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DIAGNOSIS AND TREATMENT OF EARLY STAGES OF DIABETIC POLYNEUROPATHY

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Abstract
Diabetic polyneuropathy is the earliest and most common complication of diabetes mellitus. Diabetic polyneuropathy can develop in the early stages of carbohydrate metabolism disorder, moreover, distal polyneuropathy can also develop in patients with metabolic syndrome who do not have carbohydrate metabolism disorders. Hyperglycemia is the most important, but not the only risk factor for the development and progression of diabetic polyneuropathy. Peripheral nervous system damage in prediabetes and in the initial stages of diabetes mellitus mainly affects thin nerve fibers, which causes a fairly frequent development of disorders of the autonomic nervous system. Early diagnosis of diabetic polyneuropathy is extremely important, since lifestyle changes and increased physical activity can slow down the development of this complication. The ratio of oxidative stress severity and antioxidant defense activity is considered as a potential mechanism for early damage to the peripheral nervous system in hyperglycemia and as a possible target for therapeutic intervention. The review discusses the epidemiology, diagnostics, and potential therapeutic strategies for early diabetic polyneuropathy.

Keywords: Diabetes mellitus, prediabetes, diabetic polyneuropathy, autonomic neuropathy, diagnosis of diabetic polyneuropathy

Introduction

Diabetic polyneuropathy (DPN) is one of the main complications of diabetes mellitus (DM) types 1 and 2, significantly increasing the risk of foot ulcers and amputations, and is associated with higher mortality and increased health care costs [1, 2]. In elderly patients with T2DM, DPN increases the risk of falls, which leads to negative consequences such as hospitalization and death [3]. DPN is heterogeneous in its clinical course and pattern of damage to the peripheral nervous system. Depending on the primary lesion of "thick" or "thin" nerve fibers, different onset, course and clinical manifestations of polyneuropathy are possible. In a joint consensus document (the 19th annual Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB) and the 8th International Symposium on Diabetic Neuropathy in Toronto, Canada, 13–18 October 2009), it was proposed to define DPN as a symmetrical sensorimotor polyneuropathy with damage to long nerve fibers (length-dependent polyneuropathy), developing as a result of metabolic and microvascular disorders against the background of chronic hyperglycemia and cardiovascular risk factors. It was also proposed to separate the definitions of typical diabetic sensorimotor polyneuropathy and atypical diabetic polyneuropathy [4]. The presented gradations, “typical” and “atypical” DPN, are not entirely

successful. Thus, in the 2017 American Diabetes Association consensus on DPN, it is proposed to classify DPN into three variants: with primary damage to small nerve fibers; with primary damage to large nerve fibers, and a mixed variant of damage (the most common) [5]. DPN develops as a result of prolonged hyperglycemia associated with the accumulation of advanced glycation end products, activation of the polyol pathway, the development of oxidative stress, lipid metabolism disorders, and changes in the microvascular bed [6]. DPN is the most common and earliest complication of diabetes and can occur much earlier in patients with type 2 diabetes than in patients with type 1 diabetes. In type 1 diabetes, hyperglycemia is the main pathophysiological effect, while in type 2 diabetes, other factors such as obesity, hypertension, high LDL concentration in the blood, and hypertriglyceridemia may contribute to nerve damage [7]. In type 2 diabetes, nerve damage begins at an early stage of carbohydrate metabolism disorder, i.e. before overt hyperglycemia. Impaired glucose tolerance appears to be one of the possible factors for chronic axonal neuropathy, mainly painful, most likely due to the predominant primary damage to small nerve fibers. Moreover, in patients at the earliest stages of carbohydrate metabolism disorder, positive dynamics of neuropathy may be noted with intensification of diet and physical activity [8]. Neurofilament mRNA levels have been found to be higher in the blood of patients with prediabetes, which may indicate axonal damage caused by transient hyperglycemia. Inhibition of nitric oxide-mediated vasodilation may lead to peripheral nerve ischemia, which also plays a role in the development of polyneuropathy in patients with prediabetes [9]. The presence of insulin resistance may also play an important role in the development of peripheral polyneuropathy in metabolic syndrome due to the weakening of the neurotrophic effects of insulin, which leads to mitochondrial dysfunction [10]. Metabolic syndrome without impaired glucose tolerance may be an independent risk factor for peripheral polyneuropathy, which may be related to the role of dyslipidemia in the development of polyneuropathy due to cellular and molecular effects associated with inhibition of nitric oxide production and vascular dysregulation, as well as oxidative stress. Thus, there is a link between obesity, obesity, insulin resistance and the pathogenesis of polyneuropathy [11]. The incidence of DPN in T2DM is 10–49% at diagnosis and 50% with a disease duration of 10 years [5, 12]. Painful DPN is detected in 20% of adults with diabetes or at least 30% of patients diagnosed with DPN. At least 50% of patients with DPN are asymptomatic [7]. According to the American Academy of Neurology, there is compelling evidence that symptoms alone have low accuracy in diagnosing neuropathy. Physical examination findings (hereinafter referred to as signs) are more accurate than symptoms; multiple signs are more accurate than single signs; simple physical examination methods are as accurate as complex scoring systems [3, 13]. The American Diabetes Association recommends screening all patients with diabetes when they are diagnosed with Type 2 diabetes and 5 years after diagnosis with Type 1 diabetes, and then screening should be repeated annually. Clinic The clinical assessment should include a thorough history and assessment of temperature, pain and vibration sensitivity using a 128 Hz tuning fork, as well as annual assessment of tactile sensitivity with a 10-g monofilament to assess the risk of ulceration and amputation of the feet [14].

The prevalence of DPN in prediabetes is 10–30%, with an average of 18% [15]. Moreover, quite a few studies have been published recently on peripheral nervous system damage in patients with metabolic syndrome and dyslipidemia.

The PROMICE study, which included patients with metabolic syndrome in a state of normoglycemia, is indicative. Already at the time of inclusion, 29% of patients had so-called

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cryptogenic sensory polyneuropathy. During the observation, with the development of prediabetes or diabetes mellitus, the nature of the lesion and frequency changed, namely, DPN was diagnosed in 49 and 50% of patients, respectively [16]. Screening for DPN is recommended not only for type 1 diabetes mellitus lasting 5 years or more and type 2 diabetes mellitus from the moment of diagnosis, but also among symptomatic patients with prediabetes. Diagnostics is based on the assessment of symptoms and various types of sensitivity (temperature, pain, tactile and vibration sensitivity), which allows us to assess the condition of both large-caliber and thin nerve fibers [5].To grade the stages of DPN, the classification proposed by P.J. Dyck can be used [17]. Stage 0 means the absence of polyneuropathy; stage 1 - preclinical (asymptomatic) polyneuropathy; stage 2 - clinical polyneuropathy; stage 3 – complicated DPN. Diagnosis of asymptomatic or preclinical polyneuropathy is crucial to prevent progression to late or irreversible stages of the disease and to prevent further complications [18]. Signs and symptoms of polyneuropathy have a low prevalence in the early stages of carbohydrate metabolism disorder; according to electroneuromyography, early polyneuropathy is diagnosed in 15.2% of patients [2].

DIAGNOSIS OF EARLY DPN

"Semmes-Weinstein monofilament 10 grams" is an inexpensive and simple diagnostic tool for primary care physicians and specialty care. A positive test result using a 10 g monofilament indicates an increased risk of ulcerative defects and lower limb amputation, with a negative test result, this risk is lower. Despite the lack of standardization of the method, the monofilament test is convenient for use in primary care [19]. It should be noted that the methods for assessing tactile sensitivity for identifying the risk of developing SDS and for diagnosing DPN differ. For diagnosing DPN, the algorithm for assessing tactile sensitivity proposed by the Canadian Diabetes Association is recommended [5, 20]. However, the monofilament test is not recommended as the only tool for diagnosing neuropathy [21].

Currently, validated questionnaires are widely used to diagnose DPN, assess the severity of sensory impairment and symptoms. The Michigan Neuropathy Screening Instrument questionnaire was created to facilitate the early diagnosis of diabetic neuropathy with high sensitivity and specificity with a total question index of 7 or more. The probability of DPN is high and examination is recommended if the latter determines an index of 2.5 or more [22]. For a more accurate diagnosis, a lower cutoff point can be used: 4 or more points for the questionnaire and more than 2 points for examination [23, 24]. The Utah Early Neuropathy Scale was developed specifically to identify and quantify early sensory polyneuropathy with an emphasis on the assessment of small nerve fibers [25]. The Norfolk QOL-DN questionnaire was developed and validated to measure patient perception of neuropathy: it is a specific neurological questionnaire for assessing the quality of life of patients with diabetic neuropathy, with a sensitivity > 75% and a specificity of 71–89%, a positive predictive value of 90.9% and a negative predictive value of 85–90% [26]. Standard nerve conduction studies are the method of choice for diagnosing neuropathy because they are specific, sensitive, and reproducible in diagnosing nerve dysfunction [27]. In addition to using standard methods (motor and sensory conduction studies), some additional methods should be included in the diagnostic process. A sural/radial nerve amplitude ratio of less than 0.5 with a normal standard sensory nerve conduction study has demonstrated a sensitivity and specificity of 90% in one study [28]. In some cases, the use of composite indices for the diagnosis of DPN, as they are more sensitive, reproducible, and better predict the severity

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of polyneuropathy than individual nerve conduction parameters [29]. Nerve conduction in the upper extremities should also be assessed, since median nerve neuropathy can be considered an early manifestation of diabetic neuropathy [30, 31]. Testing the excitability of sensory nerve fibers may be a potential screening tool for the detection of subclinical neuropathy [32]. Excitability of motor fibers of the common peroneal nerve was assessed in adolescents with T1D, and reduced axonal excitability was demonstrated in patients with diabetes compared with the control group. The authors suggested that this method may be useful for detecting subclinical neuropathy [33]. Consensus from the San Antonio DPN Conference recommends the inclusion of F-wave testing in the electrodiagnostic test panel [34]. F-wave assessment is one of the best ways to detect early changes in nerve conduction [28, 35–37]. H-reflex studies have also been shown to play a role in detecting early neuropathy [38, 39]. Long-latency evoked potentials are easy to describe, reproducible, and can be performed in any EMG laboratory without the need for special equipment [39]. Small fibers may be primarily affected in the early stage of diabetes, resulting in early reduction in pain and temperature sensitivity. Moreover, early and subclinical selective damage to small fibers has been demonstrated in patients with type 1 diabetes, type 2 diabetes [40]. In addition, in patients with impaired glucose tolerance, polyneuropathy is more often limited to small fibers, while in patients with diabetes there is a combined damage to small and large fibers [41]. Small fiber neuropathy is often not detected by standard electrophysiological methods, so other methods should be used to quantify peripheral small fiber dysfunction [42].

Quantitative sensory testing (QST) allows the assessment of sensory thresholds related to large and small fiber function. These tests can be included in the assessment of DPN even at the preclinical stage. QST should not be used as the sole criterion for the diagnosis of DPN, but these tests can be used to assess the degree of peripheral sensory impairment over time [43]. However, QST tests are highly subjective, variable, and have limited reproducibility [44].

The cutaneous silent period was described by Hoffmann in 1922 and evaluates the spinal inhibitory reflex after electrical stimulation of a sensory nerve (the delay time of the signal to muscle contraction in response to electrical stimulation of the cutaneous nerves). It can be obtained with any EMG device and is used to study A-delta fibers in peripheral neuropathy [45, 46]. It may be a useful method for early diagnosis of diabetic small fiber neuropathy [43, 47, 48].

Sympathetic skin reactions are used for the early diagnosis of autonomic neuropathy [47]. Some studies have found the following abnormalities in early diabetes and impaired glucose tolerance: absence of sympathetic skin reactions, increased latency, and decreased amplitude [49, 50]. Sympathetic skin reactions may deteriorate earlier than vagus function in relation to the heart. For example, the Sudoscan device was developed for non-invasive testing of sweat gland function. Based on reverse iontophoresis and

chronoamperometry, this device measures the electrochemical conductance of the skin and may have potential as a rapid screening test for early diabetic neuropathy and for assessing the response to therapeutic interventions in patients with diabetes with comparable efficacy compared to skin biopsy [51–56]. Neuropad is an easy-to-use patch that assesses sweat secretion on the sole of the foot by changing color from blue to pink with a sensitivity of 95% and a specificity of 68.9% [57]. The Quantitative Sudomotor Axon Reflex Test can assess the sympathetic sudomotor response to chemical or electrical stimuli.

It has been shown that assessment of postganglionic sympathetic sudomotor neuron function can detect early diabetic neuropathy more accurately than sympathetic cutaneous responses [58, 59].

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However, this technique is time-consuming and requires special equipment that is not available in all clinics [60].

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