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Review

Diabetic Peripheral Neuropathy in Children and Adolescents - Prevalence, Diagnostic Methods and Risk Factors

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Abstract
Diabetic peripheral neuropathy (DPN) is the most common form of acquired neuropathy. In children with type 1 diabetes (T1D), the reported prevalence of DPN varies widely, ranging from 3% to 62%, mainly due to differences in screening methodologies and patient population characteristics. While intraepidermal nerve fiber density (IENFD) assessment via skin biopsy remains the gold standard for detecting small fiber neuropathy, nerve conduction studies (NCS) are the established diagnostic tool for large fiber involvement. However, several novel and non-invasive diagnostic tools have emerged recently, offering improved screening options for early-stage and subclinical DPN. The frequent presence of asymptomatic neuropathy in pediatric populations, combined with its limited treatment options, underscores the importance of early identification of modifiable risk factors thus reducing the risk of developing clinically significant DPN.
This review provides a comprehensive overview of the current evidence on the prevalence, risk factors, and modern diagnostic approaches for DPN in children with diabetes.
Keywords: Diabetes type 1, diabetic neuropathy, children

Introduction
Diabetic peripheral neuropathy (DPN) is a common complication of diabetes and the most common type of acquired neuropathy. Classically, DPN is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes(1). Typically, this is a chronic complication of diabetes; however, acute cases also occur(2). Sensory, motor, or autonomic nerves could be affected, often coexisting(1). There is no universally accepted classification for DPN. The American Diabetes Association (ADA) classified diabetic neuropathies into three main categories: 1 - diffuse neuropathy (distal symmetric polyneuropathy and autonomic); 2 – mononeuropathy; 3 - radiculopathy or polyradiculopathy (Figure 1). There are two stages of DPN - subclinical and clinical. Subclinical DPN implies neurophysiological changes in nerve function without clinical symptoms. The manifestation of nervous dysfunction characterizes clinical DPN(4).
The most common type of DPN is distal symmetric polyneuropathy(3). It may involve large-fibre nerves (related to touch, vibration, position perception, and muscle control) and small-fibre nerves (affected thermal perception, pain, and autonomic function) (Table 1). Most patients, however, have both large- and small-nerve fiber damage. Sensory symptoms include numbness, paraesthesia, and neuropathic pain. Symptoms begin in the toes before progressing in a stocking and then a glove distribution as the disease progresses. In the pediatric population, most patients present subclinical neuropathy. In the case of clinical manifestation, pain, and dysesthesias are the most common presentations(5).
The US Food and Drug Administration (FDA) has not approved any casual treatments for DPN. Hence, prevention, reducing risk factors, and finding appropriate screening tests that enable diagnosis at an early stage of the disease are essential(3).
The review aims to summarize the data on the prevalence, diagnostic methods, and risk factors of DPN in children and adolescents, especially in type one diabetes (T1D).
Figure 1. The classification of diabetic neuropathy modified from American Diabetes Association(3).

Prevalence of diabetic neuropathy
The prevalence of DPN ranges from 3% to 62% in T1D(6,7,8). There is a significant difference between the results of the studies, which are limited and hard to compare due to various diagnostic test methods. The data are summarized in Table 2. The Pittsburgh Epidemiology of Diabetes Complications Study revealed diabetic neuropathy only in 3% of patients under 18 years old, 18% for 18- to 29-year-old patients, and 58% for > 30-year-old patients(6). Similarly, the EURODIAB Insulin-Dependent Diabetes Mellitus (EURODIAB IDDM) Complications Study — one of the largest and most important epidemiological studies on T1D in children and adolescents in Europe — reported diabetic neuropathy in 19% of patients aged 15 to 29(9). In Danish Study Group research, subclinical neuropathy was found in 62% of patients aged 12-27 (diagnosed by vibration detection threshold (VDT))(10). In Nelson et al.'s study, neuropathy was diagnosed at 57% by the gold standard methods – nerve conduction study (NCS)(11). The SEARCH for Diabetes in Youth Study (SEARCH) is a multicenter, population-based study designed to assess the incidence, prevalence, and complications of diabetes among children and adolescents in the United States. Data from SEARCH revealed that 7% of adolescent patients with neuropathy (diagnosed by the Michigan Neuropathy Screening Instrument (MNSI))(12).

Diagnostic Methods
According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), screening for DPN in young people with T1D should start at puberty or from age 11 years with 2–5 years of diabetes duration and be repeated annually(13).
Clinical findings of DPN include a loss of sensation to pinprick, temperature, vibration, and proprioception(5). Neurological examination should consist of reflex testing because loss of ankle reflexes can occur in the early stage of DPN. Weakness of small foot muscles and dorsiflexion is usually observed later(5).

1. Screening tests:

Touch sensation tests
Touch sensation tests assess the integrity of Merkel touch domes and Meissner corpuscles and their associated large-diameter fibers.

Semmes-Weinstein monofilament test, Neuropen, and Ipswich touch test can be used to evaluate touch sensation. Frey's hair additionally allows to examine touch perception thresholds(14).
There are different types of monofilament, e.g., 0.5 g, 2 g, 10 g, 50 g, and 200 g. A 10 g monofilament test is the most common in practice. The Neuropen combines an interchangeable 10 g monofilament and a calibrated sterile Neurotip for assessing pain sensation. Ipswich touch is a simple method where we can use the tip of our index finger to elicit the sensation of light touch on the tips of the patient's first, third, and fifth toes for 1-2 seconds. Compared with the 10-g monofilament, the Ipswich Touch Test has a sensitivity and specificity of 76% and 90%, respectively, and can be done at home without equipment(7). Frey's hairs are based on a method similar to that of a monofilament; touch perception thresholds can be assessed by buckling the hairs with a force ranging from 0.026 g to 110 g(15).

Thermal perception testing

Thermal perception testing determines the function of free-nerve endings and their associated unmyelinated and thinly myelinated fibers. It is more valuable to test cold and warm perceptions separately. Thermal threshold uniquely indexes small fiber dysfunction(5,14,16).
One of the simple screening methods for testing thermal perception is tip-therm. It is an instrument with two flat sides of a special polymer and a metal alloy. Due to the different thermal conductivity of both materials, the faces of the instruments are perceived differently. Compared to the biothesiometer, thip-therm has high specificity (100%) and sensitivity (97.3%) in diagnosing diabetic neuropathy(16).

Vibratory sensation test

Vibration perception testing assesses function in Meissner, Pacinian corpuscles, and large-diameter fibers. Typical testing sites are the glabrous skin of the fingers and toes(5,14,17).
For the vibration perception assessment, a 128-HZ standard tuning fork, vibra tip, Rydel-Seiffer fork, or biothesiometer are used(5). 128-Hz standard tuning fork determines the presence or absence of vibration perception. There are two methods of examination: on-off and timing method. In the first method, a tuning fork is applied to the bony prominence bilaterally situated at the dorsum of the first toe. The patient reports the start and the cessation of the vibration sensation. In the timing method, a tuning fork is applied to the same area, and the patient reports the time at which vibration diminished beyond perception. The results compare to the examiner's timing of vibration sensation(17).
There is also a pocket-size device, VibraTip for assessing vibration perception in DPN screening. It provides a stimulus of 128 Hz(5). Quantitative methods including the Rydel-Seiffer tuning fork (RSTF) and the biothesiometer(5), have been developed to determine VDT, RSTF enables the patient to discriminate various vibration intensities to be examined. A triangle and an arbitrary scale from 0 to 8 imprinted on the weights allow assessment of the vibration threshold(18). The VDT is the value nearest to the point where vibration is no longer perceived. Tuning fork VDTlower than four is abnormal(19).
The biothesiometer determines VDT on a scale from 0 to 50. It measures VDT by adjusting the amplitude of an electrical vibrator. Contrary to a Rydel-Seiffer tuning fork, a biothesiometer measures the VDT as the point at which the first sensation of the vibration appears(20). Assessment of VDT using the biothesiometer is quick and reliable. Compared with a tuning fork, the biothesiometer is reported to be more accurate(21).

New quantitative sensory test (QST)

QST determines the sensory threshold, which is defined as the minimal energy detected for a particular modality. Using direct patient feedback, QST measures sensory thresholds such as vibration, cold, warmth, heat, or cold pain. There are two schemes: the method of limits and the method of levels. In the method of limits, a patient indicates a response as an increasingly strong stimulus is detected or when a decreasing stimulus is no longer felt. In the method of levels, stimuli of defined intensity levels are tested, and the patient is asked to indicate if the stimulus is or is not detected. In the method of limits, the result is dependent on the rate of change of the stimuli and is more variable than the method of levels. The reason could be a patient's reaction time(22).

Scoring system

Various clinical scoring systems are used to screen DPNs. They may involve symptom scoring, sign scoring, or both **(Table 3)**(23-30**)**. The scoring system is a suitable and easy-to-perform method for the early detection of DPN. Michigan Neuropathy Screening Instrument (MNSI) is a widely used screening tool, including in the pediatric population; however, it has not been formally validated in children. Research among the adult population revealed a range of sensitivity (35-79%) and specificity (65-94%) compared to NCS, depending on the cut-off value used for abnormality in MNSI(23).

2. <u>Gold standard</u>

Skin Biopsy :

A skin biopsy is a minimally invasive technique; the specimen is taken from the distal calf. Assessing intraepidermal nerve fibers (IENF) counts, lengths, and densities is crucial to identifying small fiber neuropathy (SFN). IENFs are the last endings of C and A-delta fibers, participating in pain perception and thermal stimuli(31). There are two evaluation methods of IENFs: immunohistochemical (bright-field) or indirect immunofluorescence with or without confocal analysis. Nerve fiber staining is performed with protein gene product 9.5 (PGP9.5), a member of the ubiquitin hydrolase system, a nonspecific pan-neuronal marker(31,32).
In clinical practice, intraepidermal nerve fiber density (IENFD) is the gold standard for diagnosing conditions with small nerve fiber involvement. Diabetes is the most common cause of SFN, and a decrease in IENFD is noticed in the earliest stage of the disease. Additionally, IENFD can be used to monitor the progression of diabetic SFN, and the decrease in IENFD correlates with the severity of SFN(32).
Mechanoreceptors, innervated by A-beta fiber endings, can also be found in skin biopsy. NCS is a gold standard in diagnosing large fiber neuropathy (LFN); however, skin biopsy allows assessment of early abnormalities of receptors and their distal part of myelinated fibers. Autonomic involvement can also be assessed through skin biopsy. In DPN, a significant loss of sudomotor (innervating sweat glands) and pilomotor (controlling arrector pili muscle contraction leading to hair follicle erection) nerve fibers has been demonstrated(32).

Nerve Conduction Study

NCS is the gold standard for the diagnosis of LFN(5). According to the Toronto consensus, a definite diagnosis requires at least one symptom and/or at least one sign of neuropathy and abnormality in NCS(33). During the examination, small pads are inserted into the skin, deliver mild electric shocks, and detect electric signals. Routine NCS includes evaluation of the motor function of the median, ulnar, peroneal, and tibial nerves and the sensory function of the median, ulnar, radial, and sural nerves. Recommended attributes are amplitude, distal latency, distance, conduction velocity, and F-wave latency. Diagnostic criteria involve the abnormality of one or more attributes in two or more separate nerves to define DPN(34). NCS has limits on the availability of routine diagnostic evaluation of DPN. Additionally, NCS is insensitive to diagnose SFN(35).

3. Other methods

Neuropad

A simple indicator test that can detect the early stage of peripheral neuropathy is Neuropad. The neuropad is applied to the plantar aspect of the first metatarsal head and removed after 10 minutes. It assesses sweat production by the color change of a cobalt II compound from blue to pink. It indicates sudomotor dysfunction in DPN, which develops before the sensory loss. The sensitivity of the test was 70-83% (validated against Neuropathy Disability Score (NDS), NCS, and VDT)(36).

Sudoscan

Sudoscan is a non-invasive, quantitative test to assess sudomotor function using reverse iontophoresis to measure electrochemical skin

conductance (ESC) of sweat in the hands and feet. It evaluates the function of small c-fibers that innervate the sweat glands. Degeneration of these fibers results in reduced sweat gland function(37). Validation studies have confirmed good values for sensitivity (70-87.5%) when using foot ESC results to screen for DPN(38). Global collaborative analysis established reference values in healthy subjects of different ethnic groups, age, and gender(39).

Corneal confocal microscopy

Corneal confocal microscopy (CCM) is a relatively new, non-invasive diagnostic tool for SFN. Nerve fibers from the trigeminal richly innervate the cornea. Corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL), and inferior whorl length (IWL) are the main parameters used. A meta-analysis of over 3,000 participants revealed a reduction in the CCM parameter in patients with DPN compared with healthy controls and those without DPN. Additionally, the authors pointed to a lesser but significant decrease in CCM parameters in diabetic patients without DPN compared with controls, suggesting that CCM determines subclinical DPN(40). Corneal nerve loss was also observed in the patients with impaired glucose tolerance(41) and children with type 1 diabetes(42).

Optical coherence tomography angiography (OCTA)

Optical coherence tomography angiography (OCTA) is a non-invasive tool that enables quantitative assessment of retinal microcirculation. Research highlights the value of OCTA in monitoring neurodegeneration in patients with T1D. It suggests its potential as an imaging biomarker for evaluating the progression of DPN(43).

Risk factors

Diabetic neuropathy develops as a result of various risk factors, which can be categorized into modifiable and non-modifiable. Identifying these factors is essential for preventing DPN.

Non-modifiable factors include disease duration, pubertal status, tall stature, ethnicity, and genetic predisposition. Modifiable factors include glycemic control, dyslipidemia, hypertension.

1. Non-modifiable factors:

Duration of diabetes

Long-standing diabetes is a confirmed risk factor for DPN. In SEARCH, in patients with DPN, diabetes duration was significantly longer, but HbA1C values were similar between groups, indicating that longer diabetes duration is a crucial factor in DPN(12).

Tall stature

In contrast to nephropathy and retinopathy (complications of diabetes, which more often occur in patients with short stature), tall stature was associated with a higher prevalence of neuropathy. Some hypotheses exist, such as patients with longer nerves (and thus a larger total axon surface area) who may be at greater risk for neurologic impairment and have a prolonged time requirement for complete regeneration. The association of height with peripheral neuropathy might be related to the increased hydrostatic pressure in tall patients during standing up(44).

Puberty

Research has shown that puberty contributes to the development of late metabolic complications of diabetes, such as retinopathy and neuropathy(45). Peripheral nerve function is increasingly impaired during puberty. The cross-sectional study demonstrates increasing subclinical motor nerve impairment detected during late puberty and after puberty. Reduced sensory nerve conduction velocity (NCV) and sensory nerve action potential (SNAP) amplitude were confirmed. The peripheral nerve fibers of pubertal and postpubertal patients may be the most vulnerable to nerve demyelination and axonal damage caused by poor metabolic control induced by pubertal hormonal changes and poor self-care during puberty(46).

Ethnicity

The prevalence of DPN varies according to ethnicity. The studies of multi-ethnic groups have found a greater prevalence of DPN occurring in Caucasian patients compared to other ethnic groups(47).

Genetic markers

There are limited data on genetic predisposition to DPN among children with T1D. Single Nucleotide Polymorphism (SNP) is a variation at a single position in the DNA sequence among individuals, which can be linked to a higher or lower risk of diseases. A Slovak study confirmed a strong association between the *CYBA* (Cytochrome b-245 alpha chain) polymorphism *rs4673* and DPN in children and adolescents with T1D. *CYBA* encodes the p22^phox protein subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which plays a key role in the production of reactive oxygen species (ROS)(48).

A study by Stokov et al. revealed that the polymorphic markers Ala(−9)Val in the *Superoxide Dismutase 2 (SOD2)* gene and **A**rg213Gly in the *Superoxide Dismutase 3 (SOD3)* gene are associated with a higher risk of DPN. *SOD2* and *SOD3* encode different isoforms of the enzyme superoxide dismutase, which plays a key role in protecting cells from oxidative stress(49).

Whereas vascular endothelial growth factor (VEGF) is a signaling protein that plays a critical role in angiogenesis, the distribution of a VEGF gene polymorphism in the promoter region (–7C/T) differed significantly between patients with T1D with and without neuropathy, and may be implicated in the pathogenesis of DPN(50).

2. ***Modifiable factors***

Hyperglycemia

Hyperglycemia is a well-known risk factor for DPN. A study in children and youth with T1D confirmed an elevated DPN risk with poor glycemic control. EURODIAB determined the association of DPN with the duration of diabetes and highlights a strong relation with glycemic control independent of diabetes duration(9).

Glycemic variability

In addition to hyperglycemia, glycemic variability (GV) may be another independent risk factor for diabetic complications; however, the results are inconsistent. Some studies propose potential pathophysiological mechanisms through which elevated glycemic variability contributes to the development of DPN. These include the activation of protein kinase C-dependent NADPH oxidase, which subsequently induces oxidative stress. Furthermore, an oxidative stress and inflammatory response is caused by activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway(51,52).

The study by Oberhauser et al., conducted among children and adolescents with T1D, confirmed that high glucose variability is an unexpectedly strong predictor of slowed nerve conduction velocity(53). However, there are limited studies on the long-term outcomes of glycemic variability during the pediatric period, so further prospective research is needed(54).

Obesity

Obesity is an emerging risk factor for neuropathy independent of hyperglycemia. Obesity may contribute to the development of neuropathy through several mechanisms, including oxidative stress, insulin resistance, metabolic inflammation, and ischemia - all of which can lead to nerve degeneration(55). Fat distribution is likely more important than general obesity in developing neuropathy. Among adolescents with obesity, the association of central adiposity with insulin resistance and inflammation has been confirmed. This effect is observed regardless of body mass index (BMI)(56). Visceral adipose tissue is a source of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). These cytokines activate microglia and perivascular macrophages, ultimately promoting demyelination and axonal degeneration. Additionally, an excess of free fatty acids (FFA), particularly in central obesity, may cause direct damage to neural structures(57). Studies in childhood cohorts reveal a correlation between obesity and increased neuropathy risk(58).

Dyslipidemia

Dyslipidemia increases the frequency and severity of micro and macrovascular complications of T1D. Large clinical studies like EURODIAB and SEARCH confirmed the relationship between lipid disturbances and peripheral neuropathy. In EURODIAB, higher levels of total and low-density lipoprotein cholesterol (LDL-c) and triglycerides were significantly associated with the cumulative incidence of neuropathy(9). SEARCH found increased triglycerides, LDL-c, and lower high-density lipoprotein cholesterol (HDL-c) as a risk factor for DPN in youth with T1D. The authors emphasize that the lower HDL-c could be one of the crucial factors in the pathogenesis of DPN. HDL-c inhibits inflammation process, oxidation, and thrombosis, as well as vasodilatation via endothelial release of nitric oxide. Increasing HDL-c levels through lifestyle modification (dietary modification, aerobic exercise, weight loss) can be one of the therapeutic approaches(12).

Hypertension

Studies confirmed that hypertension was associated with the prevalence of neuropathy in young people with T1D(59). Hypertension is associated with impaired nerve conduction in T1D(60). Glycemic control has to be supported with strict blood pressure control to prevent and delay the onset of DPN. According to EURODIAB the risk factors for DPN in youth with T1D are increased diastolic blood pressure(59). The angiotensin-converting enzyme inhibitor (ACEI) may improve peripheral neuropathy even in normotensive patients with diabetes(61). Hyperglycemia increases tissue angiotensin II, causing oxidative stress, endothelial damage, and vascular changes. These contribute to DPN and can be diminished by blocking the renin-angiotensin system, explaining the beneficial effect of ACEIs(62).

Conclusion

DPN is one of the most common complications of diabetes, which can result in foot ulcers and potentially necessitate amputation. The prevalence of neuropathy in patients with T1D differs based on the screening methods used and the characteristics of the study groups. Nevertheless, the studies reviewed indicate a relatively high occurrence of subclinical neuropathy, highlighting the need for early detection of risk factors to prevent this complication. Additionally, the therapeutic options are currently very limited, so early screening and modification of risk factors is crucial.

Authorship Contributions

Concept: Marta Baszyńska-Wilk, Monika Nowacka-Gotowiec, Elżbieta Moszczyńska. Design: Marta Baszyńska-Wilk. Data Collection and Processing: Marta Baszyńska-Wilk, Monika Nowacka-Gotowiec. Analysis and Interpretation: Marta Baszyńska-Wilk, Monika Nowacka-Gotowiec, Elżbieta Moszczyńska, Literature Research: Marta Baszyńska-Wilk. Writing: Marta Baszyńska-Wilk, Elżbieta Moszczyńska

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Table 1. Diabetic peripheral neuropathy: Small Fiber vs. Large Fiber (4,5)

Nerve Type	Fiber Class	Nerve Function	Fiber Myelination	Function	Symptoms of neuropathy
Large-fiber	Aα	Motor	Myelinated	Muscle control	- Impaired vibration sense, - Loss of position sense, - Muscle weaknes, - Loss of deep tendon reflexes,
	Aα/β	Sensory	Myelinated	Position perception, touch, vibration	
Small-fiber	Aδ	Sensory	Thinly myelinated	Cold, pain (fast and well-localized)	- Pain and paresthesia, - Loss of temperature perception - Normal tendon reflexes, - Autonomic signs and symptoms,
	C	Sensory	Unmyelinated	Cold and warmth, pain (slow and poorly localized)	
	C	Autonomic	Unmyelinated	Blood pressure, heart rate, sweating, gastrointesinal and genitourinary system control	

Table 2. The summary of studies evaluating diabetic neuropathy in children and adolescents

Study	No. of Patients	Diagnostic methods	Prevalence of DPN (age range)
Maser et al. Pittsburgh Epidemiology of Diabetes complications study(6)	400	- Clinical symptoms, - Neurological examination,	3% (<18 years)
Tesfaye et al. EURODIAB IDDM(9)	3250	- Clinical symptoms, - Neurological examination, - Vibration perception threshold, - Autonomic dysfunction,	19% (15-29 years)
Olsen et al. Danish Study Group(10)	339	- Vibration perception threshold,	5% (10-15 years) 46,8% (15-20 years)
Nelson et al.(11)	73	- NCS,	57% (mean age 13,7±2,6 years)
Jaiswal et al. SEARCH(12)	1734	- MNSI,	7% (mean age 18±4 years)
Moser et al.(8)	151	- MNSI, - NCS (in case of a positive result of MNSI or in a high risk group).	10,6% (8-21 years)

IDDM - insulin-dependent diabetes melitus; NCS - nerve conduction studies; MNSI - Michigan Neuropathy Screening Instrument

Table 3. Clinical scoring for DPN screening

Test	Description	Score
Signs and symptoms		
Michigan Neuropathy Screening Instrument (MNSI)(23,24)	Consist of 15 questions completed by patient, and physical assessment : appearance of feet, ulceration, ankle reflex, vibration perception at great toe, monofilament testing.	≥7/15 positive results of the questionnaire; ≥2 /8 positive results of physical examination.
Toronto clinical neuropathy score (TCNS)(25)	Three items: Symptomes (pain, numbness, tingling, weakness, ataxia, upper -limb symptoms), reflex (knee and ankle reflexes) and sensory test score (pinprick, temperature, light touch, vibration sense, position sense)	0-5 points without DPN; 6-8 points mild DPN; 9-11 points moderate DPN; 12 to 19 points severe DPN.
The Douleur Neuropathique en 4 (DN4)(26)	Includes questions for different types of neuropathic pain and a physical exam to test for touch and pin hypoesthesia and tactile dynamic allodynia	≥4 /10 positive result. Available pediat[illegible]sion
Symptoms		
Neuropathy symptoms score (NSS)(27)	17 items, symptoms of muscle weakness, sensory disturbances, autonomic symptoms	≥1/[illegible] positive res[illegible]
Diabetic neuropathy symptoms score (DNS)(28)	Four questions, simplified scoring system, assessing pain, numbness, tingling and ataxia.	≥1 /4 positive result
Signs		
Neuropathy disability score (NDS)(29)	35 items evaluating cranial nerve, sensation, reflexes, muscle strength. Revised NDS: ankle reflex, vibration, pinprick and temperature sensation at both sides of the biggest toe	≥2/10 positive result
Diabetic neuropathy examination (DNE)(30)	Tree items: muscle strength (quadriceps femoris - extension of the knee; tibialis anterior - dorsiflexion of the foot), reflex (triceps surae), sensation index finger (pinprick) and big toe (pinprink, touch, vibration sensation, sensitivity to joint position).	>3/16 positive result
DPN – diabetic peripheral neuropathy		

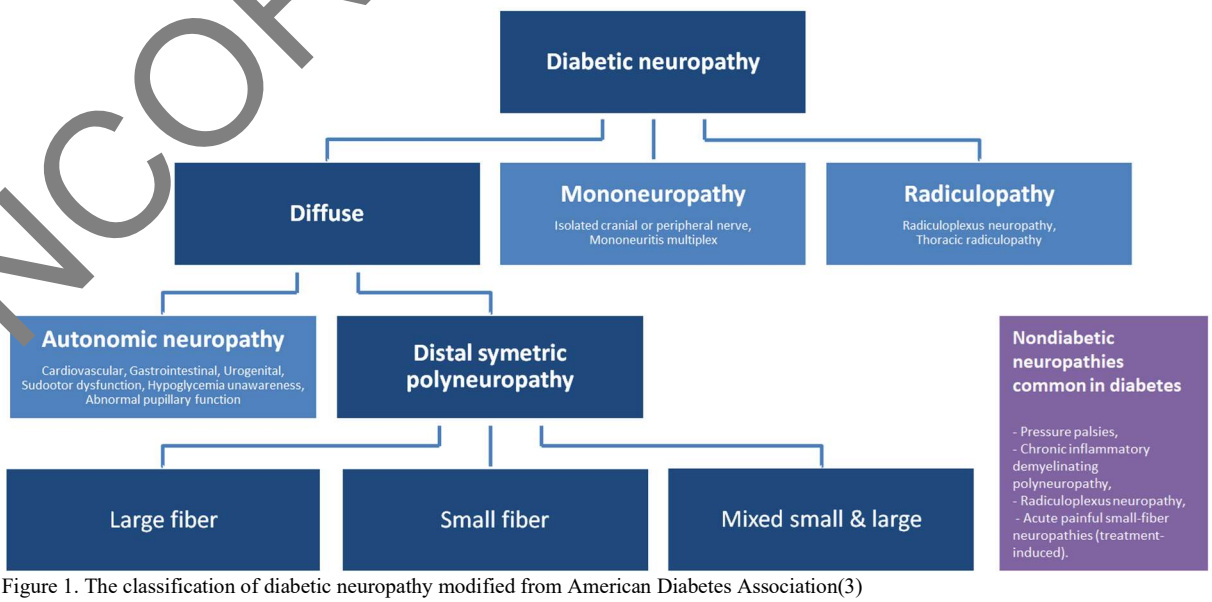

Figure 1. The classification of diabetic neuropathy modified from American Diabetes Association(3)