UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL STUDIES SCHOOL

DOCTORAL THESIS

ABSTRACT

REHABILITATION OF PATIENT WITH DIABETIC PERIPHERAL NEUROPATHY

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CRAIOVA

2014

SUMMARY

STATE OF KNOWLEDGE

PERSONAL CONTRIBUTIONS

Key wards: diabetic peripheral neuropathy, rehabilitation treatment

STATE OF KNOWLEDGE

I. INTRODUCTION

Diabetes mellitus is one of the most frequent endocrine disease, is characterized by metabolic abnormalities and long-term complications that affect various organs and systems.

Diagnosis of diabetes is established by “fasting” hyperglycemia (over 11.1 mmol / l).

World Health Organization (WHO) defines diabetes (both type 1 and type 2) by increasing the amount of glucose in a single measurement, accompanied by symptoms or by increased values at two measurements, of any of the following parameters:

- plasma glucose "fasting" value ≥ 7.0 mmol / l (126 mg / dl)

After performing a glucose tolerance test, at two hours after administration an oral dose of 75 g glucose, plasma glucose concentration ≥ 11.1 mmol/l (200 mg/dl) and at least one other determination during 2 hours of test, i.e. two values ≥ 11.1 mmol / l (200 mg / dl) must be obtained, for diagnosis.

If the value after 2 hours is between 7.8 and 11.1 mmol / l (140-200 mg / dl) and another value during the test (2 hours), is equal to or greater than 11.1 mmol / l (200 mg / dl), it suggest a diagnosis of "impaired glucose tolerance". Interpretation would be that people in this category have increased risk for developing "fasting" hyperglycemia, or symptomatic diabetes. (2)

The diagnosis of diabetes can be put using a test and random blood glucose, greater than 11.1 mmol / l (200 mg / dl) associated with typical symptoms (3) or a glycosylated hemoglobin (HbA1c) greater 6.5%. (4)

II. DIABETIC PERIPHERAL NEUROPATHY

Diabetic neuropathy, one of the late complications of diabetes, is likely to affect every segment of central nervous system.

It is rarely a direct cause of death, but it is a major cause of early morbidity and disability, affecting 50-60% of diabetic patients.
Studies have shown that 30-40% of diabetics shows symptoms of diabetic peripheral neuropathy, the prevalence increasing with age, reaching approximately 44% among diabetic patients over 70 years.
Diabetic peripheral neuropathy is the most common form of diabetic neuropathy. Occurs both in patients with insulin-dependent diabetes and in those with non-insulin-dependent diabetes, affecting both sexes in approximately equal proportion. Distinct syndromes or types of neuropathy may be present in the same patient. (2,77,78)

Classification :

Classification of diabetic peripheral neuropathy

- **Peripheral neuropathy** (sensory, motor, sensory-motor)
- **Autonomic neuropathy**
- **Focal neuropathy**

Peripheral polyneuropathy is the most frequent form, representing 80-85% of diabetic peripheral neuropathy, the most frequent being sensorial neuropathy.

The pain may be deep-seated, often more intense at night. Occasionally stabbing type or lightning. Extreme pain syndromes are usually self-limiting, lasting from several months to several years.

III. METABOLIC, PATHOPHYSIOLOGICAL, FUNCTIONAL, MORPHOLOGICAL NERVE CHANGES

Main cause of neuropathy in diabetes mellitus is hyperglycemia but there are multiple mechanisms (107, 108): accumulation of sorbitol and fructose, disruption of the nerve membrane, vascular causes (affecting vasa nervorum), lack of growth factors and nerve differentiation, antibodies.

There are two major theories:

- Metabolic hypothesis (hyperglycemia)
- Vascular hypothesis (ischemia peripheral nerve stimulation)

These suggests that hyperglycemia, associated with metabolic alterations, produces the pathological changes in ischemic nerve fibers. (109)

Pathological changes in diabetic peripheral neuropathy

Biopsy of sural nerve, usually made in the case of diabetic peripheral neuropathy, presents several changes: degeneration of axon of nerve fibers, axonal atrophy, damage of Schwann cell, damage of small vessels of nerve.

The skin biopsy also presents changes that can be detected before changes occurring at

electromyography (13): decreased density of nerve fibers in the epidermis in in type 2 diabetes, the decrease in the number of unmyelinated nerve fibers C and A.

IV. TREATMENT OF DIABETIC PERIPHERAL POLYNEUROPATHY

Treatment of diabetic peripheral polyneuropathy primarily involves treatment of the diabetes.
Treatment of diabetic peripheral polyneuropathy in addition to treating the underlying disease, require compliance for hygiene measures.

Drug therapy in diabetic peripheral polyneuropathy is unsatisfactory in many cases. Severe pain requires treatment with narcotics or strong analgesics that can lead to addiction. Drug treatment consists of applying mild analgesics, anticonvulsants (phenytoin, tegretol, pregabalin, gabapentin, carbamazepine), antidepressants (fluoxetine, amitriptyline, imipramine), opioids (tramadol, oxycodone)

Some studies have demonstrated the beneficial effect of alpha-lipoic acid (ALA) in the treatment of diabetic neuropathy (123)
ALA are a pathogenic treatment of diabetic neuropathy and not only symptomatic. Side effects of treatment with ALA usual doses are reduced compared with other medications symptomatic diabetic neuropathy (126). Capsaicin has been used as a topical therapy of peripheral neuropathy, for many years and showed to improve symptoms of painful. (128)

V. THE EFFECT OF THE REHABILITATION TREATMENT IN PERIPHERAL DIABETIC NEUROPATHY, THE RECENT RESEARCH FINDINGS

There are also many studies on small groups of patients who had a favorable effect of different physiotherapy procedures in diabetic peripheral neuropathy. According to the results obtained by a group of researchers from the department of rehabilitation and physical medicine of the Medical University of Vienna, which sought to centralize published studies on the effect of physiotherapy in diabetic peripheral neuropathy was found that various forms of current or physiotherapy procedures beneficial effects on diabetic peripheral neuropathy, especially the pain. Transcutaneous electrical stimulation (TENS) and nerve stimulation modulated electromagnetic frequencies (FREMS) are shown as having a favorable effect in most studies in the literature. (129)

Various studies have shown the effect of various methods of physiotherapy in diabetic peripheral neuropathy :

- Transcutaneous electrical stimulation with high frequency (TENS) reduces neuropathic pain in diabetic peripheral polyneuropathy by inhibiting the excitability of sensory nervous system (130)
- Frequency Pulsed Magnetic therapy in studies, determined : increased nerve conduction velocity , increased amplitude of muscle action potentials , increasing the number of motor units . (140.141)
- Nerve stimulation frequency modulated electromagnetic (FREMS), reduces pain, improves perception of tactile sensitivity , reduces vibratory sensitivity threshold and increase nerve conduction velocity for motor nerves. (144)
- Pain is an important symptom in diabetic peripheral polyneuropathy. Electrotherapy , through all forms of current (DC galvanic currents of low frequency , medium frequency or high frequency) have a painkiller effect . (145,154-156)

Massage has a number of manual maneuvers (smoothing, kneading, pressure, battery, friction, vibration) performed on body surface, in a certain order, depending on the region and therapeutic purpose . (160)

Kinesitherapy has an important role in improving the condition of the patient, quality of life (178.179), glycemic control (180-182), the control of fat mass. (183)

PERSONAL CONTRIBUTION

I. PURPOSE AND MOTIVATION OF RESEARCH THEME

Diabetic peripheral neuropathy is a complication of diabetes regardless of whether it is insulin or non-insulin-dependent, 4% of diabetic patients developes this complication in five years after the diagnosis of the underlying disease, rising to 15% after the twenty years after the onset of diabetes (189).

The purpose of this paper is to contribute to the development of a comprehensive

program of recovery (physical-kinetic) leading to individual quality of life of the patient, family integration, social and vocational followed by lower social and economic costs.

II. SPECIFIC OBJECTIVES OF THE STUDY

The study aims to assess how recovery program implementation affects the symptoms, functional deficits and quality of life of patients with diabetic peripheral neuropathy .

Are analysed the correlations between the initial and final value of the parameters (VAS , NSS , NDS , the screening test of functional assistance) after the recovery treatment applied , assessing how the results are maintained at three months and six months after application of treatment, following the values of these parameters .
It seeks the effect of recovery treatment in diabetic peripheral polyneuropathy (in patients with diabetes regardless of the type of diabetes) and distinct recovery treatment benefit in patients with diabetic peripheral neuropathy due to diabetes mellitus insulin-dependent (type 1) or non -insulin-dependent (type 2) .
It also seeks the effect of recovery treatment depending on the type of diabetic peripheral polyneuropathy (sensory and sensory-motor) .
It follows, the patient's tolerance to the recovery program and the emergence of effects that would result in the need for treatment interruption, adherence at the recovery treatment .

III. MATERIAL AND METHOD

III. 1. Criteria for the selection of patients

- The patient's consent to participate in the study

- Diagnosis of patients of diabetic peripheral neuropathy, based on clinical examination, laboratory (lab) and EMG

-The patients follow diet and antidiabetic treatment

-The patients will be included in the study regardless of the anti-inflammatory medications or analgesics administered before inclusion in the study.

- Patients have normal metabolic and hemodynamic parameters

III. 2. The structure and the characteristics of the lot of patients.

The study has been made on a number of 83 patients diagnosed as diabetic peripheral polyneuropathy.

1. Sex of patients: men, 30 patients (36 %), women, 53 patients (64 %).

2. Age of the patients between 50-89 years.

3. Type of diabetes: type 1, 36 patients (43%) type 2, 47 patients (57%).

4. The duration of the disease (diabetes mellitus), between 1 - 20 years.

5. Neurological damage area of peripheral neuropathy upper limb (24.1 %), lower limb

(55, 42 %), both, upper and lower limbs (20, 48 %).

6. Type of peripheral polyneuropathy sensory neuropathy (71, 09 %), sensory-motor neuropathy (28, 91 %).

III. 3. Clinical examination

Patients have been diagnosed with peripheral polyneuropathy, based on history, clinical examination and laboratory investigations (blood sugar levels, electro diagnostic evaluation).

III. 4. Laboratory investigations are blood sugar levels and electro diagnostic evaluation.

Glycaemia, determines if the treatment of diabetes is proper.

III. 5. Monitored parameters

Development of patients was monitored by determining the following parameters:

- Visual Analog Scale for pain (VAS)

- Neuropathy Symptom Score (NSS)

- Neuropathy disability Score (NDS)

- Screening test of functional assistance (TS)

- Testing of muscle tonus

III. 6. Plan of study and monitoring of patients

Evaluating patients with the help of these parameters has been determinate before applying the rehabilitation treatment, at the end of treatment, at three months after treatment and at six months after applying the treatment.

Treatment consisted of:

A.Tratamentul hygienic-dietary
The patients followed hypoglycemic diet recommended in diabetes.
The patients were instructed to follow the rules of hygiene required to avoid diabetic complications.
B. Antidiabetic therapy with insulin or oral agents, depending on the type of diabetes, was followed in diabetes patients, under medical prescription.

C. Rehabilitation treatment has been applied for a period of 15 days and consisted in electrotherapy, massage and kinesitherapy, after that, every patient must to continue at home kinesitherapy for six months, and it will be assessed after three months, and, after six months.

Electrotherapy

■ TENS, duration 15 minutes, longitudinal application at the upper limbs or/and at the lower limb, the frequency 150 Hz, pulse duration 100 ms, the frequency trains of pulses 1 Hz.

■ Medium frequency currents, duration 15 minutes, longitudinal application at the upper or lower limbs, with variable frequency ranging between 100-250 Hz.

Massage is applied to the longitudinal upper or lower limbs followed by mobilization of all the joints.

Kinetotherapy contents exercises for the maintenance and increase of joints mobility, for the muscles tonus, gait exercises, exercises to balance, exercises of ability of the upper limbs, daily sessions of 30 minutes.

III. 7. Interpretation of the results.

Statistical analysis of the data used ANOVA test program, test Welch, Post hoc tests (Multiple Comparisons), Scheffe test, Test Tamhane.

IV.A. PATIENTS ASSESSMENT , INITIALLY AND AFTER TREATMENT

IV.A. Patients assessment, initially, before treatment

IV.A.1. Clinical examination

Patients experienced pain in the upper or lower limbs in the form of painful cramping,

burning, tingling or dull ache continues, had numbness in the lower limbs (as sock) or upper limbs (as glove), feeling muscle weakness and insecurity at work.
Physical examination showed impairment of tactile sensitivity, pain, vibration, thermal sensitivity without changes, diminishing or abolishing tendon reflexes and muscle strength grade 3, 4 and 5.

IV.A. 2. **Lab investigations** determined the **glycaemia** values, ranging between 99-192mg % average values being 130 mg %.

Electro diagnostic evaluation presented a decrease in the sensory nerve conduction velocity and the motor nerve conduction velocity, the decrease in the evoked response amplitude, prolong the distal latency.

IV.A. 3. Values of parameters investigated, before treatment

Visual Analog Scale (VAS), average value 9,70 .

Neuropathy Symptom Score (NSS) presented an initial average value of 3.70.

Neuropathy disability Score (NDS), average value 2.47.

TS initial, average value 8,18.

Average value of initial muscle force of 4,60.

IV. B. Evaluation patients after applying the treatment

Visual Analog Scale (VAS), average value 3,89.

Neuropathy Symptom Score (NSS), average value 2.05.

Neuropathy Disability Score (NDS), average value 1.98.

TS - average value after treatment 5,49.

Muscle force - average value after treatment 4,60.

IV. C. The values of parameters at three months after treatment

Visual Analog Scale for pain (VAS), average value 4,19.

Neuropathy Symptom Score (NSS), average value : 2.20

Neuropathy Disability Score (NDS), average value 1.99.

TS: average value 5,51 points.

Muscle force-average value 4.73.

IV. D. The values of parameters at six months after the treatment

Visual Analog Scale for pain (VAS), average value 4.59.

Neuropathy Symptom Score (NSS), average value 2.39.

Neuropathy disability Score (NDS), average value 2.13.

TS: average value 4.75.

Muscle force- average value 4,80.

V. FINAL RESULTS AND INTERPRETATION OF THE RESULTS

V.1. RESULTS OBTAINED FOR PATIENTS WITH NIDDM AND IDDM

Visual analog scale for pain (VAS). The results obtained by applying Welch test and ANOVA test, show that at least one pair of mean scores from the six possible, difference between them is statistically significant, the Sig. being less than 0.05 (Sig. = 0.000). Cohen coefficient shows large differences between the average scores for the corresponding four stages. It shows a significant decrease in the average score of 9.70 at the initial stage to 3.89 after the treatment. In the next steps we observe an increase in the average scores of 4.19 at 3 months and then to 4.59 at 6 months.

Neuropathy Symptom Score (NSS). The results obtained by applying Welch test, and ANOVA test, shows that at least one pair of mean scores from the six possible difference between them is statistically significant, the Sig. being less than 0.05 (Sig. = 0.000). Cohen coefficient indicates very large differences between the average scores for the corresponding four stages. There is a significant decline in the average score from 3.70 to 2.05 in the initial stage after treatment. In the next steps we observe an increase in mean scores from 2.20 to 3 months to 2.39 at 6 months.

Neuropathy Disability Score (NDS). The results achieved by the ANOVA test, test and Welch, shows that at least one pair of the average from the six scores for the possible difference between them statistically significant, the value of Sig. being less than 0.05 (Sig. = 0.000). There is a substantial decrease in the average score of 2.47 at the initial stage to 1.98 after the treatment. In the next steps we observe a slight increase in mean scores from 1.99 to 3 months to 2.13 at 6 months.

Screening Test of functional assistance. The results obtained by applying Welch test, and ANOVA test, shows that at least one pair of mean scores from the six possible difference between them is statistically significant, the Sig. being less than 0.05 (Sig. = 0.000). Cohen coefficient shows medium to large differences between mean scores

corresponding to four stages. There is a significant decrease in the average score of 8.18 at the initial stage to 5.49 after the treatment. In the next steps we observe an increase in the average scores of 5.51 at 3 months and then a decrease to 4.75 at 6 months.

Muscle strength. The results shows that the Welch test application at all stages of recording muscle strength, there is no statistically significant difference between pairs of possible mean values corresponding to the three stages, value of parameter Sig. is greater than 0.05 (Sig. = 0.122). Cohen coefficient shows that the differences between the average scores for the three phases are small. Although the differences between the average values is not statistically significant, they were increased to 4.60 after the treatment, to 4.73 and 4.80 to 3 months to 6 months.

V.2. RESULTS FOR PATIENTS WITH NIDDM

Visual Analog Scale for pain. Patients with NIDDM present a significant decrease in the average score from 9.64 at 3.74 after treatment. In the next stages we observe an increase in mean scores at 4.00 at 3 months and at 4.26 after 6 months.

Neuropathy Symptom Score. Patients with NIDDM present a significant decrease in the average score from 3.70 at 1.87 after treatment. In the next stages we observe an increase in mean scores at 2.04 at 3 months and at 2.15 after 6 months.

Neuropathy Disability Score, indicates an important decrease in the average score from 2.36 at 1.77 after treatment. In the next stages we observe an increase in mean scores at 1.81 at 3 months and at 1.91 after 6 months.

Screening test of functional assistence, indicates a significant decrease in the average score from 7.98 to 5.36 in the initial phase after treatment, value that lasts three months. In the next steps we observe a decrease to 4.75 at 6 months.

Muscle strength. Although the differences between the average values is not statistically significant, increased from 4.55 them after treatment to 4.77 4.81 3 months and 6 months.

V.3. RESULTS FOR PATIENTS WITH IDDM

Visual Analog Scale for pain. There is a sharp decline in the average score from 9.78 to 4.08 in the initial stage after treatment. In the next steps we observe an increase in the average scores of 4.44 at 3 months and then to 5.03 at 6 months.

Neuropathy Symptom Score. There is a significant decline in the average score from 3.69 to 2.28 in the initial stage after treatment. In the next steps we observe an increase in mean scores from 2.42 to 3 months to 2.69 at 6 months

Neuropathy Disability Score. There is a decrease in the average score of 2.61 at the initial stage to 2.25 after the treatment. In the next steps we observe a small increase in mean scores from 2.22 to 3 months to 2.42 at 6 months.

Screening test of functional assistence indicates a significant decrease in the average score from 7.98 at 5.36 after treatment,the same value at three months. In the next steps we observe a decrease at 4.75 at 6 months.

Muscle strength. Although the differences between the average values is not statistically significant, increased at 4.67 after treatment. The values are 4.69 at 3 months and 4.78 at 6 months.

V.4. RESULTS OBTAINED FOR PATIENTS WITH DIABETIC PERIPHERAL SENSORY AND SENSORY-MOTOR POLYNEUROPATHY

Diabetic peripheral sensory polyneuropathy:

Visual Analog Scale for pain. There is a significant decrease in the average score from 9.66 at the initial stage at 3.75 after the treatment. In the next steps we observe an increase in the average scores at 3.98 at 3 months and 4.44 at 6 months.

Neuropathy Symptom Score. There is a decrease in the average score from 3.59 at 1.95 after the treatment. In the next steps we observe an increase in mean scores at 2.03 at 3 months and 2.20 at 6 months.

Neuropathy Disability Score. It shows a decrease in the average score from 2.27 at 1.81 after the treatment. In the next steps we observe a slight increase in mean scores at 1.83 at 3 months, 2.00 at 6 months.

Screening test of functional assistance. There is a significant decrease in the average score from 7.10 at to 3.93 after the treatment and at 3 months. The following is a decrease in the average score at 3.22 at 6 months.

Diabetic peripheral sensory-motor polyneuropathy:

Visual Analog Scale for pain. There is a sharp decline in the average score from 9.79 at 4.25 after treatment. In the next steps we observe an increase in the average scores at 4.71 at 3 months, 4.96 at 6 months.

Neuropathy Symptom Score. It shows a decrease in the average score from 3.96 at 2.29 after the treatment. In the next steps we observe an increase in mean scores from 2.63 at 3 months, 2.83 at 6 months.

Neuropathy Disability Score. It shows a decrease in the average score from 2.96 at 2.38 after treatment and at 3 months. In the next steps we observe a slight increase in mean scores from 2.38 at 2.46 after 6 months.

Screening test of functional assistance. There is a significant decrease in the average score from 10.83 at 9.33 after the treatment. The following is a decrease in the average score at 9.38 at 3 months, 8.50 after 6 months.

VI. CONCLUSIONS. PROPOSALS.

- Recovery treatment had a favorable effect on symptoms and functional changes of diabetic peripheral neuropathy in all patients (83 patients with NIDDM and IDDM) , revealed by values of parameter: Visual Analog Scale for pain (VAS), which presented an average final score of 3.89 compared to initial average value of 9.70, Neuropathy Symptom Score -NSS with the average final score after treatment 2.05 compared to initial average value 3.70; Neuropathy Disability Score -NDS with final average score 1.98 versus initial average value 2.47 and screening test of functional assistance (TS) with an initial average value of 5.49 compared to the final average value 8.18.

- These averages scores were maintained at similar values at three months after treatment (Visual Analog Scale for pain -VAS 4.19, Neuropathy Symptom Score-NSS 2.20, Neuropathy Disability Score -NDS 1.99, screening test of functional assistance -TS 5.51).

- Six months after treatment, although the mean values obtained were higher than those obtained immediately after treatment (Visual Analog Scale for pain -VAS 4.59, Neuropathy Symptom Score -NSS 2.39, Neuropathy Disability Score -NDS 2.13, screening test of functional assistance -TS 4.75) they were significantly lower than initial ones, which demonstrates an improvement in the condition of patients.

- Keeping outcomes at three months of treatment and reduction at six months, leading to the necessity of repeat the rehabilitation treatment every three months.

- Muscle strength gradually increased at three months of treatment and at six months, the final percentage of patients with muscle strength 5 (normal) increased from 71.09% to 84.34%. Absence of better results may be due to the absence of

strict regular program of kinesitherapy at home during the six months, which shows the need to perform kinesitherapy program in specialized centers under qualified supervision or monitoring at home patient by trained personnel.

- Observing parameter values entered in the register separately for patients with NIDDM and IDDM, it is shown that a decrease in these values, statistically significant, was obtained in both groups during the four stages, finding still lower values for patients with NIDDM.
- The results for patients with diabetic peripheral sensory neuropathy and sensory-motor, reveals a significant decrease in the value of the parameters in both groups, in all four stages, finding still lower values for patients with sensory peripheral polyneuropathy .
- All patients had relief of symptoms and functional deficits, including normal daily activities after treatment, regardless of peripheral nerve damage (evidenced by electromyographic study), type of diabetes mellitus (NIDDM or NIDM) or type of peripheral polyneuropathy.
- Combination of TENS with medium frequency currents induced a long-lasting effect on pain in diabetic peripheral polyneuropathy (between three and six months) compared with studies where only TENS was applied, studies which follow the effect of medium frequency currents or interferential currents being less numerous.
- Rehabilitation treatment proved to be a treatment showed no undesirable side effects during application and is well tolerated by all patients.
- All patients with diabetic peripheral neuropathy have indication for the rehabilitation treatment, except patients with acute or chronic complications (eg heart complications, kidney, eye).
- Improvement of symptoms and functional deficits and the patient compliance to treatment, which continued at home hygienic-dietary treatment, antidiabetic drug therapy and kinesitherapy program, had the effect of avoiding the appearance of other compticatii during the six months.
- Rehabilitation treatment has a certain role in improving symptoms and quality of life of patients with a significant impact on social and professional component
- The results confirm the need to integrate the specific methods of physical medicine in the multidisciplinary approach to the management of diabetic peripheral polyneuropathy

Proposals

- Forming a multidisciplinary teams with a well-defined structure, in diabetic rehabilitation centers, which handle both the treatment and the permanent monitoring of the diabetic patient, rehabilitation physician, diabetes physician, neurologist, physical therapist, occupational therapy specialist, psychologist and not least the family physician, must to be part of the team.
- Establish a medical protocol recovery including a standardization of rehabilitation treatment, with periodic adjustment of the protocol, according to clinical and functional condition of diabetic patients with peripheral neuropathy.

VII. SELECTED BIBLIOGRAPHY

1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1. Diagnosis and classification of diabetes mellitus,http//www.who.int/diabetes/publications/en/.
2. Foster D. W., Diabetul zaharat in Harrison- Principiile medicinei interne, 2005, Ed. Teora, Buc; 334; 2265-2288
3. Vijan, S., 2010. „Type 2 diabetes". *Annals of internal medicine* 152 (5): ITC31–15; quiz ITC316. doi:10.1059/0003-4819-152-5-201003020-01003. PMID 20194231.
4. Williams textbook of endocrinology. (ed. 12th). Philadelphia: Elsevier/Saunders. pp. 1371–1435.

77. Partanen J. et al;1995, Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 333:89,

78. Ionescu-Tirgoviste C., Licheardopol R.,2006, Diabetul zaharat tip 2, Ghid terapeutic pentru medicul de familie, J.Rom.Diabet Nutritie si Boli Metabolice;vol.13;4:238-245.

107. Malik R.A., Newrick P.G., Sharma A.K., Jennings A., Ah-See A.K., Mayhew T.M., et. al. 1989,Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. Diabetologia; 32:92-102

108. Tooke J.E.,1995,Perspectives in diabetes: microvascular function in human diabetes, a physiological perspective. Diabetes; 44:721-726

110. Polydefkies M., 2007, Diabetic Neuropathy Clinical Management, Seccond Edition, Humanna Press, Nerv Biopsy, Punch Skin Biopsy in Diabetic Neuropathy;17: 284-293

123. Ametov A.S., Barinov A., Dyck P.J. et al., 2003, The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. Diabetes Care ;26(3):770-6.

126. Ziegler D., Ametov A, Barinov A. et al., 2006, Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care;29(11):2365-70.

128. Diabetes Dispatch , 68th scientific sessions, 2008, San Francisco, Painful diabetic neuropathy remains a clinical challenge

129. Pieber K., Herceg M., Paternostro-Sluga T., 2010, Electrotherapy for the treatment of painful diabetic peripheral neuropathy: a review, J. Rehabil. Med.;42: 289-295

130. Mima T., Oga T., Rothwell J., Satow T., Yamamoto J., Toma K., et al.2004,

Short-term high frequency transcutaneous electrical nerve stimulation decreases human motor cortex excitability. Neurosci. Lett.; 355: 85–88.

140. Weintraub M.I., Cole S.P.,2004, Pulsed magnetic field therapy in refractory neuropathic pain secondary to peripheral neuropathy: electrodiagnostic parameters – pilot study. Neurorehabil. Neural. Repair.; 18: 42–46.

141.Musaev A.V., Guseiniva S.G., Imamverdieva S.S.,2003, The use of pulsed electromagnetic fields with complex modulation in the treatment of patients with diabetic poly neuropathy. Neurosci. Behav. Physiol.; 33:745-752

144.Bosi E., Conti M.,Vemigli C., Cazzetta G., Peretti E.,2005, Effectiveness of frequency-modulated electromagnetic neural stimulation in the treatment of painful diabetic neuropathy. Diabetologia; 48: 817–823.

145.Radulescu A., 2005, Electroterapia, Ed. Medicala, Buc.,

154.Popescu R., Bighea A., 1995, ”Curs de medicină fizică, balneo-climatologie şi recuperare medicală“ Ed. ACSA - Craiova

155.Popescu R., „Medicină Fizică, Balneoclimatologie şi Recuperare”, 2005, Editura Medicală Universitară – Craiova

156.Popescu R., Pătru S., 2003, „Hidrotermoterapie şi balneologie” – Editura Medicală Universitară – Craiova.

160.Sidenco E.L., 2003, Masajul in kinetoterapie, Fundatia Romania de maine, Buc, Masajul medical classic; 1:16-69

178.Kirk A.F., Higgins L.A., Hughes A.R., Fisher B.M., Mutrie N., Hillis S., MacIntyre P.D.,2001, A randomized, controlled trial to study the effect of exercise consultation on the promotion of physical activity in people with type 2 diabetes: a pilot study, Diabet. Med. 18:877-882.

179.Stewart A.L., Hays R.D., Wells K.B., Rogers W.H., Spritzer K.L., Greenfield S.,1994, Long-term functioning and well-being outcomes associated with physical activity and exercise in patients with chronic conditions in the Medical Outcomes Study, J. Clin. Epidemiol.; 47:719-730.

180.Barnard R.J., Jung T.J., Inkeles S.B.,1994, Diet and exercise in the treatment of NIDDM, Diabetes Care 17:1469-1472.

182. Kennedy J.W., Hirshman M.F., Gervino E.V., Ocel J.V., Forse R.A., Hoenig S.J., Aronson D., Goodyear L.J., Horton E.S., 1999, Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects with type 2 diabetes, Diabetes 48:1192-1197.

183.Holton D.R., Colberg S.R., Nunnold T., Parson H.K., Vinik A.I.,2003, The effect of an aerobic exercise training program on quality of life in type 2diabetes, Diabetes Educ.; 29:837-846.

189.Martyn C.N., Hughes R.A.C., 1997, Epidemiology of peripheral neuropathy, J. Neurol. Neurosurg. Psychiatry ; 62(4):310-318