Global Advanced Research Journal of Medicine and Medical Sciences (ISSN: 2315-5159) Vol. 7(10) pp. 214-220
December, 2018 Special Issue
Available online http://garj.org/garjmms
Copyright © 2018 Global Advanced Research Journals

Full Length Research Paper

Efficacy of α-lipoic acid in the treatment of diabetic polyneuropathy. A Randomized, Double–Blind Study

Millán-Guerrero RO MD. DSc[1]*, García-Ramírez AL MD[2], Trujillo-Hernández B MD. DSc[1], Caballero-Hoyos R DSc1, González–Pérez O MD.DSC[3], Isais-Millán S MD[1] and Trujillo-Magallón Erick MD[1]

[1]Unidad de Investigación en Epidemiología Clínica, Instituto Mexicano del Seguro Social, Colima, Col.
[2]Medicina Física y de Rehabilitación, HGZ No.1 Instituto Mexicano del Seguro Social, Colima.
[3]Facultad de Psicología, Universidad de Colima, Colima, México.
Registration number: 2009-601-13

Accepted 19 June, 2018

To evaluate the efficacy of α-lipoic acid in the treatment of diabetic polyneuropathy focusing on sensory symptoms, nerve conduction velocity and H reflex in type 2 diabetes mellitus. 100 diabetic patients presenting with symptomatic polyneuropathy were enrolled in a randomized, double-blind, placebo-controlled study. They received a daily dosage of 1200mg of α-lipoic acid (n = 50) or placebo (n = 50) for 4 weeks. Main results were evaluated with the Total Symptom Score (TSS). Secondary results included nerve conduction velocity, individual symptom score, and H-reflex. Mean age was 50.9±8.0 years, mean disease duration was 10±6.3 years and mean fasting glucose was 169±110 mg/mL. The statistical analysis of data collected showed no significant differences between the baseline values obtained for the alpha lipoic acid and the placebo groups (p>0.05). Analysis showed that by the end of the 4th week, there was not a significant difference between both groups in the Michigan variable, Motor Nerve Conduction Velocity and H-reflex variable. In our study after 4 weeks of treatment, the effects of α-lipoic acid oral not shown significant clinical improvement; results from both the α-lipoic acid group and the placebo group.

Keywords: Diabetic neuropathy, type 2 diabetes mellitus, α-lipoic acid, double–Blind Study

INTRODUCTION

According to the International Diabetes Federation Diabetes Atlas, 415 million people worldwide had diabetes in 2015, and this number is expected to grow by 5% annually (Gonçalves et al., 2017). The lifetime incidence of neuropathy is approximately 45% for patients with type 2 diabetes mellitus (T2DM) (Zilliox and Russell, 2011).

Many studies have indicated that diabetic neuropathy results from microvascular disease, with a focus on axonal degeneration as a consequence of ischemia and/or hypoxia (Gonçalves et al., 2017; Mizisin, 2014; Ydens et al., 2013). Diabetic neuropathy classically presents as a sensory neuropathy that result from damage to both large and small fibers, which can cause negative symptoms, such as loss of sensation to touch,

*Corresponding Author E-mail: millanrebeca@hotmail.com; Phone: 01312-31-4-17-57; Fax: 01312-31-4-17-57

vibration, pinprick, temperature (Jensen and Baron, 2003; Jensen and Finnerup, 2014), and positive symptoms, such as paradoxical pain and hypersensitivity (Truini, 2013). Approximately half of all patients with diabetes mellitus have a Distal Symmetric Polyneuropathy (DSP), this is the most common presentation of diabetic neuropathy, with a characteristic stocking–glove pattern (Peltier et al., 2014; Callaghan et al., 2012; Vinik et al., 2013).

Combination testing of vibration plus 10-g monofilament testing provides the best balance of an efficient (less than 2-minute), sensitive (90%), and specific (85%-89%) screen for diabetic peripheral neuropathy and correlates with the development of diabetic foot ulcers (Kamei et al., 2005; Al-Geffari, 2012). Neuropathy diagnosis is made with a greater degree of accuracy when neurophysiological studies (Boulton et al., 2005; Dyck, 1988; Freund et al., 1969; Strakowski et al., 2001).

Currently, no treatments exist that convincingly reverse diabetic neuropathies. However, the severity of diabetic neuropathy may be reduced (American Diabetes Association, 2013) so management of diabetic neuropathy should include: (1) treatment of risk factors; (2) a diet and exercise life style intervention; and (3) possible administration of α-lipoic acid (Russell and Zilliox, 2014). Because oxidative stress has been implicated in the pathogenesis of Distal Polyneuropathy (DPN), alpha-lipoic acid, an antioxidant, may improve nerve blood flow and distal nerve conduction through anti-inflammatory and anti-thrombotic mechanisms (Busui et al., 2006; Ziegler et al., 2006; Ametov et al., 2003; Ziegler et al., 1999; Ziegler, 2004).

The objective of the following study was to evaluate the efficacy of α-lipoic acid in the treatment of diabetic polyneuropathy focusing on sensory symptoms, nerve conduction velocity and H reflex in polyneuropathy type 2 diabetes mellitus in patients from the "*Hospital General del IMSS*", in Colima, Mexico.

DESIGN/ METHODS

This was a 4-weeks randomized, controlled, double-blind study (Hulley et al., 1997) carried out in a 100 patients diagnosed with diabetic polyneuropathy at the *Hospital General de Zona No 1 IMSS* Colima during the time frame of August 2010 to May 2011. The patients were male and female adults between the ages of 40 and 75 years, all having a history of T2DM for several years (American Diabetes Association, 2011). Alcoholic patients, patients with kidney or liver failure, with carpal tunnel syndrome or clinical radiculopathy were excluded.

The procedure was explained to patients and they were invited to take part in the study. All participants signed a letter of consent in accordance with the Helsinki statement.

Patients were recruited by the non-probabilistic consecutive case method. Medical history for the register and laboratory work-up that included fasting glucose, total cholesterol, and triglycerides were carried out. They were then divided into two groups for treatment in randomized blocks of three, double-blind fashion: the α-lipoic acid group and the control group. This randomization was carried out by a research collaborator who throughout the duration of the study had no contact with the patients and prepared vials containing either 1200 mg ofα-lipoic acid or placebo. The vials were numbered and were identical in appearance, which allowed the blinding to be effective since neither the patients nor the physicians were able to identify the placebo or active drug. The regimen began with the oral administration of a daily dosage of 1200mg of α-lipoic acid versus a daily dosage of placebo for a period of 4 weeks. During treatment, patients were allowed to take their medication for diabetes and others diseases. The relationship between an adverse event and the study treatment was assessed by a member of the research team and labeled as *none, possible, probable*, or *definite*. Patients who abandoned the study were still taken into account in the final analysis.

Variables and measuring instruments

Michigan Neuropathy Screening Instrument (MNSI) was then used to identify the presence of neuropathy (Bax et al., 1996). Applied by one of the researchers, it is a 5-point clinical neurological test with a total possible score of 10 for the left and right sides together (0/10). Foot appearance was examined for the presence or absence of ulceration, tendon reflexes were observed along with vibration testing with a tuning fork. Protective sensation was evaluated with the Semmes-Weinstein 10-g monofilament exam, which is a simple, precise, and noninvasive test for diagnosing diabetic neuropathy with 83% specificity and 79% sensitivity (Kamei et al., 2005; Al-Geffari, 2012). Among the signs that suggest autonomic neuropathy disorder, only pupillary reflex was considered (Burns and Mauermann, 2011).

Finally, another researcher who was blinded to the previous studies carried out an electrodiagnostic study recommended by the American Diabetes Association (American Diabetes Association and American Academy of Neurology, 1988) with a Nicolet Viking II electromyograph (Nicolet Biomedical; Madison, WI). Electrodiagnostic studies were performed on two occasions; at the beginning and at the end of treatment.

Nerve conduction-velocity measurements in the ulnar nerve

With the patient in the supine position and the elbow at a flexion angle of 90º, the stimulation was performed at the wrist and the elbow (4cm proximal to the epicondyle). A

ground electrode was located on the dorsal side of the right hand; an active electrode was located at the level of the abductor muscle in the fifth finger of the hand, and a reference electrode was located 4cm proximal to the same fifth finger. The stimulus intensity was in the range of 150 and 300 V, with 0.1 ms pulse duration. The parameters measured for the evoked responses were: peak amplitude, onset latency and nerve conduction velocity.

H-reflex in the posteriortibial nerve.

With the patient in the prone position and with a knee flexion of 120º, a stimulus was applied in the popliteal fossa. The cathode electrode was located proximal to the anode (for orthodromic stimulation) and stimulus intensity was in the range of 40-100 V, with 1 ms pulse duration. Recording electrodes were located as follows: the active electrode at the ventral side of the right pelvic twin muscle, and the reference electrode 4 cm away from the active one. Examination area temperature was kept at 30°C (Freund et al., 1969; Zhou et al., 1998; Strakowski et al., 2001; Lachman et al., 1980). The parameters measured for the evoked responses were: peak amplitude and onset latency. An alteration was present when latency of the response was more than two standard deviations from the normal curve, or when the response was absent.

Statistical Analysis: Main results were evaluated with a Total Symptom Score (TSS). Secondary results included nerve conduction velocity, individual symptom score, and H-reflex. Descriptive data analysis was carried out using measures of frequency, percentage, means, and standard deviation. Neuropathy percentage differences among variables were calculated with a Fisher exact test and mean differences with a Mann-Whitney U test for variables with non-normal distribution.

The above parameters were recorded at zero point, and after 4 weeks of treatment separately. Average descriptive statistics and standard deviations were applied to data obtained. A Wilcoxon rank-sum test was used to assess the statistical significance of baseline and final value differences within treatment groups. In addition, a Mann-Whitney U test was performedto evaluate the statistical significance of baseline and final value differences between treatment groups. In both cases, $P< 0.05$ was considered significant (Hulley et al., 1997). Data statistical analysis was carried out using the SPSS version 20 statistical package.The Ethical and Scientific Committee of our hospital approved this study.

RESULTS

A total of 100 patients with T2DM presenting with symptomatic polyneuropathy were enrolled and randomized into the two groups: alpha- α-lipoic acid group n=51, and placebo group n=49 (48 patients in the α-lipoic acid group and 47 in the placebo group completed the study) (Figure 1). There were 30 female-21 male patients in the alpha-lipoic acid group and 30 female-19 male patients in the placebo group. Mean age was 50.9±8.0 years, mean disease duration was 10±6.3 years and mean fasting glucose was 169±110 mg/mL.

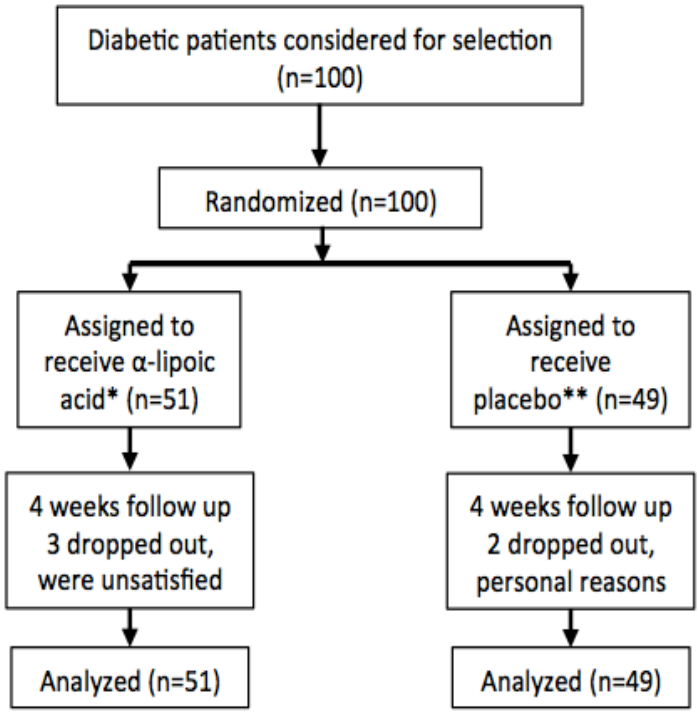

Figure 1. Flow of participants through the trial Consort diagram; *α-lipoic acid group ** placebo group

Clinical neurological examination (Michigan Neuropathy Screening Instrument) (MNSI) showed that 100 patients (100%) had peripheral neuropathy with a mean score of 4.3/10±1.78. There was a reduction or absence of pupillary function in only 16 patients in the α-lipoic acid y 15 in the placebo group. The two groups were similar at baseline based on demographic and clinical characteristics (Table 1) for all variables studied. The statistical analysis of data collected showed no significant differences between the baseline values obtained for the alpha lipoic acid and the placebo groups.

The electrophysiological study of Motor Nerve Conduction Velocity (MNCV) of the ulnar nerve was abnormal in all patients (100%) of baseline, with a result of 48.2 ± 9.1 m/sec in the α-lipoic acid group, and 44.9±8.6 in the placebo group. The H-reflex in the posterior tibial nerve was abnormal in all patients (100%), with mean latency of 7.6ms ±13.6 in the α-lipoic acid group, and 8.6ms± 13.6 in the placebo group (Table 2).

We compared the response of each group to its baseline, and the differential response of one group to the other. For the Michigan variable no difference was found between the baseline values of the α-lipoic acid

Table 1. Comparison of selected baseline characteristics by treatment groups (n = 100)

Variables	Groups		P*
	α-lipoicacid (n = 51) n (%)	Placebo (n = 49) n (%)	
Socio demographics			
Sex			
Female	30 (58,8)	30 (61.2)	0.841
Male	21 (41.2)	19 (38.8)	
Age (years), mean±S.D.	50.5±9.0	51.3±7.0	0.819
Lyfe style behavior			
Smoking	22 (43.1)	11 (22.4)	0.034
Anthropometric measures			
Height (m), mean±S.D.	1.60±0.1	1.62±0.1	0.305
Weight (kg), mean±S.D.	74.2±11.8	82.7±20.1	0.021
Abdominal perimeter (cm), mean±S.D.	94.7±12.1	100.6±16.5	0.122
Diabetes-related			
Years with Diabetes Mellitus, mean±S.D.	9.3±7	11.0±6.2	0.067
High Blood Pressure	23 (45.1)	33 (67.3)	0.020
Absent Pupillary function	16 (31.4)	15 (30.3)	0.553
Monofilament test abnormal	49 (96.1)	46 (93.9)	0.675
Vibration reduced (128 Hz)	21 (41.2)	22 (44.9)	0.840
Absent reflexes	51 (100.0)	47 (95.9)	0.500
Absent H-reflex	51 (100.0)	49 (100.0)	n.v.
Glucose level (mg/mL), mean±S.D.	151.3±65.9	167.3±52.8	0.661
Cholesterol (mg/dl), mean+S.D.	188.6±36.8	207.9±58.9	0.508
HDL-cholesterol (mg/dl), mean+S.D.	42.4±9.1	50.7±17.3	0.140
LDL cholesterol (mg/dl), mean+S.D.	96.0 ±25.9	107.0±28.5	0.671
Triglyceride level	242.7±81.0	193.9 ±55.6	0.024

* Fisher exact test for categorical variables; Mann-Whitney U for continuous variables
n.v. = no variation

Table 2. Comparison of treatment mean values and statistical significances of changes within groups and between groups (n = 100)

Variables	α-lipoicacid (n = 51)				Placebo (n = 49)				Intergroup (n = 100)	
	Baseline	Final	Wilcoxon*		Baseline	Final	Wilcoxon*		Baseline/final differences	p**
	Mean±S.D.	Mean±S.D.	z	P	Mean±S.D.	Mean±S.D.	z	P	Mean	
Michigan Neuropathy Screening Instrument	4.6±1.9	4.3±2.0	-2.4	0.015	4.5±2.1	4.2±2.0	-1.6	0.103	0.1	0.986
Motor Nerve Conduction Velocity (m/s)	48.2±9.1	52.7±9.7	-4.7	0.000	44.9±8.6	48.5±7.1	-2.6	0.009	1.0	0.159
Latency (ms)	2.5±1.1	2.6±1.0	-0.5	0.646	2.4±1.0	2.3±1.2	-1.7	0.082	0.1	0.066
Amplitude (mV)	1.1±0.9	1.2±1.2	-0.2	0.832	1.2±0.9	1.1±0.9	-1.2	0.239	0.1	0.575
H-reflex onset latency (ms)	7.6±13.6	8.7±13.6	-0.6	0.551	8.6±13.6	10.1±14.2	-0.7	0.499	0.4	0.581

* Two times Wilcoxon signed rank sum test.
** Mann-Whitney U test

group and the placebo group. Analysis of the temporal course of events showed that by the end of the 4th week, there was not a significant difference between both groups (when compared to baseline values) in the Michigan variable, as a result of the administration of α-lipoic acid or placebo(p= 0.986) (Table 2).

Both the α-lipoic acid group and the placebo group showed differences in the Motor Nerve Conduction Velocity variable when comparing basal values to values after the 4th week of treatment (p = 0.000 and p = 0.009, respectively) but analysis of the difference between the two groups had no not statistical significance (p=0.159) (Table 2).

For the H-reflexvariable no difference was found between the baseline values of either group. After the administration of α-lipoic acid or placebo for 4 weeks there was not a significant difference between both groups when compared to baseline values (p= 0.581) (Table 2).

After 4 weeks of treatment, the effects of α-lipoic acid and placebo remained identical to the values found with respect to basal values. Side effects (nausea, vomiting, and dizziness) were found to be dose-dependent, with the lowest effective dose being 1200 mg/d.

DISCUSSION

Diabetes mellitus (DM) is a common condition and diabetics are prone to develop a spectrum of neuropathic complications ranging from symmetric and diffuse to asymmetric and focal neuropathies that may be associated with significant morbidity (Izenberg et al., 2015). Diabetic peripheral neuropathy (DPN) affects up to 40-66% of patients with T2DM in their lifetimes (Watson and Dyck, 2015).

The pathophysiology of DSP is complex and several important mechanistic pathways have been identified, including oxidative and nitrosative stress, accumulation of advanced glycation end products, direct toxic effects of free fatty acids and proinflammatory adipokines. These pathways produce microischemia of nutrient nerve arterioles, dysregulate axonal mitochondrial function, inhibit axonal transport of proteins necessary for distal axonal function, and elicit an autoimmune response (Gonçalves et al., 2017; Vincent et al., 2009; Singleton and Smith, 2012).

That strict glucose control alone is not enough to ameliorate the onset and progression of T2DM diabetic polyneuropathy (Callaghan et al., 2012). The first-line therapies for DSP include tricyclic anti-depressants, serotonin-norepinephrine reuptake inhibitors, anti- convulsants and dietary supplements including alpha- lipoic acid (Mijnhout et al., 2012). Despite a number of promising therapies in cell culture and animal models of diabetic neuropathy, no treatment has proven effective at preventing or slowing the progression of DSP. Antioxidant therapy with alpha-lipoic acid has reduced pain in some trials (Freund et al., 1969). Alpha lipoic acid (ALA) is an orally bio-available antioxidant (Singleton and Smith, 2012) that acts by multiple physiologically and pharmacologically mechanisms to improved insulin sensitivity, oxidative stress, and neuropathy in diabetic patients. It appears that the major benefit of ALA supplementation is in patients with diabetic neuropathy (Singh and Jialal, 2008). Although the results have not been definitive, treatment with alpha-lipoic acid was shown to improve neuropathic symptoms and deficits in patients with diabetic sensory neuropathy when treated for 12 weeks to 4 years (Ziegler et al., 2011; Gu et al., 2010). Most clinical measures of neuropathy severity did not significantly improve; previous studies had reported modest improvement in neuropathy measures following IV ALA injection (Ziegler et

al., 2004). Several additional studies are underway; it is possible than an early diagnosis facilitates effectiveness of ALA.

In our study after 4 weeks of treatment, the effects of α-lipoic acid oral not shown significant clinical improvement; results from both theα-lipoic acid group and the placebo group remained identical to the values found with respect to basal values.

Our study only included patients with T2DM; no patients with type 1 DM were studied. Following the diagnostic criteria of the Toronto Expert Panel on Diabetic Neuropathy all our patients had confirmed clinical DN (Dyck et al., 2011) with the following characteristics: chronic, generalized, distal, symmetrical and sensory predominant (Tesfaye et al., 2010; Smith and Singleton, 2012). Distal symmetrical polyneuropathy (DSP) may affect at least 10%-15% of patients with newly diagnosed type 2 diabetes, with rates increasing to 50% after 10 years of disease (Martin et al., 2014).

While traditional dogma held that distal symmetric polyneuropathy developed only after many years of sustained hyperglycemia, growing evidence indicates that factors other than hyperglycemia play a role in neuropathy risk and pathogenesis. Hypertension, smoking, obesity, and dyslipidemia are contributory to T2DM diabetic polyneuropathy to an equal if not greater degree than hyperglycemia (Callaghan et al., 2012; Smith and Singleton, 2012; Callaghan et al., 2011).

In this study all our patients had a disease progression of less than 12 years but a history of poorly controlled disease as well as 1 or more of these risk factors shown to be important in inducing nerve fiber damage.

Because DSP is a leading risk factor for foot ulceration and eventual limb amputation, education regarding proper foot care is especially important in this population. The American Diabetes Association (ADA) recommends a comprehensive foot exam ever year in every patient with diabetes (American Diabetes Association, 2013) that includes a careful palpation of pulses, examination of skin integrity, exploration for foot deformities, evaluation of nail beds, and assessment of foot sensation.

The therapy targeting chronic sustained hyperglycemia for DPN prevention without considering glycemic variability may be inadequate. However, this hypothesis remains provisional, and future research is warranted to enrich our understanding regarding the role of glycemic variability in the pathogenesis of DPN.

Our study has important limitations. First, although no evidence exists to support the use of a complete blood cell count, a panel 7 test, a liver function test, or a thyrotropin test, these tests have seemingly become the standard of care for patients with neuropathy. Most physicians indicate that these testsare not needed as part of the routine initial evaluation of patients with DSP, but there is still substantial use for them in the full workup. Future investigations are needed to clarify the role of these tests (Callaghan et al., 2012). Second, we could not absolutely exclude the possibility of unrecognized and residual confounding variables. Third, the combination of neuropathic symptoms, signs, and electrophysiologic findings provides the most accurate diagnosis of DPN. However, detailed medical history and clinical information such as serum or electrophysiologic studies were not available in the database. Furthermore, DPN is a diagnosis of exclusion. The proper exclusion of other causes of peripheral neuropathy could not be assured (e.g., alcoholic, MGUS, vitamin B12 deficiency, hypothyroidism, and uremia), which may lead to false-positive cases of DPN. However, we excluded patients with other concomitant causes of polyneuropathy at baseline, which may increase accuracy of DPN diagnosis. Moreover, patients who had other causes of neuropathy were excluded from sensitivity analysis to mitigate this possibility. Fourth, information on the subtype of DPN was not available. The effect of glycemic variability on DPN subtypes must be examined in future studies.

Diabetes is the most common cause of peripheral neuropathy in the world. More than half of patients with diabetes have neuropathy, and half of patients with neuropathy have diabetes. We advocate that more research is required to understand new mechanisms of nerve injury. Results from future studies and research tools will hopefully lead to novel therapies for distal symmetric diabetic polyneuropathy.

REFERENCES

Al-Geffari M (2012). Comparison of different screening tests for diagnosis of diabetic peripheral neuropathy in primary health care setting. Int. J. Health Sci. (Qassim). 6:127-134.

American Diabetes Association (2011). Standards of medical care in diabetes--2011. Diabetes Care. 34(Suppl 1):S11-S61.

American Diabetes Association (2013). Standards of medical care in diabetes--2013. Diabetes Care. 36(Suppl 1):S11-S66.

American Diabetes Association, American Academy of Neurology (1988). Report and recommendations of the San Antonio Conference on Diabetic Neuropathy. Diabetes Care. 11:592–597.

Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ, et al (2003). The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. Diabetes Care. 26:770–776

Bax G, Fagherazzi C, Piarulli F, Nicolucci A, Fedele D (1996). Reproducibility of Michigan Neuropathy Screening Instrument (MNSI). A comparison with tests using the vibratory and thermal perception thresholds. Diabetes Care. 19:904-905.

Boulton AJ, Vinik AI, Arezzo JC,Bril V, Feldman EL, Freeman R, et al (2005). Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 28:956-962.

Burns TM, Mauermann ML (2011). The Evaluation of Polyneuropathies. Neurol. 76 (Suppl 2):S6–S13

Busui RP, Sima A, Stevens M (2006). Diabetic neuropathy and oxidative stress. Diabet. Metab. Res. Rev. 22:257–273.

Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL (2012). Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 11:521–534.

Callaghan BC, Feldman E, Liu J, Kerber K, Pop-Busui R, Moffet H,et al (2011). Triglycerides and amputation risk in patients with diabetes: ten-year follow-up in the DISTANCE study. Diabetes Care. 34:635-640.

Callaghan BC, Hur J, Feldman EL (2012). Diabetic neuropathy: one disease or two? Curr. Opin. Neurol. 25:536–541.
Callaghan BC, Kerber K, Smith AL, Fendrick AM, Feldman EL (2012). The Evaluation of Distal Symmetric Polyneuropathy A Physician Survey of Clinical Practice. Arch. Neurol. 69:339-345.
Dyck PJ (1988). Detection, characterization, and staging of polyneuropathy: assessed in diabetics. Muscle Nerve. 11:21–32.
Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, et al (2011). Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab. Res. Rev. 27:620–628
Freund FG, Martin WE, Hornbein TF (1969). The H-reflex as a measure of anesthetic potency in man. Anesthesiol. 30:642–647.
Gonçalves NP, Vægter CB, Andersen H, Østergaard L, Calcutt NA, Jensen TS (2017). Schwann cell interactions with axons and microvessels in diabetic neuropathy. Nat. Rev. Neurol. 13:135-147.
Gu XM, Zhang SS, Wu JC, Tang ZY, Lu ZQ,Li H, et al (2010). Efficacy and safety of high-dose α-lipoic acid in the treatment of diabetic polyneuropathy. Zhonghua Yi XueZaZhi. 90:2473-2476.
Hulley SB, Gove S, Cummings SR (1997). Elección de los individuos que participarán en el estudio: especificación y muestreo. En: Hulley SB, Cummings SR.eds. Diseño de la Investigación Clínica. España: Harcourt Brace; pp. 21-55.
Izenberg A, Perkins BA, Bril V (2015). Diabetic Neuropathies. Semin. Neurol. 35:424-430.
Jensen TS, Baron R (2003). Translation of symptoms and signs into mechanisms in neuropathic pain. Pain. 102:1–8.
Jensen TS, Finnerup NB (2014). Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol. 13:924–935.
Kamei N, Yamane K, Nakanishi S, Yamashita Y, Tamura T, Ohshita K, et al (2005). Effectiveness of Semmes-Weinstein monofilament examination for diabetic peripheral neuropathy screening. J. Diabetes Complications. 19:47-53.
Lachman T, Shahani BT, Young RR (1980). Late responses as aides to diagnosis of peripheral neuropathies. J. Neurol. Neurosurg. Psychiatry. 43:156-162.
Martin CL, Albers JW, Pop-Busui R, DCCT/EDIC Research Group (2014). Neuropathy and related findings in the diabetes control and complications trial/Epidemiology of diabetes interventions and complications study. Diabetes Care. 37:31-38.
Mijnhout GS,Boudewijn J, KollenBJ, Alkhalaf A, Kleefstra N, Bilo HJ (2012). Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. IntJEndocrinol. 2012:456279.
Mizisin AP (2014). Mechanisms of diabetic neurophaty: Schwann cells. Handb Clin. Neurol. 126:401–428.
Peltier A, Goutman SA, Callaghan BC (2014). Painful diabetic neuropathy. BMJ. 348:g1799.
Russell JW, Zilliox LA (2014). Diabetic Neuropathies. Continuum (MinneapMinn). 20:1226–1240.
Singh U, Jialal I (2008). Alpha-lipoic acid supplementation and diabetes.Nutr Rev. 66: 646–657.
Singleton JR, Smith AG (2012). The Diabetic Neuropathies: Practical and Rational Therapy. Semin. Neurol. 32:196–203.
Smith AG, Singleton JR (2012). Diabetic Neuropathy. Continuum (MinneapMinn). 18:60–84.
Strakowski JA, Redd DD, Johnson EW, Pease WS (2001). H reflex and F wave latencies to soleus normal values and side-to-side differences. Am. J. Phys. Med. Rehabil. 80:491–493.
Strakowski JA, Redd DD, Johnson EW, Pease WS (2001). H reflex and F wave latencies to soleus normal values and side-to-side differences. Am. J. Phys. Med. Rehabil. 80:491-493.
Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 33:2285-2293.
Truini A (2013). Peripheral nociceptor sensitization mediates allodynia in patients with distal symmetric polyneuropathy. J. Neurol. 260:761–766.
Vincent AM, Hayes JM, McLean LL, Vivekanandan-Giri A, Pennathur S, Feldman EL (2009). Dyslipidemia-induced neuropathy in mice: the role of oxLDL/LOX-1. Diabetes. 58:2376–2385.
Vinik AI, NevoretM, CaselliniC, Parson H (2013). Neurovascular function and sudorimetry in health and disease. Curr. Diab. Rep. 13:517–532.
Watson JC, Dyck PJB (2015). Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. Mayo Clin. Proc. 90:940-951.
Ydens E, Lornet G, Smits V, Goethals S, Timmerman V, Janssens S (2013). The neuroinflammatory role of Schwann cells in disease. Neurobiol. Dis. 55:95–103
Zhou HH, Jin TT, Qin B, Turndorf H (1998). Suppression of spinal cord motoneuron excitability correlates with surgical immobility during isoflurane anesthesia. Anesthesiol. 88:955–961.
Ziegler D (2004). Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review. Treat Endocrinol. 3:173-189.
Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, et al (2006). Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care. 29:2365-2370.
Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, et al (2011). Efficacy and safety of antioxidant treatment with *α*-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes Care. 34:2054-2060.
Ziegler D, Nowak H, Kempler P, Vargha P, Low PA (2004). Treatment of symptomatic diabetic polyneuropathy with the antioxidant alphalipoic acid: a meta-analysis. Diabet. Med. 21:114–121.
ZieglerD, ReljanovicM, Mehnert H, Gries FA (1999). Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. Exp. Clin. Endocrinol. Diabetes. 107:421–430.
Zilliox L, Russell JW (2011). Treatment of diabetic sensory polyneuropathy. Curr. Treat. Options Neurol. 13:143-159.