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REVIEW ARTICLE

Review of Diabetic Polyneuropathy: Pathogenesis, Diagnosis and Management According to the Consensus of Egyptian Experts

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Abstract: Diabetic polyneuropathy (DPN) is a complex and multifactorial entity in which various factors besides hyperglycemia play an important role. Symptoms of DPN are sensory, motor or autonomic. Intensive research proved that oxidative stress is the common denominator for the four major destructive pathways of hyperglycemia including increased hexosamine pathway flux, activation of Protein kinase-C (PKC) pathway, increased Advanced Glycated End-products (AGEs) formation, and increased Polyol Pathway flux. National data in Egypt confirms that more than 60% of Egyptian diabetic patients suffer from neuropathy. The most common complications of DPN are Cardiac Autonomic Neuropathy (CAN), diabetic foot and ulcers, neuromuscular disability, and anxiety. In addition, DPN affects the Quality of Life (QoL). According to common clinical practice, the common diagnostic tools are bed-side diagnosis and electrophysiological tests. Early diagnosis is critical to improve the prognosis of DPN and therapeutic intervention in the early phase. In this review, we provide a clear understanding of the pathogenesis, early diagnosis and the good management of DPN. Since the pathogenesis of DPN is multifactorial, its management is based on combination therapy of symptomatic; either pharmacological or non-pharmacological treatments, and pathogenic treatment. Alpha Lipoic Acid (ALA) is a potent anti-oxidant that has several advantages as a pathogenic treatment of DPN. So, in clinical practice, ALA may be prescribed for patients with early neuropathic deficits and symptoms. Patient education has an important role in the managemement of DPN.

Keywords: Diabetic polyneuropathy, pathogenesis, prevalence, diagnosis, management, protein kinase-C.

1. INTRODUCTION

Diabetic polyneuropathy (DPN) is a frequent and serious complication of both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). DPN is a debilitating and progressive condition with a major impact on patient mortality, morbidity, and Quality of Life (QoL). Five types of neurological syndromes are related to DM: Distal Symmetric Polyneuropathy (DSPN, most frequent), autonomic neuropathy, polyradiculopathy, small-fiber neuropathy (earliest), and mononeuropathies [1, 2].

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Symptoms of DPN are sensory, motor or autonomic [3, 4]. Usually sensory symptoms occur earlier than motor symptoms but [5], in many cases, patients end up suffering from sensory and motor symptoms.

Search strategy: A narrative review was performed during an expert board meeting to review 32 published articles up to March 2018. In this article, we will provide a clear understanding of the pathogenesis, early diagnosis and the good management of DPN according to the Egyptian expert practice.

2. PATHOGENESIS OF DIABETIC NEUROPATHY

The pathogenesis of DPN is multi-factorial [1]. Several studies support the concept that; the pathogenesis of DPN differs between T1DM and T2DM [6, 7]. Multiple factors are the main drivers for DPN in T2DM including oxidative stress, vascular, and metabolic factors; while in T1DM, hyperglycemia is the main driver that leads to several destructive pathways [1, 3, 8].

There are four established mechanisms regarding how chronic hyperglycemia causes DPN:

2.1. Increased Polyol Pathway Flux

This pathway affects many sites in the body and several types of tissues. Through this pathway, increased activity of aldose reductase enzyme decreases the amount of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) [9]. Increased flux through polyol pathway may activate PKC pathway. Persistent and excessive activation of PKC initiates tissue injury [10]. Experimental studies in rats suggest that increasing sorbitol levels in blood vessels and nerves leads to harmful effects [9].

2.2. Increased Advanced Glycated End-products (AGEs) Formation

Hyperglycemia results in AGEs through non-enzymatic glycation of mitochondrial respiratory chain proteins [9]. This results in covalent bonds with proteins or lipids leading to intra and extracellular cross linking and aggregation leading to deleterious effect on the nerves [11].

2.3. Activation of Protein Kinase-C (PKC) Pathway

Protein kinase is a family of enzymes controlling the function of other proteins. These enzymes affect collagen and growth factors, *e.g.*, Transforming growth factor B (TGF-B), leading to vascular occlusion followed by neuronal death. PKC is a common mechanism for neuropathy and vascular disease. Nerve degeneration is thought to develop as a result of occlusion or injury of the vasa nervosa [9].

2.4. Increased Hexosamine Pathway Flux

This pathway leads to accumulation of extracellular matrix with hyperglycemia, which may lead to neuroinflammation associated with DPN [10].

A common denominator for the four mechanisms, mentioned above, is oxidative stress and this was confirmed through intensive research [9]. There is experimental data that suggests a close link between hyperglycemia and oxidative stress [9, 11]. In rats, it was found that it affects dorsal root ganglion neurons causing impairment of mitochondrial function and oxidative stress induced apoptosis [9].

The major risk factors for DPN include hyperglycemia, diabetes duration and insulin resistance followed by dyslipidemia and hypertension. Additional risk factors include obesity, smoking and excessive exposure of AGEs through food intake [1, 6, 8, 11, 12].

Also, incidence of DPN for diabetic patients depends on the genetic factors [8]. It justifies the differences between Egyptians and other populations in the incidence and presentation of DPN. Recent studies proved the role of nerve micro vascular disease in the pathogenesis of DPN [9].

3. PREVALENCE AND MORBIDITY OF DIABETIC NEUROPATHY

According to international statistics, around one third of the diabetic patients have painful DPN [13]. National data in Egypt confirmed that 29.3% of Egyptian diabetic patients suffer from peripheral neuropathy [14]. Several studies revealed that DPN is more common in T2DM than T1DM and is more prevalent in females than males [6, 13]. In addition, several studies conducted in Europe (United Kingdom) proved that racial differences affect the neuropathic pain levels of DPN [13].

Symptoms of DPN are sensory, motor or autonomic [3, 4]. Sensory symptoms are usually associated with pain [6]. The severity of pain was found to be correlated with the severity of DPN and also to female gender [13]. Painful DPN is a complex and multi-dimensional condition, which negatively affects psychosocial functioning as expressed by enhanced levels of anxiety and depression, potentially leading to pain-related disability [15].

3.1. Autonomic Neuropathy

One of the most serious and common complications of DPN is autonomic neuropathy that can be presented by Cardiac Autonomic Neuropathy (CAN), gastroparesis, sudomotor neuropathy and / or erectile dysfunction [16, 17]. CAN is a critical condition that can lead to QT interval prolongation. It is considered a cardiovascular risk factor like hypertension and dyslipidemia [12, 17]. Detection of progressive CAN is associated with very bad prognosis [17], especially that it is irreversible. Therefore, prevention is better than intervention.

3.2. Diabetic Foot and Foot Ulcers

Some patients suffer from loss of protective sensation, which leads to diabetic foot, which is one of the major complications of DPN. Diabetic foot is the major cause of lower limb amputation. Diabetic foot occurs as a result of neuropathy and/or ischemia. According to international prevalence studies, the etiology of diabetic foot is mainly neuropathic; in around 87% of the cases. The rest of the cases are due to either vascular factors or mixed neuro-ischemic etiology [6, 18]. National Egyptian studies match the international studies' statistics. In local diabetic foot clinics, most of the cases are caused by neuropathy.

3.3. Neuromuscular Disability

Neuromuscular disability is a motor consequence of DPN. It leads to muscle weakness and fatigue [3, 15]. It occurs more in the elderly and; it is related to duration and severity of diabetes. Elderly diabetics are more prone to this complication *versus* non-diabetics [3]. Several trials proved that neuromuscular complications are more common in T2DM than in T1DM [13].

3.4. Anxiety

Anxiety is considered a common complication of DPN. Patients suffer from a number of fears including a fear of pain, falls, hypoglycemic episodes, fatigue, and kinesiophobia. Anxiety should be evaluated in patients because anxiety has a dramatic impact on the QoL of diabetic patients [15].

3.5. Quality of Life (QoL)

DPN is one of the major causes of falls, especially in elderly patients. Loss of sensation leads to fear of falls and kinesiophobia (fear of movement). So, DPN has significant adverse effects on the QoL [15, 19].

4. DIAGNOSIS OF DIABETIC NEUROPATHY

Differential diagnosis is critical. So, the first step for diagnosis of DPN should be to exclude other causes of neuropathy rather than diabetes [7]. Toronto Diabetic Neuropathy Expert Group [17] defined the grades of DPN, according to severity:

- Grade 0: no abnormality of nerve conduction
- Grade 1a: abnormality of nerve conduction without symptoms or signs
- Grade 1b: nerve conduction abnormality of stage 1a plus neurologic signs typical of DSPN, but without neuropathy symptoms
- Grade 2a: nerve conduction abnormality of stage 1a with or without signs (but if present, <2b) and with typical neuropathic symptoms
- Grade 2b: nerve conduction abnormality of stage 1a, a moderate degree of weakness (*i.e*., 50%) of ankle dorsiflexion with or without neuropathy symptoms.

According to common clinical practice and the American Diabetes Association guidelines, the common diagnostic tools are bedside diagnosis and electrophysiological tests [3, 7].

4.1. Sensory Tests

There are different sensory profiles in diabetic DSPN. Sensory symptoms can be classified into two major types; Loss of function abnormalities "negative symptoms" (around 70% of the cases), *e.g*. thermal and tactile hypoesthesia, anesthesia and mechanical hypoalgesia and gain of function abnormalities "positive symptoms" (around 30% of the cases), *e.g*. Allodynia [18, 20]. Pain is a clear clinical symptom that guides diagnosis. Yet, painless neuropathy should be detected through routine screening and examination.

4.2. Structured Neurological Examinations

Structured Neurological Examinations are the standard assessments used for DPN diagnosis including; monofilament (pressure perception test), vibration sense tested by a 128Hz tuning fork, pinprick test (pain assessment), and reflexes (*e.g*., knee, ankle, and deep tendon reflexes) [7, 18, 20]. For greater specificity, the diagnosis of DPN often requires abnormalities in more than one diagnostic tests.

4.3. Nerve Conduction Studies (NCS)

Nerve conduction studies (NCS) are reliable and can be used to confirm the diagnosis in some patients with typical symptoms [7, 17]. But, it is relatively expensive and therefore, not feasible to all patients. Therefore, international scientific associations do not recommend the performance of NCS, as a routine method for diagnosis. But, they recommend mainly the vibration sensation test and the monofilament test [7]. On the other hand, NCS are beneficial in the field of research.

4.4. Skin Biopsies

Skin Biopsies, which is rare to be done [17]. Skin biopsy followed by Intra-Epidermal Nerve Fiber Density (IENFD) can detect DPN in patients who have normal NCS [7, 17, 20].

4.5. Sudo-scan and Electrochemical Skin Conduction (ESC)

Sudo-scan and Electrochemical Skin Conduction (ESC) can be used for early diagnosis of autonomic neuropathy (sudo - motor) in patients who have atypical or masked symptoms. Some researches concluded that it is more sensitive than the NCS but; this conclusion is still questionable [21]. On the other hand, there are many restrictions to use it as it cannot differentiate between DPN and non-DPN and is expensive. So, it cannot be used routinely in Egypt. Recently, ESC has been introduced as a sensitive and non-invasive technique for early detection of sudo - motor autonomic neuropathy [21].

4.6. Detection of CAN

All diabetic patients should be assessed for the presence of CAN if they are going to undergo any surgery, because of the effect of general anesthesia. CAN can be detected by measuring heart rate variability, ambulatory blood pressure monitoring (to detect non-dipping blood pressure which reflects parasympathetic defects and to detect postural hypotension), and continuous ECG monitoring, *e.g*. Holter monitoring (to detect QT interval prolongation) [17].

4.7. Neuropathy Severity and Neuropsychological Scores and Questionnaires

They are useful tools during follow-up visits, as they show the degree of improvement. There are several questionnaires including:

- Neuropathy Disability Score (NDS) that can be used for all patients to assess the degree of neuropathy even without pain symptoms [21].
- Visual Analogue Score (VAS) that is used to assess the severity of pain [7, 22].
- Total Symptoms Score (TSS) [23].

4.8. Early Diagnosis

Early diagnosis is critical to improve the prognosis of DPN. Also, therapeutic intervention is recommended in the early phase [5, 21].

Total neuropathy score-reduced (TNSr) assesses the degree of sensory and motor affection using subscores for symptomatic patients [5].

Sensory nerve excitability testing is a useful tool, as it has the potential to provide greater sensitivity in early detection of axonal dysfunction even with asymptomatic patients [5].

5. MANAGEMENT OF DIABETIC NEUROPATHY

Early detection and optimal treatment of DPN result in significant improvement of the QoL of the patients. Since the pathogenesis of DPN is multi-factorial [1], its management is based on combination therapy of symptomatic and pathogenic treatment [4]. The pathogenic factors of DPN differ between T1DM and T2DM [6, 7]. So, the management of T1DM might differ from T2DM. Regarding T1DM, glycemic control can halt the progression of neuropathy, while for T2DM, many other factors are implicated. Also, controlling modifiable risk factors (*e.g*. smoking and weight reduction) is more effective in patients with T1DM than in patients with T2DM [7, 8].

Comorbidities of DM and DPN including depression, hypertension, dyslipidemia, and macrovascular complications decrease the response to pharmacotherapy [24]. So, it is advisable for the clinician to screen for and monitor them as part of the overall management plan for DPN [8].

5.1. Symptomatic Treatment

Pain is a disabling symptom that should be treated with either pharmacological or non-pharmacological treatments [22, 25].

5.1.1. Pharmacological Therapy

There is a widespread international acceptance on pharmacological treatment of neuropathic pain [26]. Three drug classes are recommended for pain relief; antiepileptic, antidepressants, and non-specific analgesics [7].

1) Antiepileptics include gabapentin and pregabalin and; they are equally recommended as first line therapies [6, 26].
2) Anti-depressants are mainly used to overcome the anxiety and depression associated with neuropathic pain such as duloxetine and amitriptyline. Duloxetine is more recommended than amitriptyline because of the anticholinergic side effects of amitriptyline *e.g*. dry mouth, constipation and urinary retention [6].
3) Analgesics including opioids that are recommended by most guidelines for second- line treatment due to their safety issues [19, 27], and topical preparations of capsaicin and lidocaine which are recommended as second line treatment for peripheral neuropathic pain but they have low evidence level and limited efficacy [22, 25, 26].

5.1.2. Non-pharmacological Therapy

Low intensity laser therapy, magnetic field therapy and spinal cord stimulation [22].

5.1.3. Follow-up Period

VAS and QoL questionnaires can be used as useful tools in evaluating the extent of improvement during the follow up period. Treatment is considered successful if VAS detected at least 30% improvement [7, 22].

5.2. Pathogenic Treatment

Pathogenic treatment is critical, as it can halt the progression of DPN [12]. It should be used as long term and even in asymptomatic patients. The recommended effective treatment of DPN is glucose control, especially in T1DM rather than T2DM [7]. Moreover, agents interfering with the three major destructive pathways of hyperglycemia; AGEs, PKC, and hexosamine pathways, are recommended [18, 28].

5.2.1. Aldose Reductase Inhibitors

Epalrestat was used in the past in Japan, but it was withdrawn from the markets due to lack of efficacy and safety concerns [28, 29].

5.2.2. Benfotiamine

Benfotiamine was proven to reduce the AGEs and to improve endoneurial blood flow, the nerve conduction velocity and motor function [28].

5.2.3. Antioxidant Therapy

Reactive oxygen species (ROS) are highly predominant in DPN. And, oxidative stress is suggested to contribute to defective nerve blood supply (neural ischemia) and endoneurial oxidative damage [30]. Many data supported prescribing a treatment that significantly counters oxidative stress as it was proved that oxidative stress is the main driver for DPN, as mentioned above. Potent agents that reduce oxidative stress are more beneficial than other agents targeting a specific hyperglycemic destructive pathway of the pathogenesis. Among the agents that have anti-oxidant properties are Vitamins A, C and D, L-carnitine, melatonine, curcumin and flavonoids, but these agents did not prove to be effective in clinical studies [28].

5.2.4. Alpha Lipoic Acid (ALA)

ALA is considered a valuable therapeutic option for diabetic neuropathy [31]. ALA is a potent anti-oxidant [7] and a free-radical scavenger that acts on many pathways of the pathogenesis and; it also reduces lipids peroxidation [31, 32]. It plays a predominant role in the redox-dependent mechanisms of various cellular targets [32]. ALA has the advantage of being the only anti-oxidant that is amphiphilic (both water soluble and lipid soluble) [28]. In addition, it has

an anti-inflammatory effect and; it improves microvascular complications and endothelial dysfunction [23, 32]. Several clinical studies showed that treatment with ALA improves paresthesia, numbness, neuropathic deficits and muscle strength, in addition to neuropathic pain [31, 32]. And, other studies proved that ALA is preferable in patients with CAN [31].

Till now, the pathogenesis of DPN is not fully understood [3, 32]. Therefore, there is no agent with strong level of evidence, as a pathogenic treatment. But, ALA is the only available option that should be considered [4, 12, 28, 31]. In clinical practice, ALA may be prescribed for patients with early neuropathic deficits and symptoms, in whom clinical improvement is more likely to be achieved [31].

5.3. Management of the Complications

5.3.1. Diabetic Foot Prevention

Early identification and education should be considered in all patients with peripheral neuropathy. The most important step that medical practitioners can take to reduce the incidence of ulceration and amputation in patients with diabetes is to examine the feet of their patients without shoes and socks at every visit. Neuropathic foot problems can be entirely preventable by providing patients with identified risk factors, podiatric treatment, and general preventive foot self-care education [18]. Specialized therapeutic footwear is recommended for diabetic patients with high-risk including those with severe neuropathy or history of amputation [7, 25].

5.3.2. CAN Assessment

CAN assessment may be used for cardiovascular risk stratification in patients with and without established cardiovascular disease. It is also considered an indicator for more intensive pharmacotherapy and lifestyle management of comorbid conditions. It is considered a marker for patients requiring more intensive monitoring during the perioperative period and other physiological stresses [17].

5.4. Patient Education

Patients should understand the fact that lifestyle management is a fundamental aspect of management. Patient education involves the patients and their close relatives, who are going to take care of them most of the time. Proper patient education can help in delaying or preventing the development of diabetes complications including DPN and its complications. Also, it can improve outcomes and reduce overall costs of management. Patient education should be done initially at diagnosis and also as an ongoing process throughout the follow-up period.

Diabetic patients with high-risk foot conditions should be provided with general preventive foot self-care education, general education about risk and the importance of foot monitoring on a daily basis and the implications of the proper care of the foot (including nail and skin care). Patients should be educated on ways to change other sensory modalities (palpation or visual inspection using an unbreakable mirror) for surveillance of early foot problems [7, 25].

CONCLUSION

DPN is a multifactorial and complex entity in which various factors besides hyperglycemia play an important role. The diagnostic tools for DPN are bed-side diagnosis and electrophysiological tests. Its management is based on a combination of symptomatic treatment including pharmacological and non pharmacological therapies and pathogenic treatment such as ALA, benfotiamine, and antioxidant therapy. The most common complications of DPN are CAN, diabetic foot, neuromuscular disability, anxiety, and its adverse effects on the QoL. Management of complications and patient education play important roles in the managemement of DPN.

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CONFLICT OF INTEREST

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