REVIEW OF THE ASSOCIATION BETWEEN DIABETIC PERIPHERAL NEUROPATHY AND DEPRESSIVE SYMPTOMS

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Abstract

The diabetic peripheral neuropathy is present in approximately 50% of the diabetic patients, being a major health problem, frequently associated with physical, psychological and social "sequelae". Its presence leads to a significant raise of the risk for the lower limbs ulcer and, consequently, of the amputation risk, which, in their turn, imply supplementary costs for treatment, disruption in employment and decrease the quality of life.[1,2]

On the other hand, clinical studies have emphasized the fact that the diabetic patients present a high risk of depressive disorder, the stress of daily care, the social isolation feeling, the difficulties in the obtaining of an optimum glycemic control and in the management of complications and comorbidity (when they are present) being only a part of the factors that contribute to the decrease in the quality of life and to the appearance of the depressive symptoms.[3,4]

In literature we find contradictory data regarding the association between diabetic neuropathy and depression, data that may be partially explained by the fact that in different studies different tests have been used in order to establish the diagnosis of peripheral nerves damage or to evaluate the relationship between the presence of the symptoms characteristic to neuropathy and to depression.

Based on the current information regarding the pathogenetic mechanisms of the diabetic peripheral neuropathy, the research has focused on the development of drugs which would interfere in the perception of pain and modulate descending inhibitory pain pathways. Duloxetine is used both in the treatment of painful diabetic neuropathy and of major depressive disorder (it is a selective serotonin and nor epinephrine reuptake inhibitor at the synaptic level).[5]

Key words: diabetic peripheral neuropathy, depressive disorders, duloxetine

The diabetic peripheral neuropathy

Worldwide, 246 million people were diagnosed with diabetes mellitus (DM) in 2007, and it is estimated to reach 380 million in 2025 (7.1% of the adult population); 46% of the diabetic patients (113 million) belong to age group 40-59 years old.[6]

More than 60% of the non traumatic amputations of the lower limbs are caused by diabetes (approximately 1 million per year), the diabetic patients being up to 40 times more likely to suffer one of this surgical intervention than people without diabetes.

Every 30 seconds a lower limb is lost to diabetes somewhere in the world. Statistics also provides an image of the impact on life expectancy; thus, 30% of people who have undergone a lower limb amputation die within one year, 50% die within three years and 70% die within five years.[7,8]

The diabetic neuropathy is defined as the damage of the nerve fibres caused by metabolic disorders specific to this disease. The glucose represents the only energetic layer of the nervous cell, its intraneuronal uptake being insulin-independent. In other words, the extra cellular hyperglycemia will induce an intraneuronal increase of the glucose level/ hyperosmolarity. Thus, all peripheral and central, somatic and vegetative nerves will present morpho-functional changes in diabetes.

Statistics indicate a prevalence of this complication varying between 0 and 100%, the smaller percentages referring to the most common form–the peripheral hyperalgic polyneuropathy, while the higher ones are the results of some studies, where, in order to diagnose the diabetic neuropathy, neuro-physiological parameters and nervous biopsies have been used. According to both *American Diabetes Association* and *The National Institute of Diabetes and Kidney Disease,* 60-70% of the 18.2 million persons diagnosed with diabetes in the USA present moderate or severe forms of diabetic peripheral neuropathy, this representing at the same time one of the most commonly encountered neuropathic pain syndromes in the clinical practice.[5]

Clinically, there are two common types of nerve damage in diabetes. The first is the sensorimotor neuropathy (also known as peripheral neuropathy), and the second one is the autonomic neuropathy.[5]

The diabetic peripheral polyneuropathy is the most frequent form in the clinical practice. It affects both the patients with type 1 DM and with type 2 DM. It has been noted that the prevalence of diabetic peripheral neuropathy increases with age, while Rundles states that only 25% of neuropathies appear under 40 years old. Mincu considers that the age of the diabetic patient is important in determining the clinical form (the chronic form frequently appears with adults and elders; for the youngsters there are subacute forms favored by metabolic disorders and precipitated by ketoacidosis). [9,10] Pirart considered that sex cannot influence the prevalence of diabetic neuropathy, while Rundles described a light predominance of the male sex (55%).[9,10,11] It has been shown that the sensorimotor peripheral neuropathy is a complication of long-standing diabetes, the incidence of the neurological modifications increasing as the disease progresses. A poor metabolic control is also associated with a higher prevalence of the peripheral nerves damage. [9,12]

The main symptoms are those related with the sensory neuropathy (these are present since the debut phase of neuropathy and frequently increase because of metabolic decompensation), autonomic manifestations being present as well. Symptoms often exhibit distal symmetric pattern and they are predominantly sensitive; the symptoms and the clinical signs may dominate unilaterally. Regarding the sensory manifestations, this begin distally at the base of the toes, the patients describing stabbing, tingling, shooting pains, burning, pricks, pinching and cramps. In the severe forms, even the most delicate

touch may be the trigger for the pain (disestesy), the patients explaining its appearance, for example, at the contact with common objects (bed clothes, socks). The pain may be deaf or intense, with night paroxysms (due to the predominance of the parasympathetic tonus) and with pain-relief when walking. Its evolution is centripetal towards the ankle (symptomatology in "socks"), then the leg, the hip and rarely, the abdominal area. The damage of the superior limbs nerves has a less frequency. [13,14,15.,16]

Regarding the pathogenesis of the diabetic peripheral neuropathy, though the exact mechanism of the nerves damage is poorly understood, several hypotheses have been stated:

- the vascular theory (it sustains the ischemia-hypoxia mechanism as a determinant in the appearance of neuropathy)[16]
- the metabolic theory (the persistent hyperglycemia initially determines electro-physiological, then histological modifications, and finally the clinical manifestations appear)[17,18,19]
- the alteration of the neurotrophic support (among the neurotrophic factors, we mention the NGF–nerve growth factor, neurotrophin 3 and insulin-like growth factor)[18]
- the abnormal expression of the gene for the beta2 chain of laminin may contribute to the appearance of diabetic neuropathy (heteromeric glycoprotein, in the cell cultures promotes the extension of the nervous cells)
- the theory of self-immunity (for patients with diabetic neuropathy it has been noted the presence of anti-bodies against the vague nerve and not only, but also modifications of the capillary endothelial cells of self immune nature).

The depressive disorders for diabetic patients

Although a lot of studies pointed out that there is a high risk for the depressive disorders among patients with diabetes, it is difficult to know exactly how common depression is as long as the results are very different, varying between 3.6% and 27.3%.[20]

In *"Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes–SHIELD-"* by Grandy and colleagues and published online in February 2008, the levels of health-related quality of life and depression among people with type 2 diabetes and those who was at high risk for developing it have been evaluated and compared. 3530 diabetic patients, 5335 persons with low risk and 5051 with high risk of diabetes have been included in the study. Participants were asked to complete two questionnaires measuring their quality of life and symptoms of depression. Using statistical analysis, the results obtained by the three groups were further compared in order to determine which are the factors associated with low quality of life and depression. The following have been found:

- quality of life was lower and depression was more common among the diabetic patients and those at high risk compared to those at low risk for developing diabetes
- participants with lower incomes, increased age and obesity had lower quality of life
- among people at high risk for diabetes, those who presented more risk factors also

had lower scores in the life quality assessing tests, comparing with those with fewer risk factors. [21,22,23]

The 2006 Behavior Risk Factor Surveillance System" by Chaoyang Li and his collaborators is a study published in 2007 which evaluated 226646 patients with type 1 and type 2 diabetes regarding the presence of depression and its intensity (major/minor depressive syndrome). The results of this study: 8.3% of US adults with diabetes present a major depressive syndrome (with differences related to age, sex, race, location), while the highest risk of depression was noted among patients with type 2 diabetes using insulin. [24]

On the 18th of June 2008 in *"Journal of the American Medical Association"* the results of a study which confirmed the existing bidirectional link between type 2 diabetes and depression were published. The main objective of this study was that of establishing a cause-relationship between the two disorders and its meaning, knowing the fact that compared to non-diabetic persons, the diabetic ones are approximately twice as likely to have symptoms of depression. The data of this study are offered by *"Multi Ethnic Study of Atherosclerosis" (MESA)* that was realized in "John Hopkins Hospital", Baltimore, Maryland. Thus, between 2000-2002 more than 6000 persons without cardiovascular disease were recruited, persons of different ethnics (white, black, Chinese, Hispanics), males, as well as females, aged 45 to 84 years. Two lots were created:

- the first evaluated 5201 participants without diabetes at baseline, the relative risk for incident diabetes during 3,2 years being determined among those who presented depression and those without a depressive disorder
- in the second lot, 4847 people without depressive symptoms at baseline were monitored, calculating the relative risk for developing its during 3,1 years among persons with diabetes (with or without treatment) and among those with impaired fasting glucose level compared to those with a normal fasting glycemia.

The depression diagnosis was sustained by the existence of a result CES-D ≥ 16 (Centre for Epidemiological Studies Depression), the use of antidepressants or both; impaired fasting glycemia by noticing a fasting glucose level between 100-125mg% and type 2 diabetes was defined as a fasting glucose level ≥ 126mg% or the diagnosis has been sustained by the treatment with oral hypoglycemic agents, insulin or both.

The conclusions were the following: the presence of the depressive symptoms is associated with the increase of the risk for type 2 diabetes, while the patients who were treated for diabetes present a high risk of developing a depressive disorder. Thus, it was noted that among persons without diabetes but who presented symptoms of depression at baseline, the risk for diabetes was 42% higher compared to those who did not have this symptoms. The increased risk for diabetes was maintained even after adjusting for age, sex, race or ethnicity, metabolic or socioeconomic factors, but there weren't any significant differences, statistically speaking, after the controlling for lifestyle factors (caloric intake, smoking status, alcohol consumption and physical activity). Though it was believed that the patients with depressive symptoms being more likely overweight, smokers, with a

higher calorie intake and reduced physical activity, have some poor health behaviors associated with depression and that those can contribute to the development of diabetes, the fact that the risk differences after the latest corrections weren't so significant, suggests that the association between depressive symptoms and diabetes risk may be only partially explained by the lifestyle factors. A graded increase in risk for diabetes was also noted for every 5-unit higher score of the CES-D.

In the second study lot, the following have been noted: the patients who were treated for diabetes presented a 54% higher risk of depressive disorder compared to the people with normal glycemia, the differences remaining valid statistically even after controlling for other risk factors of depression. The risk of developing depressive symptoms was 25%, respectively 21% lower among patients with untreated diabetes and among those diagnosed with impaired fasting glycemia. All these results suggest the fact that the psychological stress associated with the diabetes management may be a factor related to the high risk of depressive disorder.[25]

The presence of a chronic disease such as diabetes may be associated with depressive symptoms secondary to the intervention of several factors. Of these, we may mention the contribution of a supplementary stress related to the necessity of keeping a diet, the need to adopt healthful habits, the difficulties related to the treatment administration (especially when it is about insulin-therapy); the marginalization feeling (the patient may feel alone or set apart from friends and family), the social isolation feeling, intervenes by the fact that you are "different" from the others, as well as the 'losing control" of diabetes management feeling (when there are difficulties in obtaining the metabolic targets and not only). The presence of comorbidities or of acute or chronic complications of diabetes presents an important role through the creation of some dietetic supplementary restrictions, a supplementary medication and the decrease the quality of life. The existence of a depressive syndrome may lead to the creation of a vicious circle through the consequences that it induces (when a person is anxious, he/she also has difficulties of good diabetes self-care translated in clinical-metabolic disorders).

Therefore, on the one hand, the recognition of the symptomatology characteristic to depression is needed and, on the other hand, the intervention for its elimination. Of the frequently described symptoms, we mention:

- loss of interest/pleasure for things that were used to enjoy
- sleep disorders (change in sleep patterns)
- change in appetite
- trouble concentrating
- loss of energy
- unjustified guilt feeling (feel that never do anything right)
- irritability
- morning sadness
- suicidal thoughts.

In order to intervene in the correction of depressive symptomatology it is absolutely necessary for the diabetic patient to address himself to his physician, lack of communication proving to be responsible for many failures in the recognition and approach

of depressive disorders. Once this step is accomplished, the diabetologist will have to establish if there is a physical cause which has lead to the appearance of the depressive symptoms, and in this case he/she will intervene, etiologically, to eliminate it. For example, if we refer to the presence of diabetes, an poor metabolic control may cause symptoms similar to those of depression; high glycemic variations during daytime may create anxiety or fatigue; frequent hypoglycemia leads to exaggerated hunger which may be interpreted as an appetite modification, and if it are presented at night it could disturb the sleep; on the contrary, the increase of the blood sugar levels during night will lead to nicturia, which will have as final result the sleep disorders and the feeling of tiredness in the early morning. At the same time, the alcohol or drug abuse and the thyroid disorders may create similar symptomatology to the depressive syndrome.

If, as a result of a correct examination, it has been established that the symptoms described by the patient do not recognize any of the above-mentioned etiologies, and they belong to the depressive syndrome, the next step is represented by the psychologist's intervention or, in some cases, the psychiatrist's in the management of the disease. [5,22]

The association between diabetic peripheral neuropathy and depression

There are contradictory data regarding the association between diabetic neuropathy and depression, data that may be partially explained by the fact that in different studies different tests have been used to diagnose nerve damage or to evaluate the relationship between diabetic nerve damage and symptoms characteristic to depression.

494 patients with diabetes mellitus and diabetic neuropathy were evaluated in a clinical study in order to establish if there is an association between the presence of this chronic complication of the diabetic disease and depression. In order to increase the accuracy of results, for the neuropathy diagnosis was used some well-established tests: "The Neuropathy Disability Score and the Vibration Perception Threshold"; at the same time, there have been used a well-established test to evaluate the symptoms of depression and specific tests and instruments to measure symptoms of diabetic nerve damage, how active the patients were and the patients' perception of themselves, their illness and symptoms. The average age of those included in the trial was 62 years; regarding sex, 70% were men, while regarding the presence of diabetes, 72% of the patients had type 2 DM. According to the reported results, it has been demonstrated that there is an association between the symptoms of diabetic nerve damage and the symptoms of depression. It is interesting to find out that depression had a higher frequency among patients who described unsteadiness on their feet as a symptom associated to neuropathy. The depressive symptoms were also more frequent in patients who thought that there were little possibilities for the neuropathy treatment (to improve their symptoms), patients who presented lower activity levels because of their symptoms and in those who thought of themselves as a burden to their families. What was also surprising was the

fact that was no statistically significant association between symptoms of depression and the diabetic neuropath ulcer. [26]

Several studies have been evaluated the impact of diabetic peripheral neuropathy on quality of life. In such a trial it has been proved that the patients with painful diabetic peripheral neuropathy presented greater sleep disorders and, secondarily, significant impairment in both physical and mental functioning compared to diabetic people without neuropathy. Moreover, the researchers reported that the painful diabetic neuropathy (a score ≥ 4 on a 0-10 scale of pain quantification) hasn't only interfered with the daily activity but also substantially affects patients' moods and their "enjoyment of life". Although approximately 91% of the patients with diabetic neuropathy included in the study were treated in order to ameliorate the pain symptomatology, they frequently described a moderate interference with activities of daily living. 43% of the participants needed a concomitant medication for anxiety, depression or sleep disorders, while 35% of them reported disruptions in employment. [5,27,28]

Is there the possibility of a treatment which would regard both diabetic peripheral neuropathy and depression?

Currently there isn't any pharmacologic agents available to repair the underlying nerve damage of diabetic peripheral neuropathy. In order to ameliorate the pain, physicians recommend drugs that belong to various pharmacologic classes (as adjuvant analgesics). Thus, the therapeutic options are largely limited to drugs currently used in the management of other diseases; therefore are used tricyclic antidepressants, antiarrhythmics, antiepileptics, first- and second-generation anticonvulsants, N-methyl-d-aspartate receptor antagonists, opiate analgesics and topical agents. [5,29] Unfortunately, there are few patients who describe significant benefits using substances from the above-mentioned categories.[30]

Based on current information regarding the pathogenesis of diabetic peripheral neuropathy, the research has focused on the development of a drug which would intervene in the perception of pain and modulate/interrupt the perpetuation of pain. Knowing the possibility of the association of diabetic peripheral neuropathy with the depressive syndrome, the discovery of a pharmacological therapy which would simultaneously intercept the two conditions has become the target of the latest studies in this direction. [31]

Duloxetine obtained in 2004 the FDA approval for its use in the treatment of neuropathic pain secondary to diabetes, a drug also used in the treatment of depressive disorders, but without being a narcotic. [32] It is a selective serotonin and norepinephrine reuptake inhibitor. Clinical evidence suggest that the use of dual acting agents may better modulate pain compared to those that inhibit the reuptake, and so, increase only the activity of serotonin or noradrenaline. It is available as 20, 30 and 60 mg delayed-release capsules for oral use.

Although its mechanism of action is not completely elucidated, it is believed that the antidepressant, anxyolitic and central pain inhibitory effects are related to the increase of the activity of serotonin and norepinephrine in the central nervous system. These are two

naturally occurring substances that aid communication in areas of the brain and spinal cord (that are thought to modulate mood); the hypothesis according to which the above-mentioned mediators are part of the body's natural pain suppressing system has also been advancered. [5,33,34,35,36]

Preclinical studies have demonstrated that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. It doesn't have a significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate and GABA receptors in vitro. It doesn't inhibit MAO (monoamine oxidase).

After the oral administration, there is a median 2-hour lag until absorption begins, with maximal plasma concentrations occurring 6 hours post dose. Foods do not influence the maximal plasma concentrations of duloxetine, but delays its time from 6 to 10 hours and decreases the extent of absorption by almost 10%.[37] Half-life is around 12 hours (between 8 and 17 hours). Steady-state plasma concentrations are achieved in three days after the treatment initialization. It is more than 90% bound to proteins in human plasma, especially albumin and alpha 1 acid glycoprotein. The elimination of duloxetine is mainly through hepatic metabolism, the cytochrome p450 two isozymes (CYP1A2 and CYP2D6) intervening. [32,33,35]

The duloxetine efficacy in the management of neuropathic pain associated with diabetic peripheral neuropathy has been evaluated in two randomized, 12-weeks, double-blind, placebo-controlled, fixed-dose studies. In the two trials there have been enrolled a total of 791 patients of whom 592 (75%) completed the studies. Study 1 evaluated 457 patients (342 duloxetine, 115 placebo) [38]; in Study 2, of a total number of 334 monitored patients, 226 had an active medication (duloxetine), while 108 received placebo. [39] The patients included in these studies were diagnosed with type 1 or 2 diabetes mellitus and with diabetic distal symmetrical sensorimotor neuropathy for at least 6 months. When the treatment was initialized, the patients presented a pain score of $\geq$ 4 on a 11-point scale ranging from 0 (no pain) to 10 (worst possible pain) (figure 1).

Associated with duloxetine treatment, the patients were allowed a maximum dose of 4g acetaminophen per day. Every day, the participants in the above-mentioned studies have recorded in a diary data regarding the symptomatology evolution. Both studies evaluated the efficacy of duloxetine 60 mg once daily or 60 mg twice daily compared to placebo. Study 1 has also followed the effects of an inferior dose, of 20 mg, compared to placebo. The following results have been reported: treatment with duloxetine determined a significant decrease of mean pain scores from baseline; moreover, an important number of patients had a reduction of this score with $\geq$ 50%. Some participants experienced an amelioration of symptomatology as early as Week 1 which persisted throughout the monitoring period. It has been concluded that the efficient dose for the diabetic peripheral neuropathic pain is 60 mg/day given once a day; there is no evidence that doses higher than 60 mg offer additional benefits, while the adverse effects proved to be dose-dependent. [5,37,38,39] The patients who did not participate in the entire study were considered as being without amelioration of

symptomatology, in other words, without a diminishing of pain score and were assigned 0% improvement. [38,39]

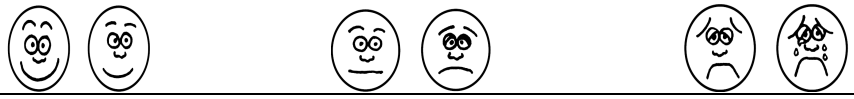
0-10 numeric pain intensity scale	0	1 2	3 4 5	6 7	8 9	10
Verbal descriptor scale	No pain	Mild pain	Moderate pain	Moderate pain	Severe pain	Worst pain possible
Activity tolerance scale	No pain	Can be ignored	Interferes with tasks	Interferes with concentration	Interferes with basic needs	Bedrest required
Pain faces scale						

Figure 1: Universal pain assessment tool from: Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline, No.1. AHCPR Publication No.92-0032, February 1992. Agency for Healthcare Research and Quality, Rockville, MD: 116-117 and Wong DL, Hockenberry-Eaton M, Wilson D, Windelstein ML, Schwartz P.Wong's essentials of pediatric nursing. 6th Edition, St. Louis, 2001:1301-modified

The most frequent observed adverse event in the two clinical studies was nausea; in most cases it disappeared after 1 or 2 weeks of treatment. Among the other adverse effects, we mention somnolence, dizziness, constipation, hyperhidrosis, dry mouth, decreased appetite; these were minimum ones and did not lead to discontinuation of duloxetine. [5,34]

Duloxetine was not administered in the following situations:

- recent treatment with MAOI (monoamine oxidase inhibitor);
- uncontrolled narrow-angle glaucoma;
- concomitant with thioridazine.[5,34,37]

The following warnings and precautions were recommended related to: the increase of suicide risk; especially during the first months of treatment or when the dose is modifies; hepatotoxicity: elevated transaminases, bilirubin and alkaline phosphatase; orthostatic hypotension and syncope; the appearance of the serotonin syndrome; the abnormal bleedings that may appear if it is concomitant use with nonsteroidal anti-inflammatory drugs, warfarin or other anticoagulants; abrupt discontinuation that may lead to the following symptoms: dizziness, paresthesias, irritability, headache; co-administration with potent CYP1A2 inhibitors or thioridazine; the possibility of hyponatraemia appearance; the existence of a hepatic insufficiency or severe renal impairment; the possibility, in diabetic peripheral neuropathic pain, of a small increases in fasting blood glucose, HbA1C and total cholesterol secondary to the duloxetine treatment; the coexistence of some conditions that slow gastric emptying; the possibility of urinary retention. [34,37]

As a conclusion, both the peripheral neuropathy as well as the depressive disorder, present in patients with diabetes mellitus represent major health problems due to the magnitude of the impact they have regarding the patient, but also at the level of society as a whole. Thus, we need an exact understanding

of the pathogenesis of the two disorders, their natural history as well as the focusing of research towards the discovery of as many therapeutic options as possible which may be used for prevention or treatment (when the diabetic patients have already been diagnosed in the stage of chronic complications and, respectively, with depressive syndrome). The identification of a pharmacological therapy which would simultaneously target the two pathologic conditions is nonetheless necessary as, considering the fact that we are in front of some polytreated patients, they would benefit from an increase compliance regarding administration.

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