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Review Article

Early Diabetic Neuropathy - a

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Diabetic neuropathy is one of the major complications in patients with type-1 and type-2 Diabetic Mellitus (DM). This disorder is the main contributing factor to the increased risk of foot ulceration an amputation in such patients [1], together with higher mortality rate as well as a huge economic burden. In older adults with type-2 DM, the risk of falling is higher than those without DM, resulting in deleterious consequences such as hospitalization and injury-related death: neuropathy is strongly linked to falling [2].

According to the San Antonio Conference on Diabetic Neuropathy, this is a demonstrable disorder, either clinically evident or subclinical, in the setting of DM, without other causes for peripheral neuropathy [3]. It develops as the result of a long-standing hyperglycaemia, associated with the accumulation of advanced glycation end-products, poliol shunting, lipid abnormalities and microvessel alterations [4].

Diabetic polyneuropathy is the most common and earliest complication of DM and it may occur much earlier in patients with type-1 DM than in patients with type-2 DM. In the former, hyperglycaemia has a main pathophysiological effect, while in the latter, other factors such as obesity, hypertension, high serum LDL concentration and hypertriglyceridemia may contribute to nerve injury [5]. In type-2 DM the impairment of nerve starts early in glycemic dysregulation prior to overt hyperglycaemia. Impaired glucose tolerance appears to be a possible factor for chronic axonal neuropathy, mostly painful, so small fibers might be the first ones to be impaired. Moreover, patients with "near impaired glucose intolerance" might benefit neurologically from intense dietary and physical exercise interventions [6]. Neurofilament m-RNA levels can be found to be higher in pre-diabetic patients´ serum which might indicate axonal damage induced by transient hyperglycaemia. Inhibition of nitric oxide-mediated vasodilation may lead to tissue ischaemia in peripheral nerves, which could cause neuropathy in pre-diabetics [7]. The presence of insulin resistance might play an important role in the development of peripheral neuropathy in the metabolic syndrome due to the attenuation of the neurotrophic effects of insulin, thus resulting in mitochondrial dysfunction [8]. Metabolic syndrome, other than impaired glucose tolerance may represent independent risk factors for peripheral neuropathy: this may be related to the role of dyslipemia in neuropathy development, due to cellular and molecular consequences related to nitric-oxide inhibition, vascular dysregulation and oxidative injury. Therefore, there seems to be a link between obesity, adiposity, insulin resistance and neuropathy pathogenesis [9].

The lifetime incidence of neuropathy is approximately 45% for patients with type-2 DM, and 54% for patients with type-1 DM Neuropathic pain occurs in 7.5 to 24% of all patients [10]. Diabetic polyneuropathies can be classified into generalized (with typical and atypical varieties), and focal or multifocal groups [4]. Fifty percent of patients are asymptomatic [5].

As regards the diagnosis of diabetic peripheral neuropathy, according to the American Academy of Neurology, there is good evidence that symptoms alone have a poor diagnostic accuracy in predicting the presence of neuropathy. Signs are better predictors than symptoms; multiple signs are better predictors than single signs; and simple examinations are as accurate as complex scoring systems [2,11]. The American Diabetes Association recommends that all patients with diabetes should be screened at diagnosis in type-2 DM, and 5 years after diagnosis in type-1 DM, and screening should be repeated annually. Clinical evaluation should include a careful history and assessment of either temperature or pinprick sensation, and vibration sensation using a 128-Hz tuning fork, as well as, annual 10-g monofilament testing to identify feet at risk of ulceration and amputation [12].

The Norfolk QOL-DN was developed and validated to measure the patient´s perceptions of the effects of neuropathy: this is a nerve-specific questionnaire for evaluating the quality of life in patients with diabetic neuropathy, with a >75% sensitivity, and 71-89%, specificity 90.9% positive predictive value and 85-90% negative predictive value [13].

The Michigan Neuropathy Screening Instrument was created to facilitate the early diagnosis of diabetic neuropathy with high sensitivity and specificity. To confirm the diagnosis, the Michigan Disability Neuropathic Score was designed to play an important role [14].

The Utah Early Neuropathy Scale was designed specifically to detect and quantify early small-fiber sensory neuropathy, and is more sensitive than Michigan Disability Neuropathy Score. This is a simple, rapid and reproducible examination [15].

Diabetic neuropathy should be staged whether it is symmetric or asymmetric. Stage 0 means no neuropathy; Stage 1, asymptomatic neuropathy; Stage 2, symptomatic neuropathy; Stage 3, disabling neuropathy [16]. The diagnosis of asymptomatic or preclinical neuropathy is crucial in order to stop progression to advanced or irreversible stages, and to prevent further complications [10]. Once symptoms appear, there are few effective therapeutic strategies [17]. Signs and symptoms have a low prevalence in early diabetes; by electrophysiology, 15.2% of patients were diagnosed early neuropathy [1].

The Semmes-Weinstein Monofilament (SWM) is an inexpensive, reliable and painless device for primary and special care physicians. A positive result is associated with an increased risk of ulceration and lower extremity amputation, with a negative result, such risk is lower. In spite of the lack of standardization for its use, SWM is a practical tool to be used in primary care [18]. However, the use of SWM is not recommended to be used as the sole tool to diagnose neuropathy [19]. Bijli et al designed footboards for screening peripheral neuropathy with a high level of performance ion detecting at-risk feet [20].

Standard nerve conduction studies are the method of choice for In detecting neuropathy, as they are specific, sensitive and validated means of nerve function impairment [21]. Besides the use of standard techniques (motor and sensory conduction studies), some techniques should be included. A sural/radial amplitude ratio less than 0.5, with a normal standard sensory nerve conduction study had 90% sensitivity and specificity in one study [22]. Composite scores should be considered in search of abnormality, as they are more sensitive, reproducible and indicative of the polyneuropathy severity than individual attributes of nerve conduction [23]. Upper limbs should be evaluated as well, as median neuropathy could be used to identify an early manifestation of diabetic neuropathy [24,25]. Sensory nerve excitability testing may be a potential screening tool for the detection of subclinical neuropathy [26]. Motor nerve excitability of the common peroneal nerve was assessed in type-1 adolescents: reduced axonal excitability was demonstrated in diabetic patients, compared to their controls in one study. The authors proposed this compound muscle action potential scan technique might be useful to detect subclinical neuropathy [27].

The San Antonio Conference on Diabetic Neuropathy recommended the inclusion of F-waves in the battery of electrodiagnostic test [3]. Assessment of F-waves is a better measure

for detecting early conduction changes as it studies a diffuse process [22,28-30]. H-reflex studies have been found to have a role in early neuropathy as well [17,31,32]. Long latency responses are simple to determine, as well as it is reproducible and can be performed in any EMG laboratory since there is no need of specialised equipment [31].

Small fibers may be damaged in the early stage of DM leading to an early impairment of pain and temperature sensations. Moreover, it has been demonstrated an early and subclinical selective damage of small nerve fibers both in type-1 and type 2 DM patients [33]. Besides, patients with impaired glucose tolerance more often had neuropathy restricted to small nerve fibers than patients with DM who had more often involvement of both small and large nerve fibers in on study [34]. Small fiber neuropathy is easily missed by standard electrophysiological techniques, so other methods ought to be used to quantify peripheral small fiber dysfunction [35].

Quantitative Sensory Testing (QST) enables an assessment of sensory thresholds related to large and small fiber function. This test should be included in diabetic polyneuropathy evaluation, even in the pre-clinical stage. QST should not be used as the sole criteria for diagnosing neuropathy, but may be a good measure of the longitudinal worsening [36]. However, QST is highly subjective, highly variable and has limited reproducibility [37].

The cutaneous silent period was described by Hoffmann in 1922, and assesses a spinal inhibitory reflex after an electrical stimulus of a sensory nerve. It can be obtained in any EMG device [38], and has been used to study A-delta fibers in peripheral neuropathy [39]. It may be a useful method for the early detection of diabetic small fiber neuropathy [36,40,41].

Sympathetic Skin Responses (SSR) serves in the early diagnosis of autonomic neuropathy [42]. In some studies, abnormalities included absence of SSR, prolonged latency and lowered amplitude in early diabetic [43,44], and impaired glucose tolerance neuropathy [45]. SSR may deteriorate earlier than cardiac vagal function.

Sudoscan was recently developed to test sweat gland function non-invasively. Based on reverse iontophoresis and chronoamperometry, this device measures Electrochemical Skin Conductance, and might have a potential as a quick screening test for early diabetic neuropathy, and for assessment of response to therapeutic interventions in diabetic patients [46-50], with a similar diagnostic efficiency to skin biopsy [51].

Neuropad is an easy-to-use patch that assesses plantar sweat production through a color change from blue to pink with a sensitivity of 95% and specificity of 68.9%. This indicator test contributes to encourage patients´ self examination and promotes education about foot care [52]. Neuropad response was quantified through the use of sudometrics software with a higher sensitivity and specificity for detecting small finer damage in one study [53].

Quantitative Sudomotor Axon Reflex Test (QSART), which assesses sympathetic sudomotor response to chemical or electrical stimuli. Thus, representing functions of postganglionic sympathetic sudomotor neurons [54], has been found to evaluate early diabetic neuropathy more precisely than SSR [55]. However, it is time consuming and requires special equipment which is not available in all clinics [56].

Corneal confocal microscopy is an imaging instrument in which the cornea is illuminated with a focused light spot and then is focused by an objective lens into a small focal volume, permitting improved optical sectioning of the cornea and a three-dimensional reconstruction [57]. It quantifies early small nerve fiber damage, and has a high sensitivity and specificity for detecting diabetic polyneuropathy. Moreover, it detects subclinical prediabetic nerve injury [37], even before reduction of intraepidermal nerve density [58]. However, it cannot be applied in all centers due to the lack of equipment and staff [41].

Skin biopsy is currently the gold standard to quantify small fibers which are invisible to conventional neurophysiological tests even though they might be affected in early neuropathy. It is commonly performed using a 3mm punch under sterile technique with topical anaesthesia, and assesses the density of Intraepidermal Nerve Fiber Density (IENFD) by marking nerve fibers with PGP 9.5, a pan-axonal marker. The result is expressed as IENF per millimetre [59]. Intraepidermal denervation is an independent indicator of neuropathy. Besides, the clinical management of diabetic neuropathy is follow-up under treatment [60]. Epidermal nerve fiber density is abnormally decreased in only about three-fourths of patients suspected of having small fiber neuropathy. Therefore, a normal biopsy does not exclude small fiber neuropathy [61,62]. The disadvantage is that this test is invasive, costly, and requires specialist histological technique to quantify IENFD [37].

Cardiac Autonomic Neuropathy (CAN) may occur very early in the course of type-2 DM patients. Subtle autonomic function abnormalities may begin before the diagnosis of diabetes mellitus, even before insulin resistance, during the initiation of metabolic syndrome [63]. CAN is progressively impaired with increasing severity of insulin-resistance: hyperinsulinemia takes effect on hypothalamus, and thus has a sympathoexcitatory effect which is associated with parasympathetic withdrawal [64]. The prevalence of CAN is 7.7% at diagnosis of type-1 DM patients, and 5% at diagnosis of type-2 DM patients. Patients may be asymptomatic for decades: earlier diagnosis is needed before it is symptomatic because CAN is an independent risk factor for cardiovascular mortality [65].

The Survey of Autonomic Symptoms can be an aid in the early detection and diagnosis of early diabetic CAN [66]. However, cardiovascular reflex tests are gold standard in clinical autonomic testing. The combination of these tests with those of sudomotor function may allow a more accurate diagnosis of autonomic neuropathy [67]. If possible, time domain (four Ewing tests), and spectral analysis frequency bands (three tests) should be used: if two of seven tests are abnormal, then CAN is incipient. In absence of spectral analysis, Ewing tests should be performed: if one of the four tests is not normal, then CAN is early or incipient [65]. In (table 1), there appear all neurophysiological tests that should be used to diagnose early diabetic neuropathy.

Non-electrophysiological studies, such as magnetic resonance imaging [68] or nerve ultrasound [69,70] were tested for early diagnosis of neuropathy, with promising results. Magnetic resonance neurography with the use of high-field scanners (3 TESLA) and T2-weighed imaging sequences with strong fat suppression might enable the visualization of early fascicular nerve lesions that remain undetected by nerve conduction studies [68].

In one study, through magnetic resonance neurography, a predominant site of microstructural nerve alteration was found at the thigh level with a strong proximal-to-distal gradient. Nerve proton spin density at the thigh level might be a novel biomarker for early diabetic neuropathy in the future [71]. On the other hand, tibial nerve sonoelastography was assessed in diabetic patients with and without neuropathy, compared to healthy control: sonoelastography was

Table 1: Neurophysiological techniques to diagnose early diabetic neuropathy
Large fibers
• Sensory and motor conventional studies [20]
• Sural/radial amplitude ratio [21]
• Composite scores [22]
• Evaluation of upper limbs [23,24]
• Sensory nerve excitability [25]
• Motor nerve excitability [26]
• Late responses: F-wave and H-reflex studies [17,21,27-31]
Small fibers
• Cutaneous silent period [35, 39,40]
• Sympathetic skin responses [41-44]
• Quantitative sensory testing [35]
• Quantitative sudomotor axon reflex test [54]
• SUDOSCAN [45-50]
• Neuropad [51,52]
Cardiovascular denervation
• Time domain tests (Ewing´s test) [63,65]
• Frequency domain tests [63,65]

decreased in patients without neuropathy and further decreased in those with neuropathy; besides, the cross-sectional area of the tibial nerve larger in patients than in controls: the larger the cross-sectional area is, the more severe the neuropathy results [70].

In one study, the association between early retinal abnormalities (measured by spectral-domain optical coherence tomography) and CAN (measured by cardiac autonomic function tests) was found in type-2 DM patients: eyes with retinal nerve fiber layer defects had a significantly thinner average ganglion cell-inner plexiform layer in patients with early and definite CAN: the authors emphasize the utility of the search of retinal early abnormalities. Careful attention is recommended to patients with abnormal thinning in macular cell-inner plexiform layer, as this has a strong association with CAN [72].

In one study TyG index (Triglyceride-Glucose Index) showed a positive correlation with some autonomic tests (heart rate variation during deep breathing, heart rate variation during standing, blood pressure response to handgrip and blood pressure response to standing). This index might be useful as an alternative tool for the early screening for diabetic autonomic neuropathy [73].

^{123}Iodine-Metaiodobenzylguanidine (^{123}I-MIBG) SPECT imaging has its role in the diagnosis of early CAN. MIBG is a noradrenaline analogue, labelled with ^{123}I for imaging: it is injected intravenously at rest, and planar and SPECT images of the myocardium are acquired fifteen minutes after injection and four hours thereafter. Healthy patients show a good uptake of the radiotracer, slightly lower in the inferior wall. Patients with symptomatic sympathetic neuropathy have a profound loss of myocardial uptake [74]. In the early stages of CAN, uptake is decreased in the inferior wall, and then progresses to adjacent segments. An inferior-to-anterior radio index is sensitive when assessing early neuropathy, even though global uptake indices remain within normal ranges [75]. Cardiac sympathetic dysinnervation is observed, through this imaging technique, before ECG-based cardiac autonomic neuropathy is diagnosed [76]. The explanation for this might be that abnormalities in cardiac sympathetic innervation occur prior to heart rate variability dysfunction, which assesses parasympathetic fibers [77]. In (table 2), there appear imaging techniques that can be useful for diagnosis of early neuropathy.

Glycemic control may be the most effective treatment to slow the progression of neuropathy or delay its onset in type-1 DM patients [78]. Intensive metabolic therapy is designed to achieve blood glucose values as close to normal as possible through the use of three or more injections of insulin per day, or insulin administration through pump. The Diabetes Control and Complications Trial (DCCT) showed that patients receiving intensive therapy had a significantly lower decrease in sensory nerve and peroneal amplitudes, and had less prolonged F-wave latencies than patients receiving conventional therapy. Besides, intensive treatment slowed the decrease of the R-R variation: intensive diabetes management reduces the prevalence of clinical and laboratory indicators of neuropathy [79].

On the other hand, in a Cochrane review, enhanced glucose control in type-2 DM patients does not significantly reduce the incidence of clinical neuropathy However, it significantly reduces nerve conduction and vibratory threshold abnormality. Therefore, more aggressive treatments of hyperglycaemia might delay the onset of diabetic neuropathy in such patients. Nevertheless, this has to be balanced against the significantly increased risk of hypoglycaemia which can lead to brain injury and death [80]. In a more recent meta-analysis (ACCORD, ADVANCE, UKPDS and VADT trials were analysed), intensive glucose control in type-2 DM patients reduced the risk of kidney and eye events, but not nerve events in a median five-year´s time [81] (table 3).

Since metabolic syndrome plays a central role in peripheral nerve injury, the treatment of metabolic changes is a sensible strategy as early in the disease course as possible. Once neuropathy is established, it is difficult to reverse. Besides lifestyle-based strategies such as improving diet, reducing weight and increasing exercise ought to be implemented; strategies to reduce sedentary behaviour should be followed when not exercising (i.e., by using a vibrotactile stimulator to remind patients to move if they sit or lie down for more than 20 minutes) [82]. In one study of 32 subjects with impaired glucose tolerance neuropathy, diet and exercise counselling was provided as a standard of care during one year follow-up. Body weight, glycaemia and cholesterol improved. Intraepidermal nerve fiber density and QSART significantly improved, as well as pain after the intervention [83]. In another study, patients with type-2 DM without neuropathy were assigned to quarterly lifestyle counselling or structured supervised weekly exercise for one year. In the group with supervised exercise, distal leg IENFD increased, but in the counselling cohort, it remained unchanged: preclinical injury to unmyelinated axons may be reversible [84]. As metabolic syndrome is associated with early reduced IENFD, supervised exercise-induced improvement in metabolic syndrome increased cutaneous reinnervation even in those patients who improved only one feature of the syndrome. Besides, both weight loss and exercise reduce sympathetic nervous system over activity that characterizes this syndrome [85] (table 3).

Physical activity improves autonomic nervous system function: it enhances heart rate variability by increasing large artery compliance: in this way, baroreceptor nerve traffic and parasympathetic tone is increased. Furthermore, brain stem cardiorespiratory system may be remodelled: this results in the reduction of sympathetic and the enhancement of parasympathetic nerve outflow: heart-rate vagal modulation turns higher and cardiorespiratory fitness generally improves. Moderate intensity exercise training is beneficial for autonomic function in type-1 and type-2 DM patients with early

Table 2: Imaging techniques that may aid for the diagnosis of early neuropathy.
• Sonoelastography of the tibial nerve [69]
• Magnetic Resonance neurography [67,70]
• spectral-domain optical coherence tomography [71]
• 123I-MIBG Spect [73,74]

Table 3: Therapeutic strategies in early neuropathy
• Intense glucose control in type-1 DM [78]
• Diet improvement [78,81]
Physical activity
• quarterly lifestyle counselling [82,83]
• structured supervised weekly exercise [82,83]
• moderate intensity exercise training for early CAN [63,85]

CAN. Moderate endurance and aerobic exercise improve cardiac autonomic function [86]. Patients suspected to have CAN should undergo a cardiac stress test before starting an exercise program. CAN, once developed, may not be reversible with lifestyle intervention [87] (table 3).

Alpha-lipoid acid, a natural product which plays an essential role in mitochondrial energetic reactions, has been used as an antioxidant in managing diabetic complications: it quenches reactive oxygen species, chelates metal ions, reduces the oxidized forms of other antioxidants (vitamin C, vitamin D and glutathione), and boosts antioxidant defence by regulating several genes. Besides it has anti-inflammatory effects [88]. Its use has been studied as a co-adjuvant therapy in the metabolic syndrome (in which modest reductions of plasma nonesterified fatty acid concentrations has been seen, without alterations of glucose or insulin plasma levels) [89], obese patients (with a slight reduction of body weight and body mass index; however, more studies are needed for confirmation) [90], and early diabetic nephropathy (lipoic acid might protect the kidney in early diabetes mellitus against oxidative stress) [91]. α-lipoic acid is a safe and effective drug for the treatment of symptomatic diabetic neuropathy [92,93], as well as autonomic neuropathy [94,95]. Benfothiamine [96] and epalrestat [97], have beneficial effects in patients with symptomatic diabetic neuropathy. Studies on the effects of α-lipoic acid, benfothiamine and aldose-reductase inhibitors on early, asymptomatic neuropathy are needed. Some animal studies on the effects of olive leaf extracts [98] and coenzyme Q10 [99] have shown promising results.

In conclusion, impairment of the peripheral nervous system occurs early in the course of type-1 and type-2 DM patients. Its diagnosis in the pre-clinical stage is mandatory, as well as challenging, since successful treatment with diet and lifestyle intervention may be warranted before symptoms appear.

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