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Painful diabetic polyneuropathy; generating processes and future therapeutic considerations

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SUMMARY

Painful diabetic neuropathy (PDN) is a chronic complication of diabetes mellitus (DM). The prevalence of DM in the general population is 6.9% and the prevalence of PDN ranges from 20 to 24% among diabetic patients. The clinical manifestations of PDN are distal weakness, absence of tendinous reflexes, pain and loss of distal sensitivity. These manifestations are the final outcomes of a series of mechanisms that are involved in its pathogenesis; thus, some authors suggest a pharmacologic approach mechanism-based. The main objective to treat PDN is to control blood glucose and pain. To achieve this goal, diverse drugs such as aldolase-reductase and serotonine re-uptake inhibitors, tricyclic antidepressants, anticonvulsants, mexiletine, tramadol, levodopa, gamma-linolenic acid, alpha-lipoic acid, dextromethorphan, capsaicin, transcutaneous electrical nerve stimulation, acupuncture, among others had been used. The objective of this paper is to present to the reader updated information helpful to identify, evaluate and treat this complication.

Key words: Pain, diabetes, painful diabetic neuropathy.

RESUMEN

La neuropatía diabética dolorosa (NPDD) es una complicación crónica de la diabetes mellitus (DM) observada frecuentemente en la práctica clínica. Se ha reportado que la prevalencia de DM en la población general es del 6.9% y que la prevalencia de NPDD en los pacientes diabéticos es del 20 al 24%. La neuropatía diabética se caracteriza por la presencia de debilidad distal, ausencia de reflejos tendinosos, dolor y pérdida distal de la sensibilidad en extremidades. Estos hallazgos, son el resultado de los diversos mecanismos que se encuentran involucrados en su etiología. Por ello, diversos autores sugieren que el abordaje terapéutico debe fundamentarse en sus mecanismos de producción. El objetivo terapéutico principal de la NPDD es la obtención del control de la glicemia y del dolor. Para alcanzarlo, se ha propuesto el empleo de diversos fármacos entre los que se encuentran: inhibidores de la aldosa-reductasa y de la recaptura de serotonina, antidepresivos tricíclicos, anticonvulsivantes, mexiletina, tramadol, levodopa, ácido gamma-linoleico, ácido alfa-lipoico, dextrometorfan, capsaicina, estimulación nerviosa eléctrica transcutánea, acupuntura, entre otros. Con base en estas consideraciones, nuestro objetivo es proporcionar al lector elementos actuales que faciliten la identificación, evaluación y tratamiento de esta entidad.

Palabras clave: *Dolor, diabetes, neuropático, polineuropatía diabética.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic-degenerative disease whose frequency is rising; its complications both, acute and chronic, target different organs and systems, decreasing the quality of life and functional status of patients afflicted with this condition.

Painful diabetic polyneuropathy (PDPN) is a chronic nerve damage caused by diabetes mellitus. This condition is commonly observed in clinical practice; it has different forms of presentation and can be disabling. It is still unclear how pain is generated because the mechanism has not been identified in detail. Nevertheless, a number of investigations have proven that hyperglycemia triggers the nervous lesion. Several authors suggest that therapeutic schemes should be focused in this causal mechanism [hyperglycemia] with the aim to reducing neuropathy.

In the last decade, a great deal of information addressing PDPN from several perspectives has been published, such as: a) changes that PDPN produce in sensitive fibers; b) mechanisms of pain generation; c) effectiveness of therapeutic analgesia.

The objective of this paper is to provide the reader state of the art elements to simplify the identification, evaluation and treatment of PDPN.

DEFINITION

Painful diabetic polyneuropathy is defined as the finding of signs and symptoms suggesting peripheral nervous dysfunction of a patient with DM and after excluding other causes[1]. Therefore, to facilitate its diagnosis and treatment, a thorough clinical examination should be performed routinely[2].

The absence of pain symptoms in a patient with DM is not a criterion to exclude the presence of a nervous lesion (sensory, motor or autonomic); some types of neuropathy are asymptomatic[2] and the clinician cannot identify them.

PDPN may have somatic and/or autonomic manifestations and the diagnosis of PDPN requires to fulfill at least two of the following criteria: a) signs; b) symptoms); c) abnormalities of the nerve impulses; d) quantitative sensory tests or e) quantitative autonomic tests[2].

EPIDEMIOLOGY

Diabetes mellitus is regarded as a public health problem. It is estimated that between 110 and 120 million people worldwide have diabetes. Approximately 62 million of patients with diabetes live in Latin American countries[3] and more than 14 million live in the United States[4].

Its prevalence has increased in the general population (from 4.9% in 1990 to 6.9% in 1999). Among people older than 69 years, DM prevalence is higher[4] (14.4% in 1999) and it is estimated that 2.8 people die annually due to causes attributable to this condition[3].

Neuropathy is the most common chronic complication of DM[5]. The annual incidence[6] of this affection is 2% and is occurrence is related to an increase of morbidity and mortality[7]. Its presentation is associated with the time in which DM has progressed. It has been documented that approximately 50% of patients having DM for more than 25 years will develop possibly some kind of neuropathy[8].

In 1995, Partanen et al reported a 10-year follow-up study that included patients with diabetes and a control group. The results showed that 20% of patients with DM and 3% of control group patients had developed neuropathy[9].

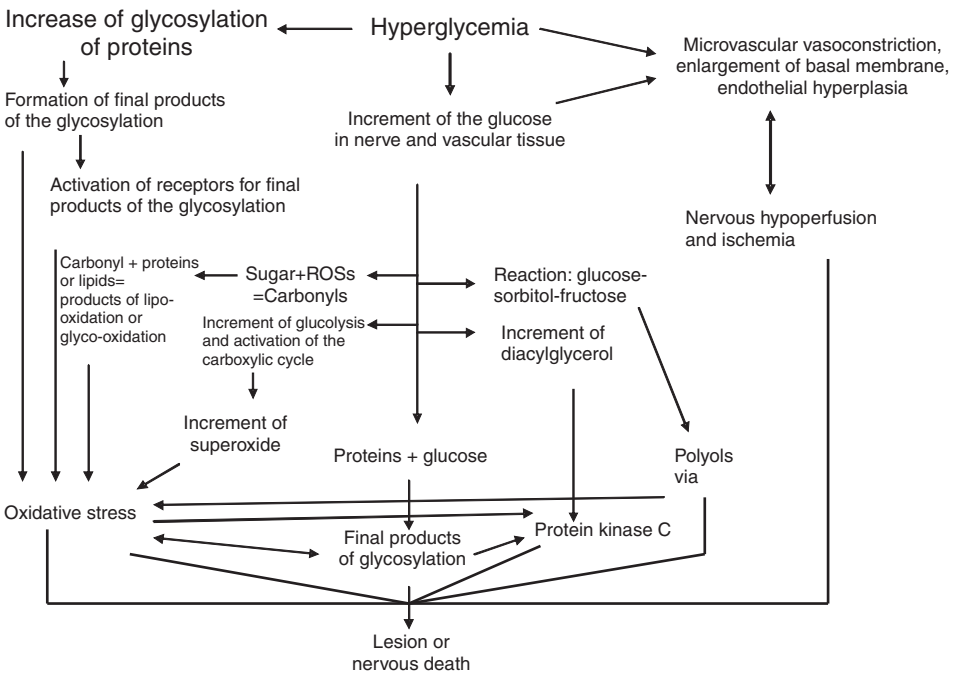
Painful diabetic polyneuropathy is a form of neuropathy that has a considerable impact on the quality of life of those afflicted with such a condition; its prevalence ranges from 20% to 24% in the general population[4]. Poor glycemic control favor an increase in neuropathic symptoms. Among patients with type 2 DM, poor glycemic control is directly related to the increase in neuropathy and between 43% and 53% of them suffer pain in their legs as a consequence of such a poor glycemic control. For this reason, hyperglycemia has been identified as the main cause of PDPN[11].

Nevertheless, the risk factors for this condition have not been clearly documented. It has been proposed that: a) the time of progress of diabetes; b) ageing; and c) poor glycemic control (high levels of hemoglobin A1c), are the risk factors for developing distal symmetric sensory neuropathy which in turn causes pain.

GENERATING MECHANISMS OF PAINFUL DIABETIC POLINEUROPATHY

Several generating mechanisms of PDPN have been identified, such as: a) hyperglycemia; b) microvascular factors; c) metabolic pathways (polyoles, myoinositol, C-peptide, protein kinase C, glycosylation and oxidative stress; d) growing factors (nerve growth factor, brain-derived neutrophic factor, insulin-like growth factor, endothelium-specific growth factor, and e) immunologic mechanisms. Each of these elements interacts with each other causing nervous damage that will end in PDPN. Therefore, the treatment should have a mechanistic approach[12] (Figure 1).

Hyperglycemia: The duration and severity of hyperglycemia are related directly to the severity of neuropathy[13].



(*)ROSs: Reactive species of oxygen.

Figure 1. Physiophatology mechanisms involucrated in the generation of the diabetic neuropathy.

Microvascular factors: There is a relationship of hyperglycemia with abnormalities of the microvascular system and of peripheral nerves. The increase of glycemia favors thickening of the vascular basal membrane and endothelial hyperplasia. These elements cause a decrease of the tissue oxygen tension, thus causing hypoxia and generating the appearance of neuronal dysfunction[14].

Polyol pathway: The enzyme aldolase-reductase causes oxidation reduction of glucose that is converted into sorbitol and this reaction oxidizes NADPH to NADP+ (nicotinamide adenine dinucleotide phosphate). Accrual of sorbitol (hyperosmolar substance) results in osmotic stress causing neuronal damage[15]. Preclinical studies have proven that this pathway is involved in the generation of nervous anomalies and decrease the speed of nervous transmission. These observations suggest the possibility that administering aldolase-reductase inhibitors would decrease the abnormalities that this metabolic pathway produces. Nevertheless, human trials have reported controversial results, because the levels of sorbitol and fructose increased slightly after the administration of aldolase-reductase and the severity of neuropathy did not change[16].

Myoinositol: The deficiency of production of myoinositol is related to neuropathy. Even though, in one clinical study in which the investigators performed biopsies of nerves from healthy patients and from patients with diabetes, myoinositol concentrations in the nervous fibers were similar in both groups, without statistically significant differences[17].

Glycosylation: Hyperglycemia occurs due to the formation of the final products of advanced stages of glycosylation. These substances participate in different immunological mechanisms. Glycosylation induces monocytes and endothelial cells and increase production of cytokines and adhesion molecules that participate in the genesis of the nerves damage[18,19].

Oxidative stress: Diabetes mellitus causes a hyper metabolic state that promotes the increase in intracellular glucose and participates in the formation of advanced glycation end products (carbonyls). These groups bind to proteins and lipids causing the glycoxidation and lipoxidation reactions[20]. The excess of intracellular glucose increase the production of reductive agents (NADP and FADH2) through glycolysis and through the tricarboxylic acid cycle[15]. These biochemical changes favor continuity of the metabolic state.

Growth factors: Neurotrophins are a class of growth factors that promote the survival of neurons by inducing morphologic differentiation of the cell. This process: a) increases nerve regeneration; b) stimulates the expression of neurotransmitters; c) changes physiological features of neurons. These substances could possibly have a clinical application on the damaged nerve fibers. Use of the human recombinant nerve growth factor has shown controversial results and is currently in a preclinical stage. Brain-derived neurotrophic factor in animal models has reported promising results[21].

C-peptide: This substance acts on: a) the sodium-potassium ATPase; b) the synthesis of endothelial nitric oxide

and c) the expression of neurotrophic factors that influence in the neural node degeneration that occurs in patients with type I diabetes. C-peptide bounds to transcription factors and intervenes in cellular apoptosis[22,23]. This mechanism inhibits oxidant stress and possibly intervenes in generating neuronal damage.

Protein kinase-C (PKC): This is a family of twelve isozymes that are activated by phosphorylation, act inside the cell and bind to diacylglycerol (a second messenger). PKC participates in the transduction pathway that originates the production of some mechanisms involved in generating neuropathic or neurogenic pain. During hyperglycemia, there is an increase of PKC and diacylglycerol in the tissues; however, in the nervous fibers, concentration of these substances remains unchanged[12]. Concentration (tissue-nerve) differences are possibly involved in generating neuropathy. Administering PKC inhibitors (ß1 and ß2) improve the speed of nervous transmission in diabetic animal models and the biological activity of the Na-K ATPase, averting the decrease of neuronal blood flow[24].

Immunologic mechanisms: Patients with type 2 diabetes with neuropathy have a calcium-dependent autoimmune immunoglobulin, which is independent from the complement that induces apoptosis of nerve cells[24].

THE CONSEQUENCES OF AUTONOMIC ANOMALIES

The sensory-motor diabetic neuropathy is the commonest nervous affliction. However, several reports have documented an increase in the incidence of autonomic neuropathies[25]. This nervous dysfunction affect several anatomic structures and promotes the development of atypical pain symptoms.

a) The cardiovascular autonomic alteration has 27% mortality after 10 years of disease progression. Its incidence is 15% in patients with type 1 diabetes and 20% in patients with type 2 diabetes. It has been proposed that an association exists between coronary artery disease and cardiovascular autonomic neuropathy.
b) Gastroparesia is the most common clinical manifestation of gastrointestinal autonomic neuropathy. This condition can affect from the esophagus to the colon and its symptomatology includes gastro esophageal reflux, malabsorption syndrome, constipation, abdominal pain, diarrhea and fecal incontinence[12].
c) Genitourinary autonomic changes favor the occurrence of sexual dysfunction and urinary incontinence.

These types of autonomic dysfunctions can have several manifestations such as: chest pain, low back pain, abdominal pain or recurrent pelvic pain; pain in one or both shoulders, epigastralgia and dyspareunia, among others. Therefore, patients at risk with atypical pain must be thoroughly examined; this can be the initial manifestation of unidentified diabetes mellitus.

STAGING

The etiology and pathogenesis of diabetic neuropathy have not been completely portrayed. Available classifications are based upon the anatomical and clinical findings (Table I) and on the severity of the polyneuropathy (Tables II and III)[2,27,28].

DIAGNOSIS

Most peripheral neuropathies are noticeable by: a) sensory abnormalities ("stocking-glove" pattern); b) pain; c) distal weakness; d) absence of tendinous reflexes; e) autonomic symptoms. The clinical progression is variable, depending upon the type of nerve damage (sensory, motor, and autonomic). The diagnosis of diabetic neuropathy in patients with comorbidity is very difficult and should be considered after disregarding other condition[29].

The diagnostic approach should be systematized through a three-stage process.

First stage: The patient must be clinically assessed by performing clinical history, physical exam and ordering following laboratory exams (blood glucose, urinalysis for proteinuria, complete erythrocyte account, erythrocyte sedimentation rate, thyroid - stimulating hormone blood test, determination of vitamin B12 and folates; also, concentration of blood glucose, liver and renal function tests should be considered. If after analyzing the results of these tests, the cause of neuropathy is still unclear or if the patient has an atypical presentation, then referral to a neurologist is advisable.

Second stage: The diagnostic uncertainty should prompt to carry out and evaluate the results of electrophysiological tests that will register distal and proximal nerve stimuli (80% will have and axonal component and 20% demyelination); additionally following tests should be ordered: serum protein electrophoresis test, ascertainment of the angiotensin converting enzyme, rheumatoid factor, antinuclear antibodies, antineutrophilic antibodies and chest X-ray.

Third stage: if the diagnosis remains unclear, the tests that to be ordered in this third stage will depend upon the results of the neurophysiological studies (axonal damage or demyelination). Order following tests: ascertainment of Bence-Jones protein in urine, glucose tolerance curve, cerebrospinal fluid (cell counting, proteins and oligoclonal bands, HIV, antineuronal bodies (Hu, Yo), tests to identify

Table I. Classifications of diabetic neuropathy.

Clinical classification of diabetic neuropathy		Anatomoclinical classification
a) Reversible neuropathies • Hyperglycemic neuropathy	a) Polyneuropathy • Sensory (1) Acute sensory (2) Chronic sensory-motor • Autonomic (1) Cardiovascular (2) Gastrointestinal (3) Genitourinary (4) Other • Proximal motor (amyotrophic) (1) Trunk • Mono-neuropathy (1) Isolated peripheral (2) Multiple mono-neuropathy (3) Trunk	a) Extension of diabetic polyneuropathy • Distal symmetric sensory polyneuropathy • Long fibers neuropathy • Pain symmetric polyneuropathy • Autonomic neuropathy
b) Symmetric generalized polyneuropathy • Sensory-motor • Acute sensory • Autonomic		b) Focal and multifocal neuropathies • Cranial neuropathy • Extremities neuropathy • Proximal diabetic neuropathy of lower extremities • Trunk neuropathy
c) Focal and multifocal neuropathies • Cranial • Thoraco-lumbar radiculoneuropathy • Focalized to the extremities • Proximal motor or amyotrophic		c) Most common non-diabetic neuropathies in diabetic patients • Due to pressure • Acquired inflammatory demyelinating polyneuropathy

Table II. Staging of diabetic polyneuropathy.

N0	Without objective evidence of diabetic neuropathy
N1	Asymptomatic polyneuropathy • N1a: no signs or symptoms of neuropathy, but neurologic tests with abnormalities • N1b: abnormalities in conduction speeds, plus abnormalities in neurologic examination
N2	Symptomatic neuropathy • N2a: signs, symptoms and tests abnormalities • N2b: N2a plus significant knee dorsiflexion
N3	Disabling polyneuropathy

Sjögren syndrome and tests to identify genetic anomalies. Similarly, we recommend searching for carcinoma, lymphoma or solitary myeloma (by using radiology tests).

A number of diseases can be related to peripheral neuropathies, therefore, a systematic evaluation through above mentioned stages is required to make the diagnosis. Regarding diabetic polyneuropathy, a significant proportion of diagnoses can be made in the first and second stages.

Diabetes can also cause diabetic lumbosacral plexopathy (Bruns-Garland syndrome). Carrying out a systematized evaluation of its clinical manifestations and of the diagnostic tests is useful for the diagnosis. The main clinical findings to search for are: gender (it is more common in men); pain semiology, muscular weakness and significant weight loss (> 10-20 kg). Following diagnostic tests should be considered: electromyography, nerve conduction test, cerebrospinal fluid test. Carrying out a nerve biopsy is not helpful for the treatment, and is only useful to make differential diagnoses[31].

DIFFERENTIAL DIAGNOSES

Other causes of acute peripheral neuropathy are: Guiliain-Barré syndrome, porphyry, diphtheria, acute sensory idiopathic neuropathy, critically ill patients, renal failure, paraneoplasias, celiac disease, sarcoidosis, HIV, leprosy, amyloidosis, Fabry's disease, hereditary sensory neuropathies, Tangier disease, toxic neuropathies (antiretroviral drugs, antineoplastic drugs, antibiotics, alcohol, pyridoxine, arsenic, etc.); autoimmune diseases (neuropathies as-

sociated with monoclonal gammopathies, lupus, Sjögren syndrome, rheumatoid arthritis, mixed connective tissue disease, vasculitic neuropathies) and cryoglobulinemia[29,32].

Clinical differences between acute and chronic neuropathies

Table IV shows the clinical differences between sensory-motor neuropathies, acute or chronic.

THERAPEUTIC APPROACH CONSIDERING THE GENERATING MECHANISMS

Proper glycemic control can decrease the risk for neuropathy and for other complications associated with diabetes mellitus[4,33,34]. Drug treatment includes prescription of aldolase-reductase inhibitors with the aim to reducing the polyol pathway activity[35]; sorbinil is a drug that belongs to this group, although it has not shown clinical efficacy. However, tolrestat and statil have shown promising outcomes[36]. These drugs have the following effects: a) regression of the anatomical damage of the neural node; b) regeneration of nerve fibers; c) decrease of pain[37].

There is a wide variety of drugs to treat PDPN, among which we can mention: tricyclic antidepressants; serotonin reuptake inhibitors; anticonvulsants; mexiletine; tramadol; levodopa; gamma-linolenic acid; alpha-lipoic acid; dextromethorphan and capsaicin, among others[38]. After comparing several therapeutic schemes, there is significant difference between gabapentin and amitriptyline[39] or among carbamazepine, nortriptyline and fluphenazine[40]. Currently, the results about the efficacy of phenytoin are inconsistent[41]. Topiramate decreases the pain, but 28% of patients withdrew from a study due to its adverse effects[42]. Lamotrigine[43] and tramadol[44] have shown to be more effective than placebo. High doses of dextromethorphan reduce the pain, yet its use is limited due to its adverse effects[45]. In an open study, oxcarbazepine showed to be efficacious for the treatment of symmetric diabetic neuropathy; it was well tolerated at dosages ranging from 900 to 1,200 mg/day[46].

Table III. Stages of peripheral diabetic neuropathy.

Neuropathy	Clinical data
No neuropathy	No evidence of signs or symptoms
Chronic painful neuropathy	Stabbing, burning, or aching (needle points) that is worst at night, reflexes are decreased or absent
Acute painful neuropathy	Severe symptoms (hyperesthesia) after application of insulin, minor signs or no signs
Painful neuropathy with complete or partial sensory loss	Numbness of feet or no symptoms, reduced or absent sensibility, reduced sensibility to temperature, absent reflexes
Late complications	Feet lesions, deformities, non-traumatic amputation

Table IV. Characteristics of acute and chronic sensory- motor neuropathies.

Findings	Acute	Chronic
Onset	Quick	Gradual
Symptoms	Intense burning pain, weight loss	Burning pain, paresthesia, numbness, weight loss
Severity of symptoms	Severe	Mild to moderate
Signs	Light sensory abnormalities and unusual motor abnormalities	"Stocking-glove" pattern, absence of Achilles tendon reflex
Other complications	Unusual	Increase of prevalence due to diabetes
Electrophysiology	Normal or slightly abnormal	Unusual abnormalities of sensory and motor nerves
Natural history	Full recovery in twelve months	Symptoms and signs can persist intermittently for years and there is risk for feet ulceration

Gabapentin is an anticonvulsant that is related structurally to the neurotransmitter gamma-aminobutyric acid. This drug relieves the pain due to PDPN and decreases sleep disorders. To reach this effect, the daily dose ranges from 900 to 3,600 mg[47]; furthermore, this is the only licensed drug for the treatment of neuropathic pain in the United Kingdom[48].

Pregabaline is capable to reducing PDPN pain. This drug is an alpha2-delta ligand, which has analgesic, anticonvulsant and ansiolitic properties. It reduces calcium uptake in nerve terminals and releases neurotransmitters (glutamate, noradrenalin and P substance). Pregabaline has shown to reduce the pain when compared with placebo at a dose of 300 mg/day, which is escalated in 1 to 2 weeks[49,50]; additionally, improves sleep disorders and the mood[51].

Intravenous lidocaine at a dose of 5 mg/kg reached a significant reduction of pain when compared with saline solution[52]. Other drugs, such as mexiletine, have been used but its results are less than encouraging[53]. Use of lidocaine patches 5% showed that after three weeks of treatment, the pain is reduced in 30% in two thirds of patients and improves the quality of life[54].

Recently, a Mexican consensus group interested in studying pain developed the "guidelines to manage neuropathic pain". This group made a systematic review of the literature addressing the treatment of different types of neuropathic pain, including PDPN. In this report it was highlighted that: a) glycemic control; b) anticonvulsants (carbamazepine and gabapentin); c) antidepressants (amitriptyline, imipramine, chlorimipramine, desipramine) are efficacious therapeutic choices (intermediate and high efficacy) with a good level of evidence and few adverse effects[55].

CONCLUSIONS

Diabetes mellitus is a public health problem that in the medium and long term affects the quality of life of those afflicted for this condition. A significant number of patients will develop some type of neuropathy, and in some cases, this chronic complication will be painful.

PDPN is difficult to diagnose, given that numerous diseases can have similar pain symptoms. Moreover, appearance of atypical neuropathic pain can be the initial manifestation of a non-diagnosed diabetes mellitus.

The protocol to diagnose PDPN should be supported by a thorough clinical history and a detailed physical exam, and the diagnosis must be established after ruling out other possible causes of acute peripheral neuropathy. Current classifications for peripheral neuropathies are helpful to identify them and to set up the guides for its study and treatment, including preclinical and clinical research.

It is essential to be aware about the importance of hyperglycemia in PDPN. Metabolically uncompensated diabetes can cause nervous damage, thus maintaining good glycemic control is crucial. Furthermore, the treatment for pain relief should be based upon the knowledge of the mechanisms that cause PDPN. Preclinical and clinical research should be aimed at looking for drugs able to decrease the damage and to ease the symptoms of these patients.

Prevalence of diabetes mellitus in Mexico is skyrocketing. This suggests that the number of patients with neuropathy (sensory, motor or autonomic) will tend to increase. We must not forget that PDPN is a common disabling condition in clinical practice that also affects significantly the quality of life of patients.

It is important to strongly think about the preventive and educational actions that Mexican doctors have done to address PDPN. We have to duplicate our efforts to improve programs dealing with prevention, education of patients and continuing medical attention. We also must consider that providing integrated care for pain goes beyond the treatment of an isolated symptom. Only in this way, we will be able to provide to our patients high quality, informed and comprehensive medical care.

REFERENCES

1. Boulton AJM, Gries FA, Jervell J. Guidelines for the diagnosis and out-patient management of diabetic peripheral neuropathy. Diabet Med 1998;15:917-931.
2. Boulton AJM. Diabetic somatic neuropathies. Diabetes Care 2004:27:1458-1486.
3. Aguilar-Rebolledo F. Diabetic polyneuropathy. Second edition. Mexican Distributor and Editorial, Ed. México. 2004;1:47.
4. Schmader KE. Epidemiology and impact in quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002;18:350-354.
5. Yung MJ, Boulton AJM, Macleod AF. A multi-centre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetology 1993; 36:150-154.
6. The diabetes control and complications trial research group. Influence of intensive diabetes treatment on body weight and composition of adult with type 1 diabetes: The diabetes control and complications trial. Diabetes Care 2001;24:1711-1721.
7. Vinik AI, Park TS, Stansberry KB. Diabetic neuropathies. Diabetology 2000;43:957-973.

8. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. Diabet Metab 1977;3:97-107.
9. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin dependent diabetes mellitus. N Engl J Med 1995;333:89-94.
10. Spruce J. Potter and D. V. Coppini. The pathogenesis and management of painful diabetic neuropathy: a review. Diabet Med 2003;20:88-98.
11. Shaw JE, Zimmet PZ. The epidemiology of diabetic neuropathy. Diabetes Rev 1999;7:245-252.
12. Duby JJ, Cambell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: An intensive review. AM J Health Syst Pharm 2004;61:160-76.
13. Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ 3rd., O'Brien PC. Risk factors for severity of diabetic polyneuropathy; intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study Cohort. Diabetes Care 1999;22:1479-1486.
14. Britland ST, Young RJ, Sharma AK. Relationship of endoneurial capillary abnormalities to type and severity of diabetic neuropathy. Diabetes 1990;39:909-913.
15. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813-820.
16. Oates PJ. Polyol pathway and diabetic peripheral neuropathy. Int Rev Neurobiol 2002;50:325-392.
17. Sundkvist G, Dahlin LB, Nilsson H, Eriksson KF, Lindgarde F, Rosen I, Lattimer SA, Sima AA, Sullivan K, Greene DA. Sorbitol and myoinositol levels and morphology of sural nerve in relation to peripheral nerve function and clinical neuropathy in men with diabetic, impaired, and normal glucose tolerance. Diabet Med 2000;17:259-268.
18. King RH. The role of glycation in the pathogenesis of diabetic polyneuropathy. Mol Pathol 2001;54:400-408.
19. Vlassara H, Palace MR. Diabetes and advanced glycation end products. J Intern Med 2002;251:87-101.
20. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications; a new perspective on an old paradigm. Diabetes 1999;48:1-9.
21. Wellmer A, Misra VP, Sharief MK, Kopelman PG, Anand P. A double-blind placebo-controlled clinical trial of recombinant human brain-derived neurotrophic factor (rhBDNF) in diabetic polyneuropathy. J Peripher Nerv Syst 2001;6:204-210.
22. Sima AA. C-Peptide and diabetic neuropathy. Expert Opin Investg Drugs 2003;12:1471-1488.
23. Cotter MA, Ekberg K, Wahren J, Cameron NE. Effects of proinsulin C-peptide in experimental diabetic neuropathy: vascular actions and modulation by nitric oxide synthase inhibition. Diabetes 2003;52:1812-1817.
24. Srinivasan S, Stevens MJ, Sheng H, Hall KE, Wiley JW. Serum from patients with type 2 diabetes with neuropathy induces complement-independent, calcium-dependent apoptosis in cultured neuronal cells. J Clin Invest 1998;102:1454-1462.
25. Ziegler D. Cardiovascular autonomic neuropathy: Clinical manifestations and measurement. Diabetes Rev 1999;7:342-357.
26. Dey J, Shephard DM. Evaluation and treatment of erectile dysfunction in men with diabetes mellitus. Mayo Clin Proc 2002;77:276-282.
27. Boulton AJM, Malik RA. Diabetic neuropathy. Med Clin N Am 1998;82:909-929.
28. Thomas PK. Classification, differential diagnosis and staging of diabetic peripheral neuropathy. Diabetes 1997;46:2s54-2s57.
29. Sima AA, Pierson CR. Diabetic neuropathy: a heterogeneous, dynamic, and progressive disorder. J Neurosci Res 2001;66:1226-1227.
30. Hughes RAG. Peripheral neuropathy. BMJ 2002;324:466-469.
31. Llewelyn JG. The diabetic neuropathies: Types, diagnosis and management. J Neurol Neurosurg Psychiatry 2003;74:ii15-ii19.
32. Brannagam TH. Peripheral Neuropathy Pain: Mechanisms and Treatment. J Clin Neuromusc Dis 2003;5:61-71.
33. Bierhaus A, Humpert PM, Rudofsky G, Wendt T, Morcos M, Hamann A, Nawroth PP. New treatments for diabetic neuropathy: pathogenetically oriented treatment. Curr Diab Rep 2003;3:452-458.
34. UK prospective diabetes study group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-853.
35. Clarck CM Jr, Lee DA. Prevention and treatment of diabetic neuropathy. Pharmacotherapy 1994;14:689-607.
36. Gill JS. The efficacy of aldose reductase inhibitor, ponalrestat on diabetic neuropathy. Diabet Metab 1990;16:246-302.
37. Van Gerven JM. The efficacy of aldose reductase inhibitors in the management of diabetic complications: Comparison with intensive insuline treatment and pancreatic transplantation. Drugs Aging 1995;6:9-28.
38. Simons Z, Feldman EL. Update on diabetic neuropathy. Curr Opin Neurol 2002;15:595-603.
39. Morello CM, Leckbraund SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931-1937.
40. Gomez-Perez FJ, Hoza R, Rios JM. Nortriptyline fluphenazine *vs* carbamezepinein in the symptomatic treatment of diabetic neuropathy. Arch Med Res 1996;27:525-529.
41. Collins SL, Moore A, McQuay HJ, Wiffen P. Anti-depressants and anticonvulsivants for diabetic neuropathy and postherpetic neuralgia: a quantitative systemic review. J Pain Symptom Manage 2000;20:449-458.
42. Raskin P, Donofrio PD, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, Vinik AI. CAPSS-141 Study Group. Topiramate *vs* placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology 2004;63:865-873.
43. Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology 2001;57:505-509.
44. Harati Y, Gooch C, Swenson M. Double-blind randomized trial tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998;50:1842-1846.
45. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan *versus* placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology 1997;48: 1212-1218.
46. Beydoun A, Kobetz SA, Carrazana EJ. Efficacy of oxcarbazepine in the treatment of painful diabetic neuropathy. Clin J Pain 2004;20:174-178.
47. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofaldo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831-1836.
48. Rosner H, Rubin L, Kestenbaum A. Gabapentine adjunctive therapy in neuropathic pain states. Clin J Pain 1996;12:56-58.
49. Rosenstok J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628-638.
50. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005;6:253-260.
51. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neur-

opathy: a double-blind, placebo-controlled trial. Pain 2004; 110:628-638.
52. Kastrup J, Petersen P, Dejard A, Angelo H, Hilstead J. Intravenous lidocaine infusion: a new treatment of chronic painful diabetic neuropathy. Pain 1987;28:69-75.
53. Jarvis B, Couked AJ. Mexiletine: A review of its therapeutic use in painful diabetic neuropathy. Drugs 1998;56:691-707.
54. Barbano RL, Herrmann DN, Hart-Gouleau S, Vaughan JP, Lodewick PA, Dworkin RH. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. Arch Neurol 2004;61:914-918.
55. Guvara-Lopez U, Covarrubias-Gomez A, García-Ramos G, Hernandez-Jimenez S. Parámetros de práctica para el manejo del dolor neuropático. Rev Invest Clin 2006;58:126-138.