemic control remains the mainstream goal. However, glycemic control may not be the only parameter, especially in youth with T2D.[143,153] With obesity and dyslipidemia emerging as T2D risk factors, we must systematically evaluate the efficacy of weight loss and exercise on childhood DN through randomized controlled trials.[268] Targeted, mechanism-based pharmacological approaches are also needed, and may be forthcoming, as preclinical and clinical research sheds light on DN pathophysiology and alternative risk factors. For instance, in children with T1D for whom well controlled glucose does not prevent DN, investigation into additional interventions beyond hyperglycemia management can be explored in the context of T1D, for example, autoimmunity.

4 | CONCLUSION

Diabetes is a modern day epidemic with an increasing incidence and prevalence of both T1D and T2D. The increase in T2D prevalence is more dramatic as a result of childhood obesity and sedentary lifestyles, which continue to rise. Childhood onset diabetes constitutes a high risk for developing DN due to disease longevity. DN signs are usually subclinical in youth with diabetes, but can be detected if sensitive tools are used. Early DN recognition is important. If left undiagnosed, subclinical DN progresses to overt neuropathy with risk of neuropathic pain, foot injury/ulceration, and limb amputation risk—symptoms associated with increased morbidity/mortality and high economic cost. Therefore, we urge clinicians to screen for and be vigilant of DN complications in young patients with diabetes. Data from T1D studies show a clear association between DN and poor glycemic control and longer lifetime exposure to hyperglycemia; thus, achieving glycemic control still remains the main strategy to prevent DN occurrence or progression. The role of hyperglycemia, on the other hand, is less conclusive on the emergence of DN in T2D, and additional factors are likely involved. Although pediatric studies are limited, recent data from adult studies underscore obesity as an independent risk factor for neuropathy. Therefore, we advocate similar considerations for obese pediatric patients and weight loss and lifestyle interventions may potentially be beneficial.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design of the review. Gulcin Akinci and Masha G. Savelieff analyzed the literature and wrote the article. Gary Gallagher, Brian C. Callaghan, and Eva L. Feldman critically reviewed and edited the article. All authors read and approved the final article.

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ORCID

Eva L. Feldman https://orcid.org/0000-0002-9162-2694

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