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Hipocrate

SPECIAL EDITION SOCIETY FOR DIABETIC NEUROPATHY

„Coming together is a beginning
Keeping together is a progress
Working together is succes“

HENRY FORD

NEURODIAB
Society for
Diabetic
Neuropathy

www.neurodiab.org

For millions of people with diabetes mellitus, this sensation is real

Diabetic neuropathy is a severe complication of diabetes mellitus, affecting a large number of persons. One of two patients with diabetes mellitus has diabetic neuropathy.

Nerve damage in diabetic neuropathy can cause tingles, burning sensations, numbness, pain or weakness of feet and hands. Nerve damage has as a result a higher risk of amputation.

It is never too late to prevent or to delay the apparition of diabetic neuropathy.
Inform your doctor about these symptoms.

WÖRWAG PHARMA

This material has the approval of ANMDM No. 29817E from 07.19.2011

START.

Sibiu, October 2012. The establisment symposium of the Society for Diabetic Neuropathy

More than a quotation

Dr. Marius Geantă
marius.geanta@kolmedia.ro

Coming together is a beginning
Keeping together is a progress
Working together is succes

Henry Ford

The Society for Diabetic Neuropathy started with this slogan, a year ago. The following pages show how short the road from words to facts is, when we come, stay and work together for a good cause.

SUMMARY

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Coming together
is a beginning

The establishment of the Society of Diabetic Neuropathy in our country counts among the priorities that we have identified on a European level as well. The initiative has a special value, being the best form of appreciation of the NeuroDiab symposium at the anniversary of its 10 years of existence

PROF. DR. NICOLAE HÂNCU,

Honorary President of the Romanian Society of Diabetic Neuropathy

The Society of Diabetic Neuropathy is the right frame for specialists involved in disease management to do their work

PROF. DR. AMORIN POPA

First President of the Society of Diabetic Neuropathy

The main goal of the Romanian Society of Diabetic Neuropathy is to create the necessary frame for the specialists in various medical fields who deal with diabetic patients (and this mainly concerns specialists in diabetes and nutrition diseases and neurologists, but other specialties as well, such as surgery – there are specialists who deal especially with patients who have complications of diabetes, doctors in rehabilitation medicine) to convene, discuss, have common standards in a collaboration, that would permit exactly this integrative approach of patients with diabetes and particularly with diabetic neuropathy

PROF. DR. OVIDIU BĂJENARU

Honorary President of the Romanian Society of Diabetic Neuropathy

The Society of Diabetic Neuropathy was established quite recently and I believe it plays an important part in the vast approach to this pathology by organizing scientific events in which doctors from various specialties can participate (diabetes, neurology, cardiology, surgery), doctors who are confronted on a daily basis with this terrible complication of diabetes and with its consequences

PROF. DR. MARIA MOȚA

President of the Romanian Society of Diabetes, Nutrition and Metabolic Diseases

Out of 100 amputations, 70 are believed to be possible to prevent if the doctor and the patient would pay more attention to understanding this complication that may lead to one of the most important disabilities (that in the absence of adequate prosthesis, very expensive at the moment, can make life extremely complicated

PROF. DR. CONSTANTIN IONESCU TÎRGOVIȘTE

The Society seeks to actively participate as a partner of professional societies and of the professional commission of the Health Department in the elaboration of guides and protocols meant for the care of patients with diabetic neuropathy.

PROF. DR. IOAN ANDREI VEREȘIU

President of the Romanian Society of Diabetic Neuropathy

An initiative that I consider to be very important

PROF. DR. RODICA POP BUSUI

The importance of the establishment of the Society of Diabetic Neuropathy is huge. The fact that in this Society, doctors from different specialties can sit around a table and discuss not only medical issues, but also logistic issues relating to the optimization of interdisciplinary cooperation, seems very important to me. That is why I would like to congratulate those who had the initiative of the establishment, Missis Norina Gâvan playing, as far as I know, a decisive part in this

DR. ALIN ȘTIRBAN

The Society of Diabetic Neuropathy has a very difficult mission and the expectations are very high. For me personally it represents a gleam of hope that the problems connected to this impairment will be set in a natural order of priorities, will be approached with professionalism and dedication, by solving not today, perhaps not even tomorrow, but in a very near future, the extremely complex issues related to this topic

PROF. DR. DOINA CATRINOIU

The Romanian Society of Diabetic Neuropathy, by the annual organization of multidisciplinary scientific events, actively contributes to the improvement of the management and prognosis of diabetic neuropathy and of the diabetic foot

CONF. DR. ROMULUS TIMAR

NeuRODiab has established itself in the minds of Romanian diabetologists and neurologists as a reference point for excellence in medicine. This trait is shared by all the partners of the Society of Diabetic Neuropathy: The Romanian Society of Neurology; ASNER – The Romanian Society of Electrodiagnostic Neurophysiology; The Society of Diabetes, Nutrition and Metabolic Diseases and the Romanian Federation of Diabetes, Nutrition and Metabolic Diseases, that our company have worked with from the beginning

NORINA GÂVAN,

Head of representative Worwag Pharma GmBH&Co.KG in Romania


Keeping together
is a progress


Nu eşti singur!
Fii parte din Comunitatea noastră de Neuropatie Diabetică


Diabetes Center at the Heinrich Heine Univ
Leibniz Center for Diabetes Research
Department of Metabolic Diseases
University Hospital, Düsseldo


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ROOM
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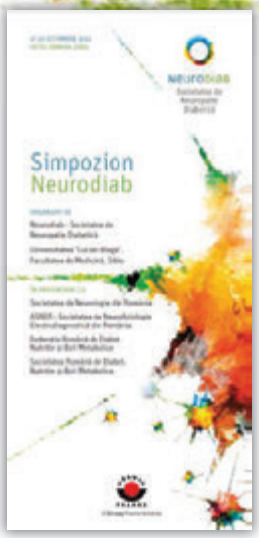
Neurodiab

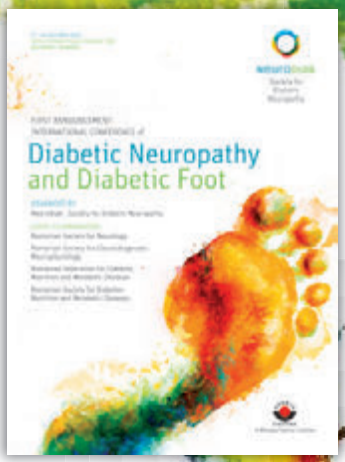

NeuroDiaB
Societatea de Neuropatie Diabetică

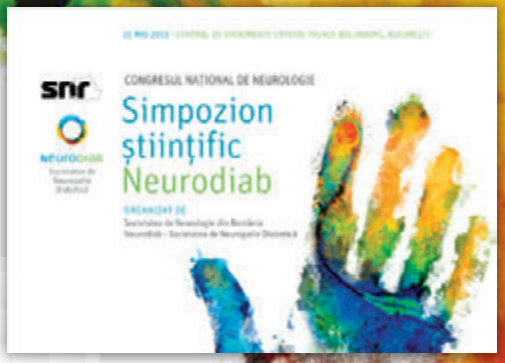

Working together
is succes

The activity of the Society for Diabetic Neuropathy during 2012 - 2013

Activities dedicated to the physicians involved in the management of diabetic neuropathy in Romania



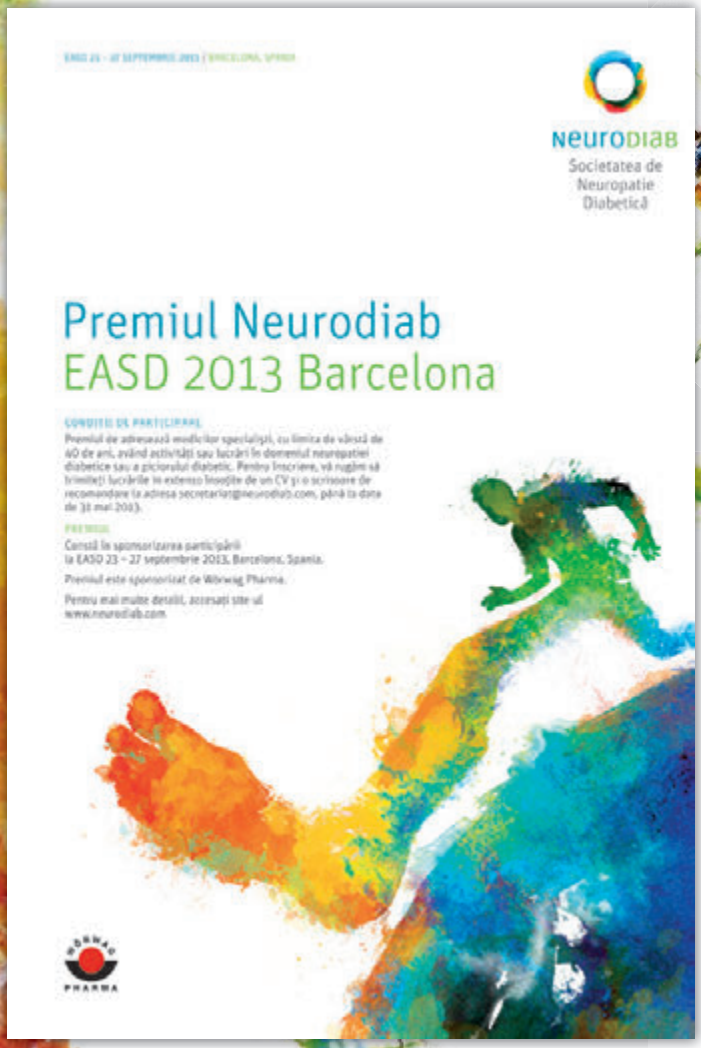




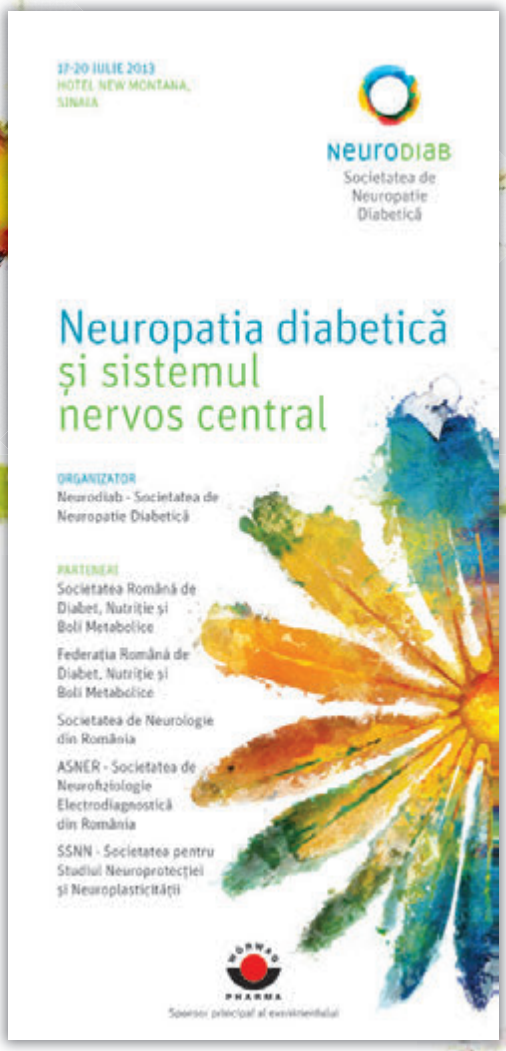
Activities for the patients with diabetic neuropathy

NEURODIAB
Society for Diabetic Neuropathy

Society's Prizes

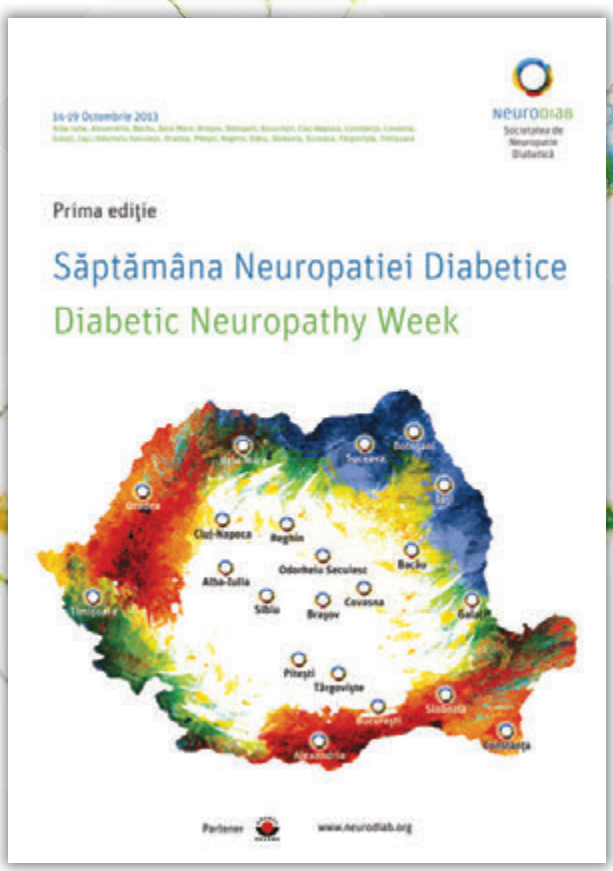


Summer School



Prime

Diabetic Neuropathy week

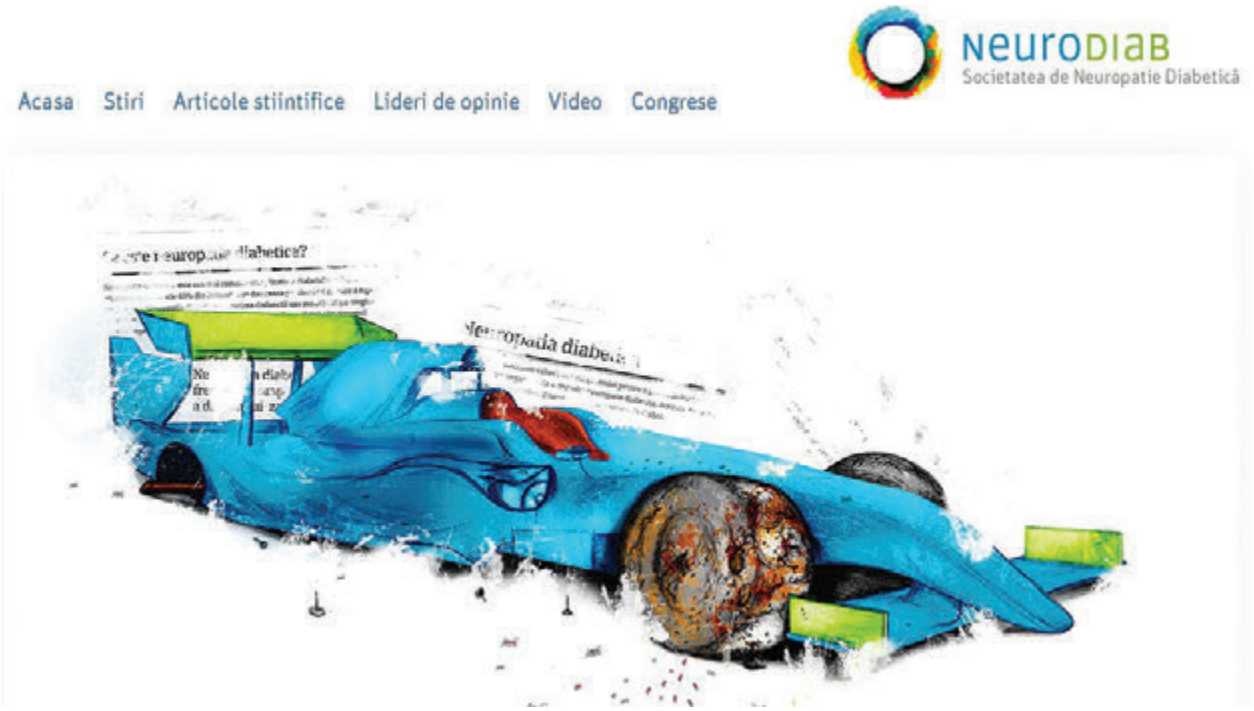


Certificate of Honorary

Symposium

app.neurodiab.org

The Society of Diabetic Neuropathy is the first medical professional society in Romania that uses the new technologies and art means to communicate to its members, in real time, the news in this area



Martin Cooper, the man who invented the mobile phone, surely wasn't thinking, in 1973, that over 40 years, globally, the number of mobile phones will be greater than that of the toothbrushes. Neither that 70% of the mobile phone owners will get to sleep with them at hand.

The technological revolution, on the axis Internet - Digital - Mobile - Social Networks, fundamentally changed the way the information is exchanged globally. If we also add to this progress the fantastic dynamics of medical research, we have a picture both complex, and also hard to comprehend with the mind of a doctor caught in the daily routine of caring his or her patients.

Recent studies show that there are needed 160 hours per week for a doctor to cover all the specialty literature. This huge volume of scientific data, in order to be valuable for patients, must be structured, adapted and explained for each area of interest.

NeuroDiab application, launched in July, represents the first scientific information vehicle of doctors in the topic of diabetic neuropathy, a common and debilitating complication of diabetes mellitus. The Society of Diabetic Neuropathy is the first medical professional society in Romania that uses the new technologies and art means to communicate to its members, in real time, the news in this area.

The latest news are not only presented in real time, but also explained and adapted to Romanian reality with the aid of Romanian and foreign opinion leaders in diabetology, neurology and other disciplines interested in diabetic neuropathy. The application adapts to each device it is accessed on, thus augmenting the reading experience.

Hipocrate iPad

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Enter in the new dimension of medical scientific communication with iPad application of Hipocrate Journal. The medical science evolves with an astonishing speed, and the science of communicating these progresses keeps the pace with innovation. We have been innovating since the beginning, in 2006. And we continue, by offering you Hipocrate iPad, superpremium application of Hipocrate Journal.

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The Story of Diabetes Football in Romania – Chapter DiaEuro 2013

Cosma Daniel-Tudor

Our adventure has begun in March, when Romania was invited to take part to the European Football Championship for diabetic persons.

After getting the medical sheets ready, there were sponsors needed for team transport, cantonments and equipment. FRDNMB, FADR, NEURODIAB and WORWAG PHARMA have supported since the beginning the Romanian initiative to prove that the diabetes is not a barrier for performance sports.

After a few cantonments, in which the relationships between the players became close, the tactic was defined, the team name was set, the education regarding the sportive activity in diabetes was accomplished, and repeated medical exams were made, we headed to Croatia with the minds set and the ambition to have honorable results at this European event.

The organization was very good, with spectacular matches that kept us breathless until the last seconds of the games. It seems that all was under the devise: "The sport unites us all". DiaRomania made its way up to a sixth position, which is satisfactory when taking into account the short notice preparations.

In this championship, the patriotism, ambition and ego have been far above the players' diabetes. The determination on the pitch made its presence noticed in the sometimes rough play and in the increased number of injuries.

The championship was also an auspicious environment in which "European" friendships were made, concluded later on Facebook and other social networks. Everybody have returned home with the regret that everything had happened so fast and we had to leave Croatia and Zadar, the beautiful town on Adriatic coastline.

16th–18th OCTOBER 2014
RAMADA PLAZA HOTEL / RAMADA PARC
BUCHAREST, ROMANIA

NEURODIAB
Society for
Diabetic
Neuropathy

2ND NATIONAL CONFERENCE of

Diabetic Neuropathy and Diabetic Foot

WITH INTERNATIONAL PARTICIPATION

ORGANIZED BY

Neurodiab - Society for Diabetic Neuropathy

PARTNERS

Romanian Society for Diabetes,
Nutrition and Metabolic Diseases

Romanian Federation for Diabetes,
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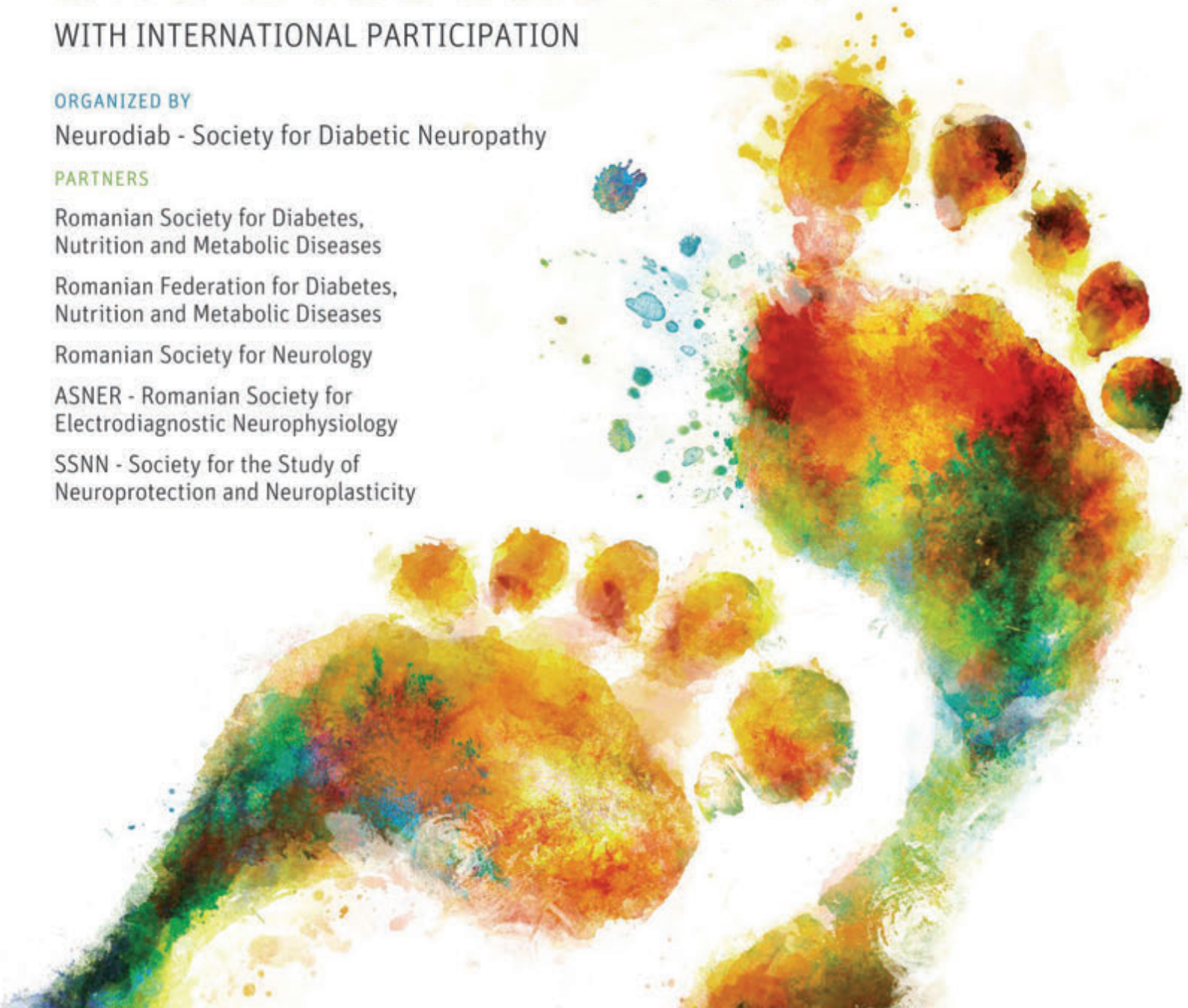
Romanian Society for Neurology

ASNER - Romanian Society for
Electrodiagnostic Neurophysiology

SSNN - Society for the Study of
Neuroprotection and Neuroplasticity



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The Establishment of the Society of Diabetic Neuropathy is a Noble Initiative

Prof. Dr. Andrew Boulton, president of the European Associaton for the Study of Diabetes: "I congratulate the founders of the Society of Diabetic Neuropathy, I wish all the best for them and I hope they will succeed to implement at national level a care system for these patients

The greatest challenges for the diabetic neuropathy in Europe are: the disease pathogenesis, the ways it can be prevented and the management of the associated symptoms. It is essential that the neuropathy to be discovered early and that we should try to anticipate its evolution.

Regarding the clinical aspects of diabetic neuropathy, the differences are quite small between the European countries. A situation existed once, and it might still exist, in some states from the Eastern Europe, about patients treated with medicines that have no efficacy proving data. In these areas we have to insist on using only the treatments that bring true benefits, according to the studies that have been made.

It is essential for the physician to try to identify the diabetic neuropathy as early as possible, in the quiet stage of the disease. It is recommended to have the diabetic patient evaluated on a yearly basis in order to see if the neuropathy is already in place or not. The evaluation must be made for each patient, in a personalized way, and not taking into account only the guidelines.

The establishment of the Society of Diabetic Neuropathy is a noble initiative, because this could be a joining platform for people from various medical specialties, interested in diabetic neuropathy. It is similar to what we have at EASD, where there is a small study group in diabetic neuropathy, but also a working group for diabetic foot. The interdisciplinarity is essential for an efficient management of diabetic neuropathy.

I congratulate the founders of the Society of Diabetic Neuropathy, I wish all the best for them and I hope they will succeed to implement at national level a care system for these patients. It is also in our benefit, because this way we will collect specific data for Romania, and this data will be helpful for the future European programs concerning diabetic neuropathy.

Prof. Boulton, with Prof. Maria Moța and Prof. Nicolae Hâncu

The Society of Diabetic Neuropathy - an Example of Interdisciplinarity

"The medicine of XXI century will be interdisciplinary or it won't be at all"

Conf. Dr. Ioan Andrei Vereșiu, University of Medicine and Pharmacy "Iuliu Hațieganu" Cluj-Napoca

Paraphrasing a famous quotation, I might say that "the medicine of XXI century will be interdisciplinary or it won't be at all". The quantity and the diversity of medical information involved over-specialisation, but the pathogenic and therapeutic complexity of non-transmissible chronic diseases (and of diabetes mellitus among them), held responsible for the majority of deceases in the world nowadays, make the continuous and efficient interdisciplinary collaboration to be indispensable.

Diabetic neuropathy is the most common chronic complication of diabetes mellitus, involving both the peripheral nervous system (most frequently) and the central nervous system (an area still insufficiently known and intensely studied), both somatic aspects and the vegetative ones. Its major consequences are the lowering of the quality of life, increasing the risk of lower limb amputations, and also the significant increase of the mortality risk generated by the involvement of cardiac autonomous nervous system involvement. Protein glication and oxidative stress are the main pathogenic mechanisms and, in the same time, the main therapeutic targets.

In this context, the Society of Diabetic Neuropathy was born as a necessity imposed on one hand by the always growing number of patients with this complication, and on the other hand by the complexity of care, these patients requiring, in time, the neurologists expertise, continuous supervising of diabetologists, but also the involvement of family physicians, of surgeons, of psychiatrist and even of other specialists. The interdisciplinary communication and the synchronisation of strategies are the main objectives of the Society. Having as founding members Prof. Dr. Maria Moța, President of the Romanian Society of Diabetes, Nutrition and Metabolic Diseases, and Prof. Dr. Ovidiu B□jenaru and Prof. Dr. Fior Dafin Mureșanu and other personalities – diabetologists, neurologists, surgeons, epidemiologists – I believe that we have among the best premises.

In the one year since the Society's establishment, under the leadership of the first President, my colleague Prof. Dr. Amorin Popa, and animated by

Conf. Dr. Ioan Andrei Vereșiu, President of the Society for Diabetic Neuropathy in Romania

the tireless endeavour of the General Secretary, Mrs. Norina Gâvan, the Society rapidly gained notoriety, proved by the increase of the number of enrolled members, but also by the number of internet site accessing. Important personalities in this field, from our country or abroad, expressed appreciative consideration regarding this initiative. The Society continued its already traditional "Summer Schools" for residents and young diabetology and neurology specialists, and initiated and led its first study on a representative number of Romanian patients, concerning the quality of life of the patients with diabetic neuropathy, having at hand a complex questionnaire used in USA and in some Europe.

This year is intended to be devoted to the Society. Its first National Conference will take place, with a remarkable national and international participation. Between the 14-th and the 19-th of October there will be the first "Week of diabetic neuropathy", with workshops for family physicians, diabetologists and neurologists taking place in numerous counties, and also a project under the Society's auspices that we consider to be a foreground one, where through there were initiated in many counties work meetings between specialists and patients, the beneficiaries of our efforts.

And not at last, the Society intends to actively participate, as a partner of the Professional Societies and Specialty Commissions of the Ministry of Health, for elaborating guidelines and protocols for caring the patients with diabetic neuropathy.

Taking over the Society's presidency in the present mandate, I am convinced that I have besides me dedicated colleagues and friends and that together we will succeed to take another step forward in increasing the quality of care for our patients.

About the Romanian Society for Diabetic Neuropathy

After one year from the first meeting

The global impact of this condition is in an obvious progression, due to at least two objective reasons. As a result of the „epidemic" of diabetes mellitus type 2, the real increase of the number of persons with diabetes also involves an increase of the number of persons with diabetic neuropathy. On the other hand, due to increasing the life expectancy of the persons with diabetes mellitus as a result of the medical advances and of the evolving life standards, we can notice lately a decrease in acute complications, but an increase in chronic ones, and also in diabetic neuropathy. Along with the improvement of medical care for the diabetic persons from Romania and of the population screenings, the national epidemiologic reality is catching up with the international one.

To exemplify, I have at hand some data kindly provided by Dr. Bogdan Florea, neurologist from Cluj. Thus, a review from February 2012 made by Gordon Smith and Robinson Singleton shows that sensorimotor diabetic polyneuropathy has an incidence of up to 50 % in patients with diabetes mellitus type 2, 20 % already having sensitive diabetic polyneuropathy when the diabetes was diagnosed.

Let's not forget that one of the main challenges of diabetes mellitus is the autonomic neuropathy. A 2004 analysis of Mayo Clinic, led by Low et al., mentions the presence of autonomic neuropathy in 54 % of the persons with diabetes mellitus type 1 (8 % accounting for orthostatic hypotension) and in 73% of the persons with diabetes mellitus type 2 (7 % accounting for orthostatic hypotension).

We, the members of the Society of Diabetic Neuropathy, have set out to direct the Romanian medicine towards the current tendencies of the evolution of the human pathology and to integrate it in the struggle for a major cause, against disability and the lowering of the quality of life.

After 1 year from our first meeting, here are a few objectives, initiated and followed:

- increasing the interest and the competence of the family physicians in early identification of diabetic neuropathy (we had dedicated meetings with family physicians, we created professional papers of wide scope),
- familiarizing the family physicians with all clinical manifestations of the disease,
- generalizing the skills and the use of the kit for diabetic neuropathy screening,

Prof. Dr. Amorin Popa, past-president of Society for Diabetic Neuropathy

- the integrated activity of diabetologists, neurologists, family physicians, kinesiologists, cardiologists, internal medicine specialists, surgeons and nurses (in all of our meetings we have invited all these guest categories),
- the compulsoriness of the neurological exam of the patient with diabetes at the time of the first diagnosis,
- specific curricula for physicians, at national level,
- the specific education of the patients with diabetes,
- providing easier access for the physicians and for the persons with diabetes to early diagnostic technologies,
- bringing IT technology in the management of diabetes and of its complications,
- collaboration at all levels of competence with international factors for using IT technology to aid scientific information.

Finally, I would like to mention of the society's motto – that defines our thoughts -, belonging to Henry Ford: „Coming together is a beginning. Keeping together is a progress. Working together is success."

Diabetic neuropathy - multidisciplinary challenge

Prof. Maria Moța,
Dr. Diana Clenciu, Craiova

Diabetes mellitus is a chronic disease that involves, in time, the onset on chronic and irreversible complications, such as nervous, renal, ocular complications or of the large vessels, etc. In the last years, the number of diabetic patients is increasing globally, and at present we can discuss of a real epidemic of this condition, and the estimates are alarming and always underestimating.

The diabetic neuropathy represents the sufferance of nerves as a result of chronic hyperglycemia and may involve the nerves in the whole body. It is the most common chronic complication, being present at almost 75% of the patients with diabetes mellitus. The diabetic neuropathy has severe consequences on health, in many cases irreversible, so that an intense approach of this problem is compulsory, on the part of the specialists, on one hand, on the part of the patients and of their families, on the other.

In this respect, the Society of Diabetic Neuropathy, founded in August 2012, opened the path for numerous activities, aiming the prevention and the treatment of this complication. In January 26, 2013 the Society of Diabetic Neuropathy organised a first meeting of the Managing Board of Neurodiab and the members of the Federation of the Associations of Diabetics from Romania. This meeting emphasized the importance of the collaboration between specialties for a most correct and early diagnose of neuropathy, but also on the role of education in preventing and controlling DM and its complications. The Society of Diabetic Neuropathy continues its activity in 2013 by organizing in Bucharest, in May 17, 2013, the symposium "Past, Present and Future in Diabetes Complications Research", and then the Neurodiab – Summer School, that took place in Sinaia between 17 and 20 of July 2013. The peak of the Romanian Society of Diabetes interest is reached with the organization, in Bucharest, of the first National Conference of Diabetic Neuropathy and Diabetic Foot, with international participation, during 17 and 20 October 2013.

There is no curative treatment for diabetic neuropathy. Once the condition installed, the treatment is focused on secondary prophylaxis (removing exacerbating factors), consisting in maintaining the glycemic levels close to a target value and

the average value of glycated hemoglobin A1c less than 7%. It is also important to maintain a healthy life style, involving regulate exercise, blood pressure control, diet, ceasing smoking, limiting the consumption of alcohol and a close supervising of the feet, in order to prevent wounds or severe complications at this level. The treatment also depends on the symptomatology and on the type of neuropathy.

Many patients with peripheral neuropathy – being affected the nerves ensuring sensitivity – have gentle to severe pain in specific regions of the body. During the medical consultation it must be brought into discussion the treatment that may ease the pains and improve the physical and psychical state of the patient. These treatments may include medicines or ointments that ameliorate the pain, such as: tricyclic antidepressants (duloxetine hydrochlorid), antiepileptics (gabapentin). Tioctic acid, the vitamins from complex B helps to improve and maintain the nervous influx, being useful in the treatment of diabetic neuropathy.

The heterogeneity of diabetic neuropathy

Prof. Aaron Vinik: "Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of neuropathy is not yet fully appreciated"

Most of my life I have worked in studying the heterogeneity of neuropathy. I also tried to establish a need for a modular approach depending on the particular nerve fiber damaged.

I have worked on studies on the relationship between neuropathy, autoimmunity, and cell toxicity, and I have also tried to the use the immunotherapy for autoimmune diabetic neuropathy.

I have contributions in research on evaluation of autonomic neuropathy, as well as on the identification of the site of pathology of diabetic peripheral neuropathy, using contact heat evoked potential stimulation.

And why is diabetic neuropathy so important to me? Because it occurs most frequently and it leads to greatest morbidity and mortality. The neuropathy largely contributes to foot ulcerations and amputations and it greatly impairs the quality of life. A person who has foot ulcers has 50 % chances to have a foot amputation in the next five years, and also 50 % chance to have a second foot amputation in five or ten years.

But not only the foot ulcers and amputations are important. The second major impact of neuropathy is that of falls and fractures. When someone reaches the age of 65 years old, which is a common age for type 2 diabetes sufferers, there is a one in three chance of falling, every year. Over that age, and with diabetes in combination, there is a 17 fold risk of falling and fracturing.

Let's look now how often we encounter diabetic neuropathy in clinical practice. We must say that despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of neuropathy is not yet fully appreciated. And the reported prevalence of diabetic neuropathy varies widely depending on the cohort studied and the methods of assessment.

VISIT CARD

Prof. Aaron Vinik, M.D.
is a member of a number of professional societies including the American Endocrine, Diabetes, Gastroenterology, and the European and International Diabetes associations. Dr. Vinik served as a member of the National Institute of Health General Clinical Research Center Study Section and the NIH Data Management committee. He was also Chairman of the American Diabetes Association task force on Nutrition, which established the guidelines for nutritional management of diabetes, and Chairman of the subcommittee for development of guidelines for neuropathy testing; in addition, he was a member of the committee to develop guidelines for managing lipid disorders in diabetes.

In the United States, for example, in 2000, based on a simple screen for reduced sensation at the foot, it was shown that 28% of adults aged 70 - 79 years and 35% of adults aged over 80 years had peripheral neuropathy.

So, when a patient enters the clinic, all we have to do is to ask the patient about pain, numbness, tickling, burning, weakness, gastroparesis, erectile dysfunction, fecal incontinence and so on. When a patient walks in your practice we have to take into account the main clinical signs of diabetic autonomous neuropathy, which also include resting tachycardia, orthostatic hypotension, exercise intolerance, constipation, sudomotor dysfunction, or impaired neurovascular function. Many organ systems, throughout the body, might be affected: gastrointestinal, genitourinary, the cardiovascular system. The gastrointestinal disturbances are common, and any section of the gastrointestinal tract may be affected. Also, gastroparesis should be suspected in individuals with erratic glucose control.

Regarding the diagnosis and the management of diabetic neuropathy, it is important that no diabetic should enter a practice with his shoes on; we always must to examine the feet and the shoes. We also have to test all the diabetic sufferers for sensory loss, using vibration of 128 Hz or a monofilament.

In managing the disease, we must educate the patient to care his feet; he must never walk barefoot, he must use emollients and hydration. Patients can put a mirror in the bathroom or they can take home a monofilament and thus you can reduce foot ulceration and amputation by 50%.

I wish to emphasize again the fact that that life style interventions, meaning – for example, the adherence to diet and exercise, can reduce the incidence of type 2 diabetes. There is also a report indicating that impaired glucose tolerance might be associated with the development of diabetic neuropathy, the sensory polyneuropathy. Should this be confirmed in large prospective studies coupled with evidences that primary intervention would prevent the development of neuropathy, this would put even greater emphasis on the importance of lifestyle interventions and screening at or soon after diagnosis. Though, the motivation to adhere and remain compliant with non-pharmacological interventions is difficult. There are current research that suggests that preventive measures, meaning the glycemic control, diet, and exercise introduced to the general diabetic population are difficult to sustain and consequently less than effective.

The high prevalence of certain subclinical diseases in the elderly may be associated with declines in peripheral nerve function. Importantly, these conditions are modifiable so early intervention on these risk factors may prevent peripheral nerve function declines and the subsequent clinical consequences associated with peripheral neuropathy.

EXPERT

International recognition

Dr. Vinik have received international recognition as a result of his research on islet regeneration and the discovery of a gene, which could prove to be a cure for diabetes. The gene, INGAP (islet neogenesis associated protein) is responsible, either alone or in combination with other factors, for stimulating immature cells in the diabetic pancreas to produce insulin. When INGAP protein was administered to diabetic hamsters it was shown to reverse diabetes in 40% to 50% of animals. Animal studies were followed by human, multi-center clinical studies in both type 1 and type 2 diabetes, carried out by some of the most highly recognized investigators in the country; the results showed that even in type 1 diabetes an increase in C- peptide, (a measure of islet function), could be induced after 3 months of treatment. In type 2 diabetes, INGAP was able to stimulate an increase in C peptide and reduce HbA1c levels by close to 1%. Phase 2 clinical trials were recently completed as multiple-center, randomized, double-blind, placebo-controlled studies to assess the safety, and efficacy of a new formulation of INGAP peptide given subcutaneously as injections for 12 weeks in adult patients with Type 1 diabetes, who have been treated with insulin for greater than 2 years and who are otherwise in good general health.

Diabetic neuropathy: the forgotten complication

An interview with Prof. Dr. Peter Kempler

The challenge of diabetic neuropathy in 2013

Diabetic neuropathy: the forgotten complication – these words of professor Andrew Boulton are unfortunately somewhat still valid for this complication. We need a better understanding of the pathomechanism. Diabetic neuropathy is still an underdiagnosed complication, and improved diagnosis and therapy might contribute to the reduction of late complications of neuropathy including amputations. Early diagnosis is also of crucial importance. We are on the way that the importance of pathogenetic oriented, disease modifying treatment should be considered as a fundamental part of therapy. In this respect, benfotiamine and alpha-lipoic acid should be considered as highly powerful agents.

The priorities in the management of diabetic neuropathy

The therapy of diabetes mellitus itself is based on pathophysiological considerations. Insulin, oral hypoglycaemic agents, anti-platelet agents, antihypertensives and lipid-lowering drugs are considered as pathogenetic oriented, causal treatment.

However, pain associated with neuropathy must be alleviated, and this way, symptomatic relief of pain is also important. Pathogenetic oriented, causal therapy is justified by objective signs of neuropathic damage, such as sensory or reflex loss, and reduced vibration perception. However, the typical consequences of neuropathic damage are often missing in patients suffering from pain and other clinical symptoms of neuropathy – this is characteristic of patients with small-fibre neuropathy. Symptomatic agents play a key role in the treatment of painful neuropathy. Nonetheless, it should be considered that neuropathic pain does not occur in the absence of nerve damage, and consequently pathogenetic oriented therapy is also justified for the therapy of neuropathy among patients with small-fibre neuropathy. Neuropathic damage and neuropathic pain affect a high number of diabetic patients at the same time. In a typical diabetic patient suffering from pain and paraesthesias usually sensory hypoaesthesia and parasympathetic autonomic neuropathy are detected. Combination treatment with pathogenetic oriented and symptomatic agents is often reasonable among these patients.

VISIT CARD

Prof. Kempler
Professor of Medicine,
I. Dept. of Medicine,
Semmelweis University,
Budapest
Since 1982 my scientific interest is closely related to diabetic neuropathy. Beside diabetic patients I have examined autonomic and sensory nerve function in chronic alcoholics as well as in patients with chronic liver diseases. As far as I know, I have firstly described autonomic neuropathy in chronic alcoholic and non-alcoholic liver diseases. I have edited a book, titled "Neuropathies" published by Springer Verlag on Hungarian (1996, 2002) and English language (1997, 2002). I have written Editor 8 books, chapters of 14 different books, 162 articles, a lot of them in journals with higher impact factors

Prof. Dr. Peter Kempler

Symptomatic and pathogenic treatment of diabetic neuropathy

The aim of pathogenetic oriented causal therapy is to delay, stop or reverse the progression of neuropathic damage as well as to alleviate symptoms of neuropathy. The potential key components of causal therapy include the optimal glycaemic control, the management of risk factors and the administration of aldose-reductase inhibitors, benfotiamine (a transketolase activator and inhibitor of alternative metabolic pathways), as well as alpha-lipoic acid (an antioxidant). Importantly, pathogenetic oriented treatment has an impact on neuropathic damage/deficit and disability, while, on the other hand, it has a documented effect on the improvement of neuropathic pain and quality of life as well.

Benfotiamine blocks four pathogenic mechanisms of diabetic complications: the hexosamine pathway, the diacylglycerol pathway (leading to PKC and NF-kB activation) and the AGE formation and has antioxidative effects.

Data suggest that benfotiamine exerts protective effects on retinal, endothelial and renal cells. However, the most extensive clinical data exist for benfotiamine used for the treatment of painful peripheral diabetic neuropathy. Here we can discern between alleviation of symptoms (assessed by symptoms scores) and morphological effects that can be assessed by clinical or computer assisted measurements culminating with the assessment of nerve conduction velocity. A short-duration therapy (6 weeks) with a high dose of ben-

fotiamine (600 mg/day) is superior to 300 mg/day for the alleviation of neuropathic symptoms. Within this time frame, the symptom "pain" can be best influenced; a decreasing influence on other symptoms occurred in that study: numbness, burning and paresthesia.

Why benfotiamine works so well on acute neuropathic pain may be partly explained by a very elegant study by Bierhaus and co-workers recently published in Nature Medicine. They have shown that methylglyoxal, an AGE precursor, depolarizes sensory neurons and induces post-translational modifications of the voltage-gated sodium channel, which are associated with increased electrical excitability and facilitate firing of nociceptive neurons. They have also suggested that several strategies that include a methylglyoxal scavenger are effective in reducing methylglyoxal- and diabetes-induced hyperalgesia. Therefore, one possible explanation why benfotiamine reduces painful symptoms even after short-term therapy is that it blocks the synthesis of AGE and their precursors like methylglyoxal.

Nowadays, the antioxidant alpha-lipoic acid is considered as the most powerful form of pathogenetically oriented treatment for diabetic neuropathy. Some thousands of clinical studies using alpha-lipoic acid have been performed by now, several of them were randomized, placebo controlled, multicenter trials. Short term treatment with daily 600 mg alpha-lipoic acid i.v. for 3 weeks reduces chief neuropathic symptoms including pain, paresthesia and numbness while improvement of neuropathic deficit has also been documented. Short term oral treatment reduces key neuropathic symptoms including pain and improves neuropathic deficit while long term oral treatment improves motor and sensory nerve conduction velocity in the lower limbs just as cardiovascular autonomic neuropathy. In diabetic patients with severe polyneuropathy, iv. administration of 600 mg/day alpha-lipoic acid is suggested for 5-15 days followed by oral treatment with 600 mg daily. The same dosage is indicated for patients starting with oral therapy. It should be emphasized that pathogenetically oriented therapy with alpha-lipoic acid has a documented effect on pain and other symptoms of neuropathy as well. In conclusion, alpha-lipoic acid is effective for treatment of autonomic and peripheral neuropathy in diabetic patients and is characterized by a highly favourable safety profile.

A combination therapy of benfotiamine and alpha-lipoic acid was also suggested to normalize complications-causing pathways in type 1 diabetes patients.

The use of symptomatic agents is associated with pain relief and improvement of quality of life, while the progression of neuropathy is not affected. Gabapentin, pregabalin and duloxetine are considered as the most powerful modern symptomatic agents. It should be noted, however, that all three agents have a wide-spread side effect profile. Interestingly, originally gabapentin and pregabalin were used as anticonvulsive agents, while duloxetine as an antidepressant drug.

Multidisciplinary approach of diabetic neuropathy

The results of the EURODIAB Complications Study unequivocally confirmed the relationship between traditional cardiovascular risk factors and peripheral neuropathy. We have shown that traditional cardiovascular risk factors (smoking, hypertension, and serum cholesterol) should be considered as potential risk factors for development of neuropathy even in newly diagnosed type 1 diabetic patients. Intensified, multifactorial 8-year-long intervention in the Steno-2 study significantly reduced the risk of the development of CAN among patients with type 2 diabetes. Nevertheless there was no impact on the development of peripheral neuropathy. In the Steno 2 study the effect of a targeted, intensified, multifactorial intervention was compared with conventional treatment on risk factors for cardiovascular disease in patients with 2 type diabetes and microalbuminuria. In the study, the reductions in the risk of microvascular complications were similar either after 8 or 4 years, confirming the long term beneficial effects of multifactorial intervention on autonomic neuropathy. The results have considerable implication for the treatment of type 2 diabetes. An approach which was used by Steno 2 study should be offered to patients with type 2 diabetes who are at increased risk for microvascular and macrovascular complications. This treatment involves multifactorial intervention with continued patient education, motivation and strict targets as well as individualized risk assessment.

A message for Romanian doctors involved in diabetic neuropathy management

I think that the message to Romanian doctors should be identical as to that of Hungarian doctors: we should strive to achieve early diagnosis of diabetic neuropathy. This complication should be revealed even in patients without symptoms. I see many patients who were told that they should simply live together with their neuropathy, and that there is no powerful treatment. Fortunately, this is not valid. Optimal glycaemic control, treatment of risk factors, early pathogenetic treatment with benfotiamine and/or alpha-lipoic acid, as well as powerful symptomatic treatment, if necessary, might improve survival and quality of life of patients with diabetic neuropathy.

The challenge of diabetic neuropathy in 2013

Dr. Vilma Urbancic, Slovenia: "Unfortunately, the patients with sensory loss, but without neuropathic pain often don't understand the full scope of the problem and only realize the real meaning of their condition when they develop ulceration or gangrene"

Diabetic neuropathy is a frequent complication of long-standing diabetes. The data about its prevalence remains controversial both due to lack of good quality registries as well as due to the fact that the diagnostic criteria are not universally accepted and the methods used to make the diagnosis differ among centers.

Diabetic neuropathy plays a major role in the pathogenesis of diabetic foot ulceration. Insensate feet are prone to trauma which may go unnoticed due to the absence of pain. Motor neuropathy leads to foot deformity due to loss of muscle strength. Painful neuropathy has a tremendous adverse impact on the patient's quality of life and treatment is often unsuccessful.

It has long been recognized that early detection of sensory loss is crucial in the prevention of foot ulceration and gangrene. Although regular foot screening can prevent many disasters, it is still not universally performed. Unfortunately, the patients with sensory loss, but without neuropathic pain often don't understand the full scope of the problem and only realize the real meaning of their condition when they develop ulceration or gangrene.

The priorities in the management of diabetic neuropathy

Early detection is the most important part of the management of the patient with diabetic neuropathy. Once the diagnosis is made, much effort should be put in patient's education, focused on the possible risks due to neuropathy as well as on avoidance of other potential noxious factors (alcohol, smoking). All these patients should also be given advice on footwear and physical activity.

Symptomatic and pathogenic treatment of diabetic neuropathy

Diabetic neuropathic pain is a therapeutic challenge. First line drugs for symptomatic management – duloxetine and pregabalin may provide relief but may also have adverse effects or undesired interactions with other drugs; in addition they have no influence on the disease itself. On the other hand, pathogenic treatment of neuropathy with benfotiamine and/or alphalipoic acid has beneficial effect on the progression of nerve damage.

Dr. Vilma Urbancic support Neurodiab concept in Romania for 8 years

Multidisciplinary approach of diabetic neuropathy

The patient with diabetes often has many comorbidities and takes many medicines. It is therefore important to treat the patient as a whole and take into account all his diseases. Most often, close cooperation of various specialists is necessary – general practitioner, diabetologist, neurologist, vascular specialist.

Their activities should be well coordinated and the potential interactions of treatments carefully considered. Last but by no means least: we have to listen to the patient, get his message and establish an atmosphere of interaction, confidence and respect.

A message for the Romanian doctors involved in diabetic neuropathy management

Diabetic neuropathy is a challenge both for health care workers and patients. Early detection and proper treatment, both pathogenic and symptomatic, can save many feet as well as significantly improve the quality of life of these patients.

The Society for Diabetic Neuropathy was a wonderful development of the Neurodiab concept

About the management of diabetic neuropathy

Team work is the core of diabetic neuropathy management. Being a doctor means acting in favor of your patients and from my experience as senior neurologist I am aware that the issues of this disease are very difficult to approach, so it is essential to have a close collaboration with all the specialists involved in the diagnosis and treatment of a patient with diabetic neuropathy.

About the „small-world" network of neuropathic pain

When speaking about neuropathic pain, we should mention that prior to 1965, it was considered that pain emanate from activation of nociceptors, which initiated pain impulses that traveled through a spinal pathway to the brain. In 1965, Ronald Melzack and P. D. Wall elaborated gate control theory that consider brain as an active system that filters, selects and modulates inputs.

Following that, in 1989, R. Melzackdeveloped the neuromatrix theory of pain that consider that pain is a multidimensional experience produced by characteristic „neurosignature" patterns of nerve impulses generated by a widely distributed neural network - the „bodyself neuromatrix" - in the brain. These neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them.

The concept of body-self matrix that generates a bodyself neurosignature of pain has gradually been transformed into an empirically driven hypothesis using imaging data. It has been shown that various brain regions form a widely distributed network within this matrix.

The regions of pain neuromatrix are densely interconnected, and also have excitatory or inhibitory projections with the rest of the brain. Imaging studies demonstrated a strong relationship between chronic pain and dysfunctional connectivity across brain networks.

VISIT CARD

Prof. Dr. Dafin Mureșanu
is a Professor of Neurology, Head of Neuroscience Department at University of Medicine and Pharmacy "Iuliu Haţieganu" Cluj-Napoca, Romania, President of the Society of Neurology from Romania and founding member of the Society for Diabetic Neuropathy

In 2005, was provided the first quantitative demonstration that the brain can be characterized as a „small-world" network (also known as „six degrees of separation").

About the Society's activities – the First National Conference in Diabetic Neuropathy and Diabetic Foot

The Society for Diabetic Neuropathy was a wonderful development of the Neurodiab concept which becomes stronger by taking new shapes, always innovative, therefore, the first National Conference in Diabetic Neuropathy and Diabetic Foot was more than welcomed and legitimate.

This event, besides being a premiere, have brought the opportunity to discuss the complexity and gravity of diabetic neuropathy, learned and thus improved, by sharing experience and knowledge. Therefore, I am glad that I was part of the first National Conference in Diabetic Neuropathy and Diabetic Foot and I hope all participants found here the information they needed.

About the Society's activities – the summer schools

The desire to train and educate the young specialists in diabetic neuropathy field represents a strategic objective of Neurodiab summer schools, which are closely encouraged by leading personalities of the Romanian medical community.

I support with all my heart the educational activity of the Society for Diabetic Neuropathy, because I am convinced that only an interdisciplinary collaboration can ensure an efficient management of diabetic neuropathy. I am glad that we managed to bring into attention actual information based on the newest scientific data regarding the therapeutic approach of this severe condition.

It is important that we spend resources for a comprehensive training of the young generation of clinicians dedicating themselves to prevent, diagnose and treat diabetic neuropathy.

Dr. Alin Știrban – The Challenge Named Diabetic Neuropathy

Diabetic neuropathy is not "just a disease", it comes with a severe reduction of the quality of life and of life expectancy

Dr. Alin Știrban

Diabetic neuropathy in 2013

In the recent years we had huge advances in understanding the mechanisms underlying the onset of diabetic neuropathy. New diagnostic methods were also developed, such as cutaneous biopsy or confocal corneal microscopy. These methods allow us an early diagnosis of diabetic neuropathy, focusing on the density of small nerve fibers, because they seem to be the first affected by diabetic neuropathy.

As a consequence we would expect that the situation concerning the diagnosis and the treatment of diabetic neuropathy to be visible improved but, unfortunately, the situation is far from it. A population study conducted in Germany (Bongaerts et al., Diabetes Care, 2013) shows that 77% of the patients with diabetic neuropathy do not know they have the disease. Among the patients with clinically manifested diabetic neuropathy, 32% have never benefited of a foot investigation. These data give a very low rank to diabetic neuropathy diagnosis even in a country as Germany. If I'm indulged, I suppose the situation in Romania is not better. It seems that now, diabetic neuropathy occupies "two worlds": a scientific one and one of clinical reality. These "worlds" communicate insufficient between them and this is one of the major challenges in the following years. On one hand it is compulsory that the information exchange to be intensified in both directions (e.g. by scientific communications, but also by communications of clinicians for researchers concerning the problems they encounter). I believe that the scientific community must take more into account the clinical reality (that struggles between the lack of money and of time) and intensify its efforts to find methods less expensive (financial and of time) for diagnosis and treatment. But it comes here a third aspect: the political one. I believe there is most important that the diagnosis and the treatment of diabetic neuropathy to be recognized at a political level and the investigations to be paid according to their price. From what I've understood from my colleagues, in Romania this problem is insufficiently managed.

The activity of the Society of Diabetic Neuropathy in its first year of existence

The Society of Diabetic Neuropathy has been extraordinarily active in its first year and I hope that this tendency will be kept over the years. I also hope that in the following years we could get more involved in making the decision factors more aware concerning the diagnosis and the treatment of diabetic neuropathy.

Priorities in the management of diabetic neuropathy, in Romania and worldwide

An absolute priority is to improve the diagnosis of diabetic neuropathy (see data above). In this respect we must make aware not only our colleagues – to make a very simple test set, but also the patients to pay attention to some symptoms that may signal this disease. And this is because diabetic neuropathy is not "just a disease", but it comes with a severe reduction of the quality of life and of life expectancy. And everybody must understand this fact very clearly.

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VISIT CARD

Dr. Alin Știrban
Director of Profil Insitute for Metabolic Research GmbH. Specialist physician in Internal Medicine, Endocrinology and Diabetology. Member of the neuropathy workgroup of the German Diabetes Association.

The price we pay for civilization and for the lifestyle we chose

„Diabetes mellitus is a challenge for the medical community as long as it keeps its epidemic status"

Diabetic neuropathy is a challenge, being a progressive chronic condition accompanying diabetes mellitus type 2 and affecting approximately one third of the patients. However, from the epidemiological point of view, the statistics are very controversial because the reports on neuropathy are not always correct, this condition being in general much under diagnosed. Diabetes itself represents a challenge for the medical community as long as it keeps its epidemic status.

If we are to define diabetic neuropathy – and I'm not talking mainly about its purely medical definition, but about what it means in the general context of the diabetic patient – then we could say that it represents the affected condition of the peripheral and autonomous nerves that severely deteriorates the quality of life and exposes the patient to an increased vascular risk.

Unfortunately, almost all patients with diabetes present a form of neuropathy. The ACCORD study demonstrated this and changed the way the diabetic patient is approached, the presence of neuropathy being an important risk factor for cardiovascular disease.

The activity of the Romanian Society for Diabetic Neuropathy is dedicated to establishing the strategies for detecting and preventing diabetic neuropathy. It aims to bring together a multidisciplinary team joining professionals from all medical specialties so that its activities can reach vulnerable issues. Also, another priority is to increase the awareness regarding the challenge of neuropathy not strictly in the medical world, but also among patients.

This is not at all a simple task; it requires information and education materials for patients, and also for healthcare providers. The purpose of these endeavours is to increase the authorities' awareness and to find the necessary support to accomplish these objectives.

The eagerness to train and educate the young specialists is another main objective of this society, that took shape in a series of activities dedicated to the young physicians and we hope that they will continue, because all these have a practical purpose, with clinical cases, with the opportunity to voice the pros and cons, which we consider constructive and absolutely necessary in these young physicians' training.

Prof. Dr. Doina Catrinoiu

Family physicians will be also involved in these projects, taking into account the fact that they really are a link between the patient and the specialist. But, first of all, we will need training programs for them and also a very well established strategy. You can't win the war with a bad strategy.

Diabetes affects us all, directly or not, and this is the reason why, more than in any other specialty, collaboration is required. Professor Serano Rios said that "diabetes is the price we pay for civilization and for the lifestyle we chose". Nothing truer or sadder. Nevertheless, it is never too late for change, and the Society for Diabetic Neuropathy is determined to make it. We also have the fortune of having an expert in neuropathy, Conf. Dr. Ioan Vereşiu, who used to work in teams and to elaborate and implement efficient strategies, in the society's board. Our duty is to support him and we will do it with conviction.

Actualities in diabetic neuropathy management

Gabriela Radulian, Irina Sima

Over 371 million peoples were diagnosed with diabetes mellitus (DZ) in 2012, and the statistics show that their number might become double in 2030. The literature data varies, it is considered that 30% up to 50% of the persons with diabetes type 1 and 2 are affected by diabetic neuropathy. In many cases, the diabetic neuropathy is present since the diabetes diagnosis. Approximately 10% of the patients have obvious clinical signs of neuropathy when diabetes is diagnosed, but the percentage rise to 50% after 25 years of evolution of the diabetic disease. The percentage of those with painful neuropathy is reduced, of approximately 15% of total.

Diabetic neuropathy is the most common of the chronic complications of diabetes mellitus and implies the affection of the peripheral and/or autonomous nervous system. The diagnosis of peripheral neuropathy is based on symptomatology, anamnesis and physical examination. An electromyogram (EMG) and nervous conduction studies can be made in order to confirm the diagnosis.

The etiopathogeny of diabetic neuropathy includes multiple mechanisms (activation of polyol pathway, non-enzymatic glycation of proteins, increasing the oxidative stress, activation of hexosamines pathway, ischemia secondary to microangiopathy, changes in fatty acids and prostaglandins metabolism, the deficit of neurotrophic substances), which makes its treatment to be a complex one.

Diagnosing the diabetic neuropathy since the prediabetes stage is of major importance. The prevalence of neuropathy in IFG (impaired fasting glucose), in Germany – Augsburg, is of 9% (versus only 1% of the population with normal tolerance to glucose). IFG is linked with a higher prevalence, and if the patient presents with idiopathic neuropathy, it is recommended an oral test for glucose tolerance in order to confirm or to exclude the supposed prediabetes or diabetes. Also, the treatment for neuropathic pain in diabetes mellitus must be started as soon as possible. This treatment has as an objective not only the reduction of pain, but also the improvement of the quality of life and of sleep.

Regarding the risk factors, the most conclusive evidences plead for chronic hyperglycemia. It is well known that the onset and the progression of neuropathy are linked to the glycemic control in both types of diabetes. The duration and the severity of chronic hyperglycemia are correlated with neuropathy's severity.

Diabetic neuropathy and its consequences involve increased costs for medical care related to work incapacity and disability.

OVER 371 MILLION peoples were diagnosed with diabetes mellitus (DZ) in 2012, and the statistics show that their number might become double in 2030. The literature data varies, it is considered that 30% up to 50% of the persons with diabetes type 1 and 2 are affected by diabetic neuropathy

Prof. Dr. Gabriela Radulian

The management of diabetic neuropathy must begin in the moment the diabetes is diagnosed.

The mixed peripheral polydiabetic neuropathy, sensory and motor, is the most common form of nervous involvement in diabetes. It can be present as burning pain, tingles, prickles or numbness of feet and pareshesia, or as loosing the distal sensitivity and an increased risk of ulcerations and amputations.

The diagnosis of polydiabetic peripheral neuropathy is clinical (based on symptoms and signs) and involves the exclusion of other causes (vitamin B12 deficit, hypothyroidism, toxic/iatrogenic renal failure, HIV, vascular disease, loosing weight/cancer, syphilis). Advances were made in deciphering the pathogenic mechanisms and, consequently, in therapeutic interventions. Today we can also speak of a pathogenic treatment (alfa-lipoic acid and benfotiamine have confirmed effects in many studies), that may be associated to the symptomatic treatment. The specific patient education is also very important.

The autonomous/vegetative neuropathy has more forms: cardiac neuropathy (lowering of heart automatism variation, nocturne tachycardia, persistent and stable tachycardia; diagnosis – the absence of bradycardia at Valsalva maneuver, the absence of tachycardia in orthostatic position or at the isometric effort of hands), vascular neuropathy (orthostatic hypotension), sexual dynamics disturbances, bladder neuropathy (diagnosis – voiding cystourethrogram, ultrasonography), digestive neuropathy (gastroparesis, diabetic enteropathy).

The prevention, the early diagnosis and treatment of diabetic neuropathy represent a challenge for the professionals involved in the management of this condition, because its consequences are irreversible and in many cases disabling. The management of diabetic neuropathy includes therapeutical measures aiming the pathogenic mechanism and the symptomatic treatment, both available for the patients from our country.

Related to prevention, the most important challenge in diabetic neuropathy management is represented by the slowing of the nervous lesions progres-

sion from the moment they are diagnosed. The main and the most important way of preventing the nervous lesions progression is the adequate glycemic control.

The therapeutical measures aim prevention, pathogenic and symptomatic treatment, and their purpose is to improve the patients' quality of life. Pathogenic treatments are available, such as the anti-oxidative one using alfa-lipoic acid, the treatment of compensating the B1 vitamin deficit with benfotiamine, and also treatments related to pain management that, on one hand they act on the central nervous system, and on the other hand they relieve the pain and improve the quality of life.

The American Diabetes Association (ADA) recommends: glycemic and lipid control, avoiding smoking and excessive alcohol consumption, blood pressure control, regular exercises and maintaining a proper body weight, balanced diet. The specific education and special footwear are recommended. There are also recommended the avoidance of the risk factors for development/progression of diabetic neuropathy (glycemic imbalance, glycemic oscillations, smoking, increased alcohol consumption, a low socio-economic status, renal failure) or for neuropathic ulcerations (loosing the pain sensation, improper footwear, inappropriate hygiene, the lack of specific education, ulcerations or amputations in patient's history, diminishing of the vibration sensitivity).

In the same time it is recommended the screening for peripheral polyneuropathy when DM type 1 or 2 is diagnosed, and then on a yearly basis, using simple clinical tests. The screening for autonomous neuropathy is recommended in the moment of diagnosing DM type 2 and after 5 from the diagnosis of DM type 1. The screening of the peripheral neuropathy helps to prevent ulcers or amputations. ADA recommends that during each medical visit, the persons with diabetes should be seen by a physician trained in foot examination for lesions or peelings, excessive or reduced sweat, vesicles, ulcers or signs of infection, bone deformities or joints alterations, gait and equilibrium. ADA also recommends that this examination to be made at least once a year. During these visits it might be detected a reduced sensitivity of the foot that may lead to severe complications.

The purpose of the pathogenic treatment is to slow, to stop or to cancel the evolution and the progression of the diabetic neuropathy and to improve its signs and symptoms.

In Romania there are available two products from the category of "pathogenic treatments of peripheral polyneuropathy": alfa-lipoic acid and benfotiamine. Benfotiamine is a possible pathogenic treatment (it increases the transketolase activity, an enzyme that counteracts some of the consequences of the oxidative stress).

Benfotiamine, a precursor of vitamin B1 (thiamine) with a better bioavailability, is efficient in the treatment of diabetic neuropathy, reducing mainly the pain. A study led by Stracke et al. has shown that benfotiamine combined with the vitamins B6 and B12 improve the nerve conduction velocity, a very important functional parameter. Moreover, there are data showing that the patients with diabetes have a B1 deficit as a result of an increased renal clearance that cannot be compensated using dietary measures. The treatment with diuretics may also increase the renal thiamine loses.

There are numerous data showing – mainly on animal models – that benfotiamine is able to offer protection against the diabetes complications by reducing some mechanisms with cellular toxic effect. The preliminary clinical studies suggest that benfotiamine has also vascular protective effects, and other studies on thiamine suggest that it may slow the progression of diabetic nephropathy. The treatment must be adjusted for each patient, according to the symptoms' severity. The initial dose must be between 300 and 600 mg per day for at least four to 12 weeks, until symptoms improvement. The BENDIP study has shown the best results when using a dose of 600 mg/day. Later, the doses must be reduced to 150 – 300 mg/day. It is also important the fact that the safety profile of benfotiamine is very good, with very few side effects. The safety of using this compound is warranted by numerous studies of bioavailability and of protection against phenomena of glucotoxicity on neuronal and endothelial function. Recently published studies demonstrate that benfotiamine and alfa-lipoic acid might be used successfully as a useful combination in the causative, pathogenic treatment of diabetic neuropathy. This combined treatment can normalize the initially increased AGE production, reducing to up to 40% the adverse effects on monocitary proteins due to the activation of hexosamine pathway and to normalize the prostaciclins sinthesis, substances with an essential role in vasodilatation (Brownlee et al.).

In the symptomatic treatment there are also included the metabolic balancing, the avoidance of the extreme glycemia fluctuations (being proved by studies that a proper glycemic control can prevent over 50% of the diabetic neuropathy cases), non-steroidian anti-inflammatory drugs, antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and noradrenalin reuptake inhibitors - duloxetine), anticonvulsivants (gabapentin, pregabalin, carbamazepine), opioides (tramadol, oxicodone) or antiaritmics (lidocaine). Among them, duloxetine and pregabalin are considered as first line symptomatic treatment. In any stage non-pharmacologic treatments, topical or physical, might be added: acupuncture, local aplications (capsaicine, isosorbide-dinitrate, lidocaine), patches.

Diabetic neuropathy is the most common form of neuropathy in developed countries and is responsible for 50 up to 75% of the non-traumatic amputations. Although this type of complication is difficult to evaluate and to treat, the early diagnosis is extremely important.

The Diagnosis of Diabetic Neuropathy: Challenges and Standardization

We need a "gold standard" in early diagnosis of neuropathy as well

Diabetic neuropathy is a composite of phenotypes in a non-linear, progressive, chronic evolution. Approximately a third of the diabetic patients will have signs of distal peripheral diabetic neuropathy. The classic form, the most common, is the distal one, which is distal, symmetrical and sensorimotor. Because the asymptomatic cases can be encountered in up to 50% of the patients, they have an increased risk of foot sufferance. The ulcerations and then non-traumatic amputations make diabetic neuropathy a redoubtable medical challenge.

In diagnosing diabetic neuropathy, we often speak about a "golden standard". It is defined as the widely accepted procedure as the best available examination for determining the status of a condition. But, in this case, the polymorphism of diabetic neuropathy – both somatic and autonomous – does not allow the uniqueness of standardization.

The nerve conduction study is the examination that confirms the diabetic neuropathy; it is not a diagnostic test. The sufferance of the large nerve fibers confirms an already advanced stage, with clinical symptomatic neuropathy, and that means that the patient misses the opportunity of being diagnosed early. We need a "gold standard" in early diagnosis of neuropathy as well.

The cornea is the most innervated structure of the human body, by the ophthalmic branch of trigeminal nerve, via cilliar anterior. The corneal confocal microscopy is an excellent surrogate candidate as a new standard in order to respond to this need for early diagnosis. It has obvious advantages – it is reproducible and feasible. More than electroneurography, it reflects the decline of the small nerve fibers, and its level is correlated with the onset of the future neuropathy. It is a promising early marker.

In fact, the autonomous neuropathy might involve any system of the body. The most important associated complication remains cardiovascular autonomous neuropathy: negative prognosis, high mortality comparing to diabetic patients without autonomous involvement. Currently we use the time and frequency analysis for establishing the variability of the heart rhythm or of the baroreceptors sensitivity, early changes in the disease progression. The central structures responsible for the autonomous nervous system's activity are imbalanced and change their gluconeogenesis, angiotensin excretion with hypertensive effect, leading up to cardiac hypertrophy.

Bogdan Florea, M.D., primary physician, neurology, UMF Cluj-Napoca, Imogen Research Center

Sural nerve biopsy is limited to two puncture sites and offers little information on small fibers. Punch biopsy of the skin offers details, but here there are also included the autonomic innervation.

The paper presented during the national conference brings pros and cons for each of the diagnosis and confirmation methods mentioned.

NEURODIAB
Society for Diabetic Neuropathy

Therapeutic education - a priority in preventing and controlling diabetic neuropathy

Today we can't conceive of an efficient management of diabetic neuropathy that wouldn't also include structured education programs, a fact scientifically proved by interventional studies that used this type of programs

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VISIT CARD

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Peripheral diabetic neuropathy is, without a doubt, the most frequent complication of both type 1 and type 2 diabetes mellitus. Uncontrolled, it leads to a decreased quality of life because of the pain symptoms and also to an increased risk of ulcerations and amputations if it is associated with the decrease or the absence of protective sensitivity. On the other hand, in diabetic neuropathy we may also encounter various forms of vegetative involvement, also associated with a decreased quality of life as a result of the distress of the digestive tract, of the cardiovascular or genitourinary systems.

The efforts of the caring system for patients with diabetes mellitus are often directed to the identification, treatment and monitoring of diabetic neuropathy, a course of action that also involves significant costs, especially when it is necessary to treat its complications, a worthy enemy being the one related to ulcerations and amputations. All these actions require an efficient interdisciplinary collaboration, that also involves, among diabetologists, physicians from other specialties such as neurologists, family physicians, surgeons, cardiologists.

Establishing a scientific society, such the Society for Diabetic Neuropathy, integrating physicians of specialties involved in the complex management of diabetic neuropathy, is a valuable initiative, which surely brings a plus of professionalism and efficiency in this area, as it has already been demonstrated by the actions organized in the first year of the society's activity.

One of the well known priorities in the management of diabetic neuropathy is therapeutic education. The persons with diabetes must be taught what are the first signs of diabetic neuropathy, what are the measures meant to prevent it, how the feet must be cared for in order to prevent complications, what are the available treatments and how they must be used, and all these – obviously, under a physician's supervision and with the help of nurses specialized in education.

The Society for Diabetic Neuropathy, in a partnership with the Romanian Association for Education in Diabetes, already organized a number of actions at the level of associations of persons with diabetes in the entire country, actions that were considered useful by the beneficiaries. We intend from now on to develop partnerships in this area of activity by increasing the number of persons with diabetes having access to the therapeutic education specific for neuropathy, and also by creating and providing informative materials on this topic.

Today we can't conceive of an efficient management of diabetic neuropathy that wouldn't also include structured education programs, fact scientifically proved by interventional studies that used this type of programs. Consequently, our common purpose is to offer for – as many as possible – persons with diabetes from Romania the opportunity to benefit of this therapeutic method, with the aid of the physicians and disciplinarian nurses experienced and interested in this field.

Diabetic neuropathy - whose problem is it, who and how manages it, and who can take charge?

The beneficiary of these answers will be at first and at last the persons with diabetes mellitus, and particularly those with diabetic neuropathy

Prof. Dr. Ioan Bocșan

● NORINA GÂVAN AND BOGDAN FLOREA initiated the Retrospective Analysis concerning the Quality of Life of Patients with Diabetic Neuropathy in Romania. Ioan S. Bocșan and Ioan A. Vereșiu joined the project

Diabetes mellitus remains one of the greatest problems of worldwide public health, involving the disease per se and also the individual and social impact of the condition and of its complications. This reality also exists in Romania.

Paraphrasing the famous collocation "rheumatism licks the joints and bites the heart", we may say that diabetes sweetens the blood and sours the life – both at individual and at population level. The diabetic neuropathy is one of the most perfidious complications of diabetes, taking into account its natural history and the perspectives of the afflicted, of the community – and not least – of the healthcare professionals caring for such a patient.

Both for the patient and for the physician, the early diagnosis of diabetic neuropathy is the fundamental desideratum. Likewise – this is a problem for the healthcare system that has to establish and apply a specific health policy – prophylactic and therapeutic – ultimately embodied in the organizational decision based on evidence and translated in human resources and available assets. In this respect, it is fundamental to acknowledge the magnitude of the phenomenon and of its particularities – if they do exist – in Romanian population.

Neurodiab – The Society for Diabetic Neuropathy – grew as a scientific society reacting to the necessities above mentioned that still are lacking a complete and satisfactory response. By the professional unrest of the clinicians, diabetologists and neurologists, stands the always active professional interest of the clinical epidemiology experts, in their attempt to find a more realistic answer to these questions – an answer that so far is only incomplete in the available statistics. The beneficiary of these answers will be at first and at last the persons with diabetes mellitus, and particularly those with diabetic neuropathy. The investigation made in this respect at a national level by a multidisciplinary team is globally one of the most comprehensive and is close to its completion. The results will show if there are national or regional particularities of casuistry and will provide solid bases for decisions or propositions in order to improve the existing situation of diabetic neuropathy.

Diabetic neuropathy and multidisciplinarity

"The Society for Diabetic Neuropathy chosed a difficult path, but hoping to accomplish this purpose: to expand the acknowledgement of diabetic neuropathy problem, a complication that deeply affects the quality of life for a patient with diabetes mellitus"

Dr. Julieta Cristescu
Primary Physician in Diabetes, Nutrition and Metabolic Diseases
Founding member of Neurodiab Society

NEURODIAB concept is one of management of specific training, of education of the physicians, patients and of all the people involved in what diabetic neuropathy in Romania means, and propose medical, scientific and professional training activities, having probative qualities and aiming the widening the material scientific basis for the development and study of diabetic neuropathy in Romania, promoting and supporting Romania's medical integration in European Union, and also offering medical services.

Thus, the Society for Diabetic Neuropathy chose a difficult path, but hoping to accomplish this purpose: to expand the acknowledgement of diabetic neuropathy problem, a complication that deeply affects the quality of life for a patient with diabetes mellitus.

The Scientific Symposium of Neurodiab: "Diabetic Neuropathy – Multidisciplinary Team", that was hosted by the National Congress of Neurology in Bucharest, May 2013, was an event appreciated by numerous participation and represented an confrontation of ideas and of establishment of scientific principles, being addressed to those who are responsible of the screening and the complex treatment of diabetes mellitus patients.

The participation of the diabetologists to the "Summer School of Neurology" during June – July 2013 at Eforie Nord, under the auspices of the International School of Neurology, is another involvement of the Neurodiab Society in the training of the youth for a complex approach of the diabetes mellitus' specific pathology.

The professional training of the multidisciplinary team in the medical assistance took another shape in the "Summer School" from Sinaia in July 2013, that already has become a tradition and that prepares – by lectures and workshops for residents – the future specialists both in diabetology and in neurology, cardiology, internal medicine, who will become those who will treat and (especially) will pass further the most adequate ways of correct approach of this complex pathology. It is thus ensured a modern prevention and treatment, complex and adequate for each complication, taking into account the fact that a glycemic control is very important but not sufficient if we do not detect and treat as early as possible the cardiovascular and neurological complications.

"The First International Conference in Diabetic Neuropathy and Diabetic Foot" that will take place in October 2013 in Bucharest, is a long and interested waited event for specialists, and also an opportunity favoring the analyses, the research and the clinical practice, but also the organization of new educational projects for specialists and patients, and it will be anteceded by numerous workshops in different towns in the country, with up to date topics from neuropathic pathology.

MEDICAL WATCH

THE MAIN TOPICS IN DIABETIC NEUROPATHY AT EASD 2013

49 EASD BARCELONA 2013

Brain atrophy correlated with the peripheral neuropathy in diabetic patients

A significant intracranial peripheral grey matter density reduction has been demonstrated in subjects with established diabetic peripheral neuropathy (DPN). This, which was localised to the sensorimotor cortex, suggests that DPN has significant impact upon the structural integrity and organisation of the brain. To explore how changes in brain volumes relates to DPN severity, researchers from the University of Sheffield selected fifty six patients with type 1 diabetes who underwent detailed clinical, neurophysiological assessments and also T1-weighted volumetric brain MR imaging at 3T. No-DPN subjects had significantly greater peripheral grey matter volume compared to Established-DPN ș632.1 vs 606.0 ml; p=0.01). Cortical atrophy was localised to postcentral gyrus, precentral gyrus and cerebellum. Adjusting for age, height, weight and HbA1c, higher peroneal nerve conduction velocity was associated with larger peripheral grey matter volume (R=0.41; p=0.02). The amplitudes in both sural and peroneal nerves were not related to peripheral grey matter volume at a statistically significant level.

Source: D. Selvarajah, Impact of neuropathy severity on brain volume loss in diabetic peripheral neuropathy, EASD Virtual Meeting 2013

Fertility restoration in patients with type 1 diabetes mellitus and autonomic neuropathy

Retrograde ejaculation (RE) in patients with type 1 diabetes mellitus (DMT1) is a complication of the autonomic neuropathy, complicated by excretory infertility. RE can be partial and total and it varies from 10% to 20% in men with type 1 DM. The aim of the study carried by researchers from Endocrinological Research Center, Moscow, Russian Federation is to assess the effectiveness of a new endoscopic method of RE correction.

10 Type 1 DM patients, age of 25,7±6,1 years with total RE recruited, diabetes duration - 19±9,6 ys. Mean level of HbA1c before operation 7,1±1,3%. All patients presented spermatozoa presence in post-orgasmic urine and the disclosure of bladder neck on ultrasonography.The patients were subjected to conventional irrigated urethrocystoscopy under local anesthesia, biocompatible material being injected under the mucous layer of posterior urethra, reaching the closing of the opposite edges of urethra. The spermogramm was examined in 1 week after the operation. After the intervention, restoration of antegrade emission of ejaculate was achieved at 9 out of 10 patients. The effect of operation maintained during: 6 months at 6 patients, 9 months at 2 patients and 12 months at 1 patient. Researchers conclude that the applying of this new method provides highly effective restoration of the physiological passage of the ejaculate. Endoscopic operation is a low-invasive and doesn't disrupt the urination.

Source: Y. Shwarts, New technologies of fertility restoration in patients with type 1 diabetes mellitus and an autonomic neuropathy, EASD Virtual Meeting 2013

Distal arterial calcification associated to diabetic neuropathy

Medial arterial calcification is common in diabetes mellitus (DM) and is an independent risk factor for major amputation, cardiovascular and all-cause mortality. Researchers from Endocrinology Research Centre Moscow, Russian Federation aimed to assess quantitatively tibial arterial calcification (TAC) and CAC in patients with DM and to correlate the extent of calcification with the presence and severity of DPN and CAN.

Nerve function was assessed and calcium scores were determined in 85 patients. Patients with DM2 had significantly higher CAC scores than DM1 patients (p=0,007) with no difference in TAC scores. Significant correlation was found between TAC and CAC scores (r=0,4, p<0,0001). The severity of CAC also correlated with vibration threshold (r=-0,3, p<0,006). In 60% of patients with TAC scores>1000 CAN was diagnosed, but there was no significant association between the quantity of TAC and CAC scores and the presence of CAN.

The authors conclude that no association between autonomic neuropathy and artery calcification was found. Medial artery calcification is strongly associated with DPN and coronary calcification. These data suggest that DPN might be an independent cardiovascular risk factor.

Source: N. Molitvoslovova,

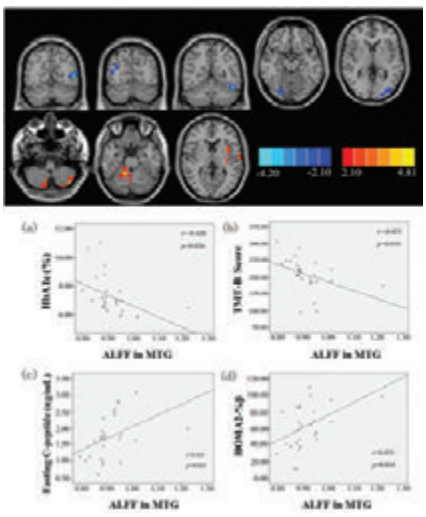
Association between distal arterial calcification and diabetic neuropathy in diabetes mellitus, EASD Virtual Meeting 2013

Neuronal loss in the rostroventromedial medulla of streptozotocin-diabetic rats

It has been reported a significant increase in oxidative stress damage in the rostroventromedial medulla (RVM), a key brainstem area involved in serotoninergic descending pain modulation, in the streptozotocin (STZ)-diabetic rat. Such damage may impair serotonin-mediated pain inhibition and explain the low analgesic efficacy of serotonin-selective reuptake inhibtitors (SSRIs) in diabetic neuropathic pain. The present study evaluated the effects of a treatment with epigalocathechin gallate (EGCG), a potent antioxidant present in green tea, in oxidative stress damage, neuronal density and number of serotoninergic neurons at the RVM of STZ- diabetic rats.
Diabetes was induced in male Wistar rats by intraperitoneal injection of STZ (60 mg/kg). During the 10 weeks post-injection, a group of STZ rats received EGCG (2g/l) in drinking water while the other experimental groups received only water (untreated-STZ and CTR). All STZ rats developed hyperglycemia, which was not affected by EGCG treatment. EGCG ameliorated the mechanical hyperalgesia and tactile allodynia. The untreated-STZ rats presented increased oxidative stress damage and decreased neuronal density at the RVM which was accompanied by a reduction in the number of serotoninergic neuron. EGCG treatment prevented those changes. EGCG could be a promising agent in preventing diabetes-induced neurodegeneration and pain.
Source: C. Morgado, Diabetes induces neuronal loss in the rostroventromedial medulla of streptozotocin-diabetic rats: the preventive effects of antioxidant treatment, EASD Virtual Meeting 2013

Altered baseline brain activity in type 2 diabetes

Type 2 diabetes mellitus (T2DM) has been associated with cognitive impairment, such as mild cognitive impairment (MCI) and Alzheimer's disease (AD). A recent study aimed to investigate whether there exists altered baseline brain activity in T2DM patients using resting-state functional magnetic resonance imaging (rs-fMRI).
28 T2DM patients were compared with 29 nondiabetic age-, sex-, and education-matched control subjects, using rs-fMRI. Compared with healthy controls, T2DM patients had significantly decreased low-frequency fluctuations (ALFF) values in bilateral middle temporal gyrus (MTG), left fusiform gyrus, left middle occipital gyrus, right inferior occipital gyrus; and increased ALFF values in both cortical and subcortical regions, including the bilateral cerebellum posterior lobe, right cerebellum culmen, and insula lobe. Moreover, we found an inverse correlation between the ALFF values in the middle temporal gyrus and both the HbA1c and the score of Trail Making Test-B in the patient group.
This study provides evidence that T2DM patients have altered ALFF in many brain regions, which may be regarded as a potential marker to identify cognitive decline associated with T2DM.



Source: W. Xia, Altered baseline brain activity in type 2 diabetes: a resting-state fMRI study, EASD Virtual Meeting 2013

Reduced cutaneous Langerhans cell number, endothelial area and nerve fibre density in type 2 diabetic subjects

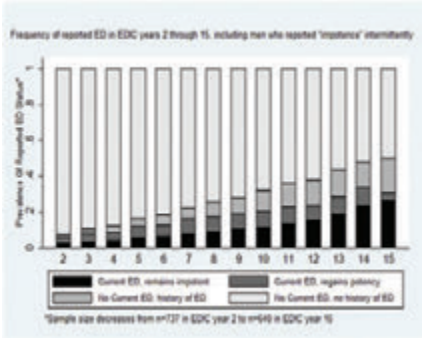
Langerhans cells (LCs) are the first antigen-presenting cells exposed to pathogens at the skin surface that play a pivotal role in the regulation of cutaneous immunity, exert tolerogenic properties, and are surrounded by sensory nerve endings. Researchers aimed to determine whether cutaneous immune-mediated and neurovascular alterations are present in recently diagnosed type 2 diabetes.
Skin biopsies and peripheral nerve function were assessed in 97 participants of the German Diabetes Study (GDS) with recently diagnosed type 2 diabetes and 83 healthy controls. When compared to the control group, type 2 diabetic patients showed reduced intraepidermal nerve fibre density, peroneal motor nerve conduction velocity, sural sensory nerve conduction velocity, and cold thermal detection thresholds on the foot as well as elevated malleolar vibration perception thresholds. Subepidermal endothelial area was smaller in the diabetic group compared to the control subjects. Moreover, a reduction of epidermal Langerhans cell number by approximately 30% was noted in the diabetic subjects compared to the control group.
Source: A. Strom, Reduced cutaneous Langerhans cell number, endothelial area and nerve fibre density in recently diagnosed type 2 diabetic subjects, EASD Virtual Meeting 2013

p66Shc mediates bone marrow denervation and impairs stem cell mobilisation in diabetes

Mobilization of bone marrow (BM) stem and proangiogenic cells is impaired in diabetes, contributing to chronic complications.
Researchers tested whether p66Shc, a life-span regulating gene linked to oxidative stress, is involved in the diabetic stem cell mobilopathy.
p66Shc gene expression was quantified in peripheral blood mononuclear cell of 20 diabetic patients and of 20 non diabetic persons. Expression of p66Shc was increased in peripheral blood mononuclear cell of diabetic patients, especially in the presence of diabetic autonomic neuropathy. In addition, BM cells from mice with streptozotocin induced diabetes showed increased p66Shc expression compared to controls. Diabetic mice showed reduced tyrosine hydroxilase immunoreactive nerve fibers and impaired stem cells and endothelial progenitor cells mobilization. The functional role of p66Shc was tested using p66Shc-/- mice which, once made diabetic by streptozotocin injection, showed preserved Tyr-OH immunostaining of sympathetic nerve fibers. In addition, induction of diabetes in p66Shc-/- mice did not impair stem cells and endothelial progenitor cells mobilization, despite they were as hyperglycaemic as wild type STZ mice.
The authors conclude that the deletion of p66Shc, by preserving BM sympathetic innervation, restores stem cell mobilization in diabetes. This can exert a protective effect against the development of complications.
Source: G. Fadini, p66Shc mediates bone marrow denervation and impairs stem cell mobilisation in diabetes, EASD Virtual Meeting 2013

Factors associated with reversibility of erectile dysfunction in men with type 1 diabetes

Diabetes imparts a 3-fold higher risk of erectile dysfunction (ED), which is associated with neuropathy, glycaemic control, microvascular complications, and duration of diabetes. Within Epidemiology of Diabetes Interventions and Complications (EDIC) study, which followed 720 subject with diabetes, ED was defined as a "Yes" response to a yearly single yes/no question querying the presence of "impotence". Subjects were classified as regaining potency if they answered "No" (absence of impotence) at any point during the five years following the index ED report.
Mean age of subjects at the most recent assessment was 50.4 years. The incidence of ED increased from 5.5% at EDIC year 1 (1994) to 33.6% (n=219) by EDIC year 16 (2009). The majority of men reported ED at least once during the 16 years of follow up (53.5%). The likelihood of regaining potency within 5 years decreased with every additional year of prior reported ED: for subjects with a single report of ED, 67.7% regained potency within 5 years; with 2 consecutive years of ED 50.7% regained potency; with 3 consecutive years of ED, 37.5% regained potency; with 4 consecutive years of ED, 32.9%; those with 5 or more consecutive years of ED had less than 20% subsequent chance of regaining potency. A1c and age were significantly associated with regaining potency only in subjects with four or less consecutive years of ED.



Source: S.K. Holt, Factors associated with reversibility of erectile dysfunction in men with type 1 diabetes: longitudinal findings from DCCT/EDIC, EASD Virtual Meeting 2013

QTc prolongation, indicator of mortality after above ankle amputation

Diabetic patients have not only an increased lower extremity amputation risk as compared to non-diabetic individuals, but also an enhanced mortality risk after above ankle amputation. Heart rate corrected QT interval (QTc) interval prolongation is a potential indicator of increased cardiovascular risk in the general population, but also in patients with chronic diabetic foot ulcers.
In a study that evaluated 66 patients with type 2 diabetes, with a median age of 72 years, QTc prolongation (QTc+ group) was present in 31 patients (47%) and not present in 35 (QTc- group). There were no differences in smoking habits, diabetes medications, dyslipidemia, hypertension, dialysis or previous vascular surgical interventions between groups. A history of myocardial infarction was more commonly present in the QTc+ group; 50 vs. 30%, p=0.04. Three-year mortality was 51.5%, being significantly higher in patients with QTc-prolongation, 67% vs. 27%, p=0.002. In a cox-proportional hazard analysis including presence of myocardial infarction, renal function, age, HbA1c and QTc-prolongation, only age (decades) (HR 2.1, p=0.049) and QTc prolongation (HR 3.4, p=0.007) were significantly associated with 3-year mortality. A history of myocardial infarction was not a significant risk factor in this analysis, HR 1.2, p=0.70.
Source: K. Fagher, QTc prolongation is associated with three-year

mortality after above ankle amputation in type 2 diabetic patients, EASD Virtual Meeting 2013

Associations between postural hypotension and neuropathy in type 2 diabetes

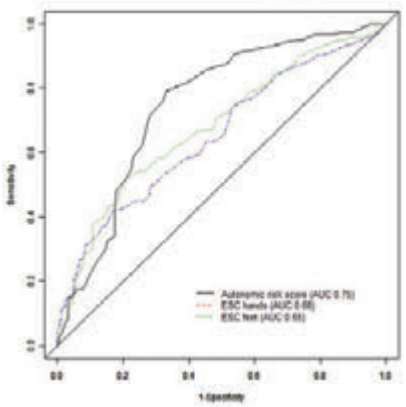
Due to its association with mortality, it has been recommended that autonomic function be assessed at diagnosis of type 2 diabetes and then annually. A simple surrogate of autonomic dysfunction is orthostatic hypotension (OH). Australian researchers studied 417 unselected type 2 patients from the Fremantle Diabetes Study Phase II who underwent assessment of autonomic neuropathy. OH was defined as a fall of ≥20 mm Hg systolic or ≥10 mm Hg diastolic blood pressure on standing. Two of the methods that evaluated the autonomic neuropathy were the 30:15 Stand test (R-R interval at beat 30/R-R interval at beat 15 on standing) and EZscan which generates autonomic risk scores based on sudomotor function.
The mean age of the patients was 65.8 years, 54.2% were male, their median diabetes duration was 10.0 years and 26.3% had OH. In logistic regression, OH was independently associated with supine systolic blood pressure (OR 1.28, 95%CI, P<0.001 for a 10 mm Hg increase), diabetes duration (OR 1,21, P=0,012 for a 5-year increase), 30:15 Stand test (OR 0.35, P=0.007), and the EZscan autonomic risk score (OR 0.97, P=0.011).
Authors conclude that OH is a manifestation of complex dysfunction of parasympathetic and sympathetic systems, and EZscan, a quick and simple procedure, can contribute to prediction of cardiovascular autonomic dysfunction independently of conventional heart rate-based tests.
Source: T.M.E. Davis, Associations between postural hypotension and neuropathy in type 2 diabetes: the Fremantle Diabetes study phase II, EASD Virtual Meeting 2013

OPG, RANKL, RANK genes polymorphisms in diabetic Charcot neuroosteoarthropathy

The etiology of Charcot neuroosteoarthopathy (CN) is not fully understood but it involves interaction of several factors including abnormalities in bone metabolism. It is likely that the cytokines of RANK, RANKL and OPG pathway may contribute to the pathogenesis of osteolysis in Charcot foot.
A total of 237 subjects: 64 Charcot neuroosteoarthropathy patients, 44 diabetic patients with neuropathy, 34 diabetic patients without neuropathy and 95 healthy controls were genotyped for 5 different single nucleotide polymorphisms (SNP) within the OPG gene, two polymorphisms in RANK gene and three polymorphisms in RANKL gene. ELISA was used to determine serum levels of OPG and RANKL proteins.
Statistically significant differences between the group of subjects with neuropathy but no Charcot neuroarthropathy and the control group were found only for T245TG (rs3134069) polymorphism in OPG gene. Previous observation of the association of Charcot neuroosteoarthropathy with C1217T(rs3102734) polymorphism in OPG gene were not confirmed. There was no significant correlation between studied RANKL gene polymorphisms. With respect to serum OPG concentration statistically significant differences were found only between the patients with neuropathy (N) in which OPG levels were higher and the group with diabetes and no neuropathy (D). Biochemical analysis showed increased levels of RANKL protein in blood serum in patients with neuropathy but not in patients with Charcot's arthropathy.
Source: A. Korzon-Burakowska, Osteoprotegerin, RANKL, RANK genes polymorphisms in diabetic Charcot neuroosteoarthropathy, EASD Virtual Meeting 2013

Assessment of sudomotor function as a screening tool for microvascular complications in type 2 diabetes

Sudomotor dysfunction is one of the earliest abnormalities to manifest in distal small fiber neuropathy. SUDOSCAN is a non invasive, quick, simple and quantitative method to measure sweat function, as a screening tool for microvascular complications in type 2 diabetes.
309 patients were evaluated for microvascular complications including peripheral neuropathy, nephropathy and retinopathy. Small C-fiber status was assessed through sudomotor function by measurement of hand and foot Electrochemical Sweat Conductance (ESC) and calculation of an autonomic risk score using SUDOSCAN.
The results of the study showed that hand and foot ESC were lower in patients with at least one microvascular complication as compared to patients without (49 ± 20 vs 62 ± 17 µS, p <0.001 and 59 ± 21 vs 69 ± 15 µS, p<0.001 respectively). Sensitivity and specificity of autonomic risk score using 35% as a threshold were 82% and 61% respectively.
Authors conclude that, based on this study, SUDOSCAN could be used for the screening of



microvascular complications in type 2 diabetes and may aid in adhering to follow-up guideline recommendations.

Source: V. Eranki, Assessment of sudomotor function as a screening tool for microvascular complications in type 2 diabetes, EASD Virtual Meeting 2013

Prevalence and risk factors of cardiac autonomic nerve dysfunction in elderly patients with diabetes and prediabetes

The population-based KORA (Cooperative Health Research in the Region of Augsburg) S4 survey included 2656 subjects aged 55-74 years, who were living in the region of Augsburg, Germany. Of these, 1332 subjects were included in a study that aimed to determine the prevalence and risk factors of cardiac autonomic nerve dysfunction in the elderly population with diabetes and prediabetes using a comprehensive set of parameters of heart rate variability (HRV) and QT variability index (QTVI).

The prevalence of the most sensitive individual HRV parameters was: for patient with known diabetes - 12-17%, newly detected diabetes: 12-14%, combined impaired fasting glucose and impaired glucose tolerance - 9-10%, isolated impaired glucose tolerance - 2-9%, isolated impaired fasting glucose - 7-10%, and normal glucose tolerance - 4-5%.

Most important risk factors for reduced HRV were heart rate, age, BMI, waist circumference, serum creatinine, hypertension, HbA1c, and medication with known adverse influence on HRV, while for increased QTVI reflecting increased sympathetic activity these were age, hypertension, low physical activity, percentage body fat, and the metabolic syndrome. A simple risk score to predict low HRV in clinical practice comprised heart rate, age, hypertension, serum creatinine, and medication suppressing HRV.

Source: D. Ziegler, Prevalence and risk factors of cardiac autonomic nerve dysfunction in the elderly population with diabetes and prediabetes: the KORA S4 survey, EASD Virtual Meeting 2013

Serum osteoprotegerin levels, associated with peripheral neuropathy

Serum OPG levels are increased in patients with PN and are associated with the presence of PN irrespective of age, diabetes duration, gender, smoking, BMI, dyslipidemia and peripheral arterial disease (PAD) status. This is the conclusion of a recent study that included 71 patients with type 2 diabetes (T2DM).

Patients with peripheral neuropathy PN (n=39) had significantly higher serum OPG levels in comparison with those without PN (744.8±296.2 vs 555.8±165.5 pg/ml). OPG levels were significantly associated with indices of PN, such as neuropathy disability score (NDS) (r=0.390, p<0.001) and vibration perception threshold (VPT) (0.412, p<0.001). Univariate logistic regression analysis showed that age (p=0.026), diabetes duration (p<0.001), male gender (p=0.003), smoking (p=0.004), BMI (p=0.024), dyslipidemia (p<0.001), presence of PAD (p<0.001) and OPG levels (p<0.001) were significantly associated with PN. No significant associations were found with HbA1c and arterial hypertension. Multivariate logistic regression analysis demonstrated that PN was associated significantly with diabetes duration (OR 1.01, 95%CI, p=0.023), smoking (OR: 8.2, 95% CI, p=0.019), dyslipidemia (OR: 4.3, 95% CI, p=0.007), presence of PAD (OR: 3.0, 95% CI, p=0.023) and OPG levels (OR: 1.0, 95% CI, p=0.007).

Source: I. Eleftheriadou, Serum osteoprotegerin levels are associated with peripheral neuropathy in patients with type 2 diabetes, EASD Virtual Meeting 2013

Autonomic neuropathy predicts severe hypoglycaemia in patients with type 2 diabetes mellitus

The development of severe hypoglycaemia was independently associated with autonomic dysfunction in patients with type 2 diabetes, in a recent study performed on 955 subjects. SH was defined as hypoglycaemic episodes requiring hospitalization or medical care in an emergency department. The severity of AFT was classified using the AFT score.

During a median follow-up time of 9.5 years, the incidence of severe hypoglycaemia was 1.54 per 100 patient-years. The patients with severe hypoglycaemia were more frequently female, were older, had a longer duration of diabetes, and received more insulin and ACE inhibitor treatment. Poor glycaemic control, renal impairment, and diabetic microvascular complications also were more present in the group with severe hypoglycaemia at baseline. The Cox hazard regression analysis revealed that the development of SH was associated with an abnormal AFT score (normal autonomic function vs. mild autonomic dysfunction, hazard ratio 2.41, P = 0.005; normal autonomic function vs. moderate to severe autonomic dysfunction, HR 4.33, P < 0.001) in a univariate analysis. After adjusting for gender, age, duration of diabetes, estimated glomerular filtration rate, HbA1c, treatment of insulin and ACE inhibitor/ARB, severe autonomic failure predicts the development of severe hypoglycaemia (normal autonomic function vs. moderate to severe autonomic dysfunction, HR 2.43, P = 0.004), and a higher AFT score

Sunteți una din persoanele cu Diabet Zaharat?

Ce simt picioarele Dvs.?

WÖRWAG PHARMA

Nu este niciodată prea târziu să prevenim sau să întârziem apariția neuropatiei diabetice. Spuneți-i medicului Dvs. despre aceste simptome.

Acest material deține viza ANMDM nr. 32472E/29.09.2011

tends to have a higher risk of the development of severe hypoglycaemia (P for trend = 0.015).

Source: Y. Ahn, Diabetic autonomic neuropathy predicts severe hypoglycaemia in patients with type 2 diabetes mellitus: a ten-year follow up study, EASD Virtual Meeting 2013

Corneal confocal microscopy detects neuropathy in children with type 1 diabetes

Whilst we have readily available diagnostic techniques for retinopathy and nephropathy, there is no equally sensitive measure for diabetic neuropathy. This is why researchers from University of Manchester, UK, aimed to assess the utility of in vivo corneal confocal microscopy (IVCCM) in identifying early nerve damage in children with type 1 diabetes.

25 children with type 1 diabetes mellitus (average age: 13±1 yrs; average duration of diabetes 8 years) with no evidence of retinopathy or microalbuminuria and 10 aged matched control subjects underwent assessment with IVCCM to quantify corneal nerve fibre density (NFD), branch density (NBD) and length (NFL). There was a significant reduction in NFD (32.5 ± 1.9/mm2 vs 41.1±1.8/mm2, P=0.007), NBD (50.6 ± 4.5/mm2 vs 72.5 ± 6.5/mm2, P=0.008) and NFL (20.6 ± 0.9 mm/mm2 vs 29.4 ±1.3 mm/mm2, P<0.0001) in children with T1DM versus control subjects. Even in patients with better glycaemic control (HbA1c-7.9±0.14), NFD mm/mm2 (34.2 ± 2.4, P=0.07), NBD (51.9 ± 4.4, P=0.04), and NFL (21.3 ± 1.2, P<0.0001) were reduced compared to controls. Those with poorer glycaemic control (HbA1c=10.08±0.04) had a further non-significant reduction in NFD (27.3 ± 1.5, P=0.2), NBD (46.7 ± 13.0, P=0.8), and NFL (18.2 ± 1.4, P=0.3) compared to those with better glycaemic control.

In conclusion, corneal confocal microscopy provides a fast, non-invasive and well tolerated technique to detect early nerve damage which precedes retinopathy and microalbuminuria.

Source: M. Tavakoli, Corneal confocal microscopy detects neuropathy before retinopathy and nephropathy in children with type 1 diabetes: a preliminary study, EASD Virtual Meeting 2013

Circulating microRNAs and micro/macrovascular complications of type 1 diabetes

MicroRNAs (miRNAs) are critically involved in many biological processes and there is preliminary evidence of a role of miRNAs in cardiovascular diseases and diabetic complications. Researchers from University of Turin, Italy, performed a cross-sectional nested case-control study from the EURODIAB Prospective Complications Study. A total of 531 DM1 patients, diagnosed at <36 years of age, were studied. Cases were defined as those with one or more complications of diabetes and control subjects were those with no evidence of any complication. MiRNA expression profiling identified 41 miRNAs expressed in pooled serum samples from DM1 patients. Among them 25 miRNAs were differentially expressed in DM1 patients with micro/macrovascular complications. The difference in miRNA expression between cases and controls was 2 to over 20 fold, depending on the type of miRNAs.

These results show that miRNA are detectable in serum samples from DM1 patients and that the expression of circulating miRNAs differs in DM1 with and without vascular complications.

Source: F. Barutta, Circulating microRNAs and micro/macrovascular complications of type 1 diabetes, EASD Virtual Meeting 2013

Long-term effect of quinapril or losartan or their combination on diabetic autonomic neuropathy and left ventricular function

Sixty patients with diabetic autonomic neuropathy (DAN), randomly allocated in 3 groups (A-24 patients receiving 20 mg quinapril, B-18 patients receiving 100 mg losartan, C - 18 patients receiving 20 mg Q +100 mg L) were followed for a 4 years period. The presence of DAN was established if 2 or more of the 4 Cardiovascular Reflex Tests (CRT) were abnormal and analyzed with Mean Circular Resultant (MCR), Valsalva index (VALS), 30:15 ratio (POST) and postural hypotension (HYPO).

In all groups, improvement was observed after 4 years of treatment in MCR (A, 16.9± 5.6 vs 29.4± 15.6, p= 0.007, B, 17.3± 9.2 vs 27.2± 17.5 p=0.014, C, 12.9± 10.0 vs 23.0± 13.9, p<0.001). In group C, a decrease in Systolic and Diastolic Arterial Pressure was observed at 4 years (142.3±23.7 vs 129.2.0±15.2, 83.2±8.8 vs 77.0±7.9, p<0.05 respectively). In group A, a decrease in atrial contribution to ventricular filling was observed (24.4±8.7 vs 20.6±7.3, p<0.05). The rest of CRT and radionuclide ventriculography indices were not significantly changed over base line values in 4 years. Heart Rate and HbA1c did not change significantly.

DAN improved after four years of treatment with quinapril, losartan, or their combination. No

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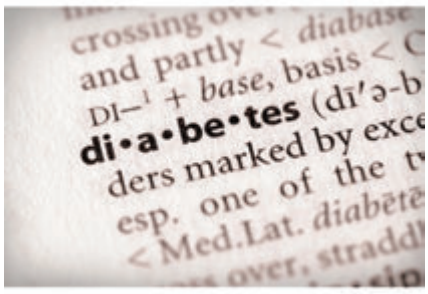
deterioration was observed in systolic and diastolic left ventricular function except for group A. Improved autonomic balance and no decline of left ventricular function may be of clinical importance in long-term prognosis of DM patients.

Source: T.P. Didangelos, Long-term effect of quinapril or losartan or their combination on diabetic autonomic neuropathy and left ventricular function over a period of 4 years, EASD Virtual Meeting 2013

Amelioration of neuropathic changes with in diabetic rats treated with vildagliptin

Recently, insulin resistance in the peripheral nerve has been proposed to contribute to the pathogenesis of diabetic neuropathy (DN) and may be a novel therapeutic target. The researchers investigated whether the treatment with DPP-IV inhibitor, vildagliptin (VG), is beneficial for neuropathy in type 2 diabetic model, Goto-Kakizaki rats (GK).

GK were divided into 3 groups; untreated, treated with restricted diet (diet group), and treated with vildagluptin. VG-treatment suppressed hyperglycemia and corrected serum level of insulin and GLP-1 in GK ($p<0.01$). Diet on GK also suppressed hyperglycemia to the extent similar to that in VG-treated GK, improved serum insulin, but not GLP-1. Both motor and sensory nerve conduction velocities were significantly delayed in GK. VG treatment on GK improved both nerve conduction velocities near normal levels, but the improvement was equivocal in diet-GK. RT-PCR disclosed an expression of GLP-1 receptor-mRNA in dorsal root ganglia, but not in sciatic nerve, and western blot revealed its protein in both dorsal root ganglia and sciatic nerve. Excessive phospho-serine residue of IRS2, as a marker of insulin resistance was demonstrated in GK, and was normalized in VG-treated GK.



Source: K. Tsuboi, Amelioration of neuropathic changes with correction of nerve insulin resistance in diabetic Goto-Kakizaki rats treated with DPP-IV inhibitor vildagliptin, EASD Virtual Meeting 2013

Association of subclinical inflammation with polyneuropathy in the older population

Inflammatory processes have been implicated in the pathogenesis of distal sensorimotor polyneuropathy (DSPN), but their possible relationship has not been assessed at the population level. Therefore, a german study aimed to investigate whether circulating concentrations of seven pro- and anti-inflammatory immune mediators are associated with clinically diagnosed DSPN in older subjects from the general population.

Serum concentrations of mediators of subclinical inflammation were evaluated among 1047 participants aged 61-82 years from the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 study. The results of the study show that serum concentrations of the anti-inflammatory interleukin-1 receptor antagonist (IL-1RA) were positively associated with the presence of DSPN ($p=0.011$) and higher Michigan Neuropathy Screening Instrument (MNSI) scores ($p<0.001$) in age and sex-adjusted analyses, whereas IL-6, IL-18, and soluble intercellular adhesion molecule-1 (sICAM-1) were positively associated only with MNSI scores ($p<0.05$). No associations were observed for adiponectin, C-reactive protein (CRP) or tumour necrosis factor-α (TNF-α).

The authors conclude that DSPN is linked to proinflammatory and anti-inflammatory, possibly compensatory, processes in the older general population.

Source: C. Herder, Association of subclinical inflammation with polyneuropathy in the older population: KORA F4 study, EASD Virtual Meeting 2013

Pain threshold values of small fibres are associated with the severity of diabetic complications

A Japanese study showed that small fiber neuropathy is closely associated with the abnormalities of clinical neurological examinations and the severity of diabetic neuropathy, retinopathy or nephropathy. The degree of small fiber neuropathy was evaluated using PNS-7000 in 87 subjects with T2DM and 36 subjects without DM.

The pain threshold value of C fibers was 0.061 mA in non-DM subjects, while that of T2DM subjects was 0.149mA ($p < 0.001$). In addition, the pain threshold value of Aδ fibers in T2DM subjects was significantly higher compared with that of non-DM subjects (0.143 vs 0.042 mA, $p < 0.001$). When the T2DM subjects were divided into two groups according to with or without abnormalities of each clinical neurological examinations, the pain threshold values of C fibers were significantly higher in the group with abnormality. Respect to pain threshold of Aδ fibers revealed a statistically significant difference only between the group with and without neuropathic symptoms (0.193 vs 0.108 mA, p: 0.013). In addition, the pain threshold values of Aδ and C fibers were significantly higher in accordance with the severity of diabetic neuropathy, retinopathy or

nephropathy in T2DM subjects.
Source: D. Kukidome, Pain threshold values of small fibres are associated with the severity of diabetic complications, EASD Virtual Meeting 2013

Function of large nerve fibres and levels of HSP27 in type 1 diabetes

Heat shock protein 27 (HSP27) is proposed as a neuroprotective factor and may even be important for axonal regeneration. Therefore, it is of interest to study whether HSP27 serves as a potential biomarker for nerve dysfunction in individuals at risk. A recent study investigates the possible associations between serum HSP27 concentration and measures of peripheral nerve dysfunction, and whether HSP27 concentrations differ between individuals with and without type 1 diabetes (T1DM).
Median serum HSP27 concentration of twenty-three patients with T1DM at baseline was 462 pg/ml. Healthy non-diabetic controls had higher HSP27 concentrations (median 900 pg/ml, p =0.014 at baseline). The dynamic change of HSP27 significantly correlated to that of large nerve fiber function, but not to small nerve fiber function. Univariate linear regressions revealed that deteriorating nerve conduction and vibration thresholds from baseline to follow-up were associated with a decrease of HSP27 concentration.
Source: K. Pourhamidi, Function of large nerve fibres and levels of HSP27 in type 1 diabetes: a longitudinal follow-up, EASD Virtual Meeting 2013

Autonomic neuropathy, sexual dysfunction and urinary incontinence in women with type 1 diabetes: findings from the DCCT/EDIC

Cardiovascular autonomic neuropathy (CAN) may play an important role in the pathophysiology of male diabetic erectile dysfunction but the impact of CAN on female sexual dysfunction (FSD) and urinary incontinence (UI) in women with T1DM remains unknown. The association of cardiovascular autonomic neuropathy and FSD and UI was evaluated in women participating in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Intervention and Complications Study (DCCT/EDIC).

At EDIC year 17, FSD and UI were present in 26% and 30% of women, respectively. Subjects with FSD had significantly lower R-R variation (p=0.002) and Valsalva ratio (p=0.003). Likewise, those with UI had similar findings. Forty seven percent of participants with FSD and 44% of participants with UI also had confirmed CAN at EDIC year 16/17 (p=0.02 and p=0.20, respectively). Participants with CAN had 1.58 greater odds of FSD (95% CI) and 1.28 greater odds of UI on univariate analysis. In adjusted analyses, participants with CAN had a 1.30 greater odds of FSD and 1.02 greater odds of UI, that were no longer significant.
Source: J.M. Hotaling, Autonomic neuropathy, sexual dysfunction and urinary incontinence in women with type 1 diabetes: findings from the DCCT/EDIC, EASD Virtual Meeting 2013

Neuropathy measures at DCCT closeout and EDIC year 16/17 by FSD or UI status						
	No FSD N=408	FSD N=146	p value	No UI N=399	UI N=172	p value
Neuropathy Measures (mean ± standard or N -%)						
At DCCT Closeout						
R-R Variation	41.50±21.01	40.04±22.63	0.4677	41.30±21.92	40.35±20.06	0.8031
Valsalva Ratio	2.05±0.40	1.98±0.38	0.1564	2.03±0.42	2.03±0.37	0.6931
Abnormal CAN	27 (7)	23 (17)	0.0014	36 (10)	15 (9)	0.8620
At EDIC Year 16/17						
R-R Variation	26.17±17.25	21.92±17.11	0.0021	25.48±17.24	22.58±16.45	0.0542
Valsalva Ratio	1.74±0.35	1.62±0.30	0.0028	1.72±0.34	1.64±0.32	0.0168
Abnormal CAN	138 (36)	65 (47)	0.0223	142 (38)	72 (44)	0.1986

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The company distinguishes itself as a specialist in the field of biofactors, cardio-vascular diseases, as well as diseases of the central nervous system

WÖRWAG Pharma is a medium sized, family owned company with headquarters in Germany nearby Stuttgart. Founded in 1971 by Dr. Fritz Wörwag, WÖRWAG Pharma now is run successfully in second generation, since the turn of the millennium. The company distinguishes itself as a specialist in the field of Biofactors, cardio-vascular diseases as well as diseases of the central nervous system and is featured as a successful worldwide player with branches in over 30 countries.

Diabetes is a global "epidemic" with a continuously increasing incidence and prevalence. Microvascular disease due to hyperglycemia-induced tissue damage causes blindness, renal failure and limb loss, whereas macrovascular complications lead to atherosclerotic cardiovascular disease, myocardial infarction and stroke. Both micro- and macrovascular complications markedly affect the patients quality of life and account for large percentage of public health costs. Since optimal blood glucose control is only achieved in a minority of patients, however, the need for additional treatment options is great. Recent knowledge about the pathogenesis of diabetic microvascular complications calls for additional treatment options exerting their effects despite hyperglycemia.

The modern treatment of diabetes employs a holistic approach that also includes the treatment of its concomitant diseases. Thus, the treatment area of diabetic polyneuropathies, the leading cause of diabetic foot syndrome and diabetes related amputations, has emerged as an area of interest over the last several years.

Within the last 40 years, WÖRWAG Pharma has developed its international competence and reputation in the treatment area of diabetes and its sequelae and has developed a specialized portfolio of micronutrients, called biofactors that covers both the pathogenetic and the symptomatic treatment of diabetic neuropathies.

International clinical studies, expert meetings and symposia, coupled with close cooperation with research laboratories, WÖRWAG Pharma is committed scientifically in order to obtain the best possible therapeutic approaches for the patients.

Therefore the company is to support research and science in awarding the "Fritz-Wörwag Research Prize" for the eighth time this year. It will be presented for works which make a significant scientific contribution and contain new experimental or likewise clinical findings on the theme of "Biofactors for Prophylaxis and Therapy of Diabetic Complications".

Thomas Schurholz, Director Medicine & Business Development, Wörwag Pharma GmbH & Co. KG

One of the most interesting substances of the biofactors is Benfotiamine, a lipid soluble thiamine derivative. Its pharmacological effects have been shown widely in different diabetic complications in experimental and clinical studies to be beneficial especially in diabetic polyneuropathy. Efficiency on parameters of neuropathic impairment has been achieved without substantial side effects. Their combined use is therefore advisable in addition to general measures and glycemic control. Benfotiamine is a pathogenetically oriented treatment and is characterized by a documented effect on pain relief and decrease of other neuropathic symptoms as well.

Diabetic neuropathy in numbers

Norina Gâvan
General Secretary of the
Society for Diabetic Neuropathy

Diabetic neuropathy is a complication of diabetes mellitus (DM) that occurs irrespective of the disease type. The neuropathy in diabetes of type 1 is fundamentally different comparing to the one in DM type 2; thus, if in type 1 the glycemic control is essential for preventing diabetic neuropathy, in diabetes type 2 it has a more discrete effect from the point of view of the preventive value. Obesity, high blood pressure, dyslipidemia, the inflammatory processes, insulino-resistance – there are just a few factors that prove to be responsible for the onset and the evolution of diabetic neuropathy in people with DM type 2! The magnitude of the issues diabetic neuropathy rises still remains underestimated, as a result of a lack of population studies with standardized and validated evaluations concerning the type and the stage.

Rochester Diabetic Neuropathy, a study made in 1986 on 65,000 persons with DM, shows that 66% of the people with diabetes type 1 have at least one form of diabetic neuropathy, and among them 54% have peripheral neuropathy, 22% of the patients present carpal tunnel syndrome, 12% have visceral neuropathy, and 11% suffer of symptomatic diabetic neuropathy.

Among the patients with DM type 2, 59% have at least one form of diabetic neuropathy, 45 % have peripheral neuropathy, and 29% carpal tunnel syndrome.

EURODIAB IDDM Complication Study, led by Tesfaye et al. in 1996 on type 1 diabetes (having Prof. Ionescu-Tîrgoviște as co-author), made in 31 diabetes centres from 16 European countries, indicates for Europe a prevalence and an incidence of diabetic neuropathy of 28%, without significant differences between the different continent's regions.

Eva Feldman and the Italian Committee for Diabetic Neuropathy, in 1997, accomplished a research of "Prevalence of diabetic neuropathy in Italy", showing that 37% of the patients with DM suffer of diabetic neuropathy; the study also indicates that by intervening as soon as possible, even solely by increasing the awareness on the neurological complications, might ensure both a reduction of the late complications of diabetic neuropathy, and also of infections and foot ulcerations.

In 2002, CODE 2 (Cost of Diabetes in Europe in Type II Study) offers us the first landmarks on total costs of type 2 DM in Europe.

Thus, 72% of the persons with type 2 DM have at least one complication of the disease, 20% suffer only microvascular complications, 10% only macrovascular complications, and 25% present both micro- and macrovascular complications.

Also, among those with microvascular complications, 30% have diabetic neuropathy, 20% diabetic nephropathy and 20% diabetic retinopathy.

The costs of caring the patients with DM and complications are 250% higher than for those with uncomplicated disease. Among these costs, 30% are EXCLUSIVELY attributable to diabetic neuropathy, without taking into account the costs for caring the diabetic foot.

The study also confirms that the prevention of DM complications in general is beneficial for patients, but especially for the healthcare system, due to lowering the total costs for medical care.

Diabetes Care, in 2003, published a study concerning the costs of caring the persons from United States with diabetic neuropathy and complications, these costs being followed during 2001; the results indicate that the diabetic neuropathy in type 1 DM, together with its complications, have caused the US government to pay 0.8 billion dollars and 10.1 billion dollars for the neuropathy in DM type 2. From this total sum of 10.1 billion dollars, 28% are EXCLUSIVELY attributable to peripheric neuropathy.

Later, in 2008, Prof. Tesfaye have shown that all the prospective studies demonstrate that besides glycemic control and the duration of the disease, the incidence of diabetic neuropathy is correlated with changing the cardiovascular risk factors, including the lowering of triglycerides levels, of body mass index and of the blood pressure values.

In a paper published by Ziegler in May 2012 it is shown that only 30% of

the patients with DM and diabetic neuropathy are diagnosed! The study also indicates that only a third of the diabetologists diagnose diabetic neuropathy or KNOW how to diagnose diabetic neuropathy!

In 2012, the only one Romanian (led by Cegedim) shows that 47% of the patients with DM suffers of already diagnosed diabetic neuropathy!

Every year, the diabetic neuropathy costs billions due to the working hours lost

The diabetic neuropathy has a great impact on the presence at work and on the productivity during the working hours. The productivity of an employee suffering of diabetic neuropathy is 10% lower than the productivity of a diabetic person without neuropathy, the estimated deficit being of approximately 5 working hours per week.

The productivity of an employee with diabetic neuropathy and patent symptomatology (pain) is 20% lower comparing to the productivity of a diabetic employee that has no symptoms.

The unemployment rate of the persons with DM is twice as high comparing to the unemployment rate of the people without diabetes.

Therefore, we may say that neuropathy is the most common complication of diabetes that has social and economic implications that must NOT be neglected anymore. The patient with diabetic neuropathy requires more time for care and more attention from the professionals in the healthcare services in general, and especially from diabetologists.


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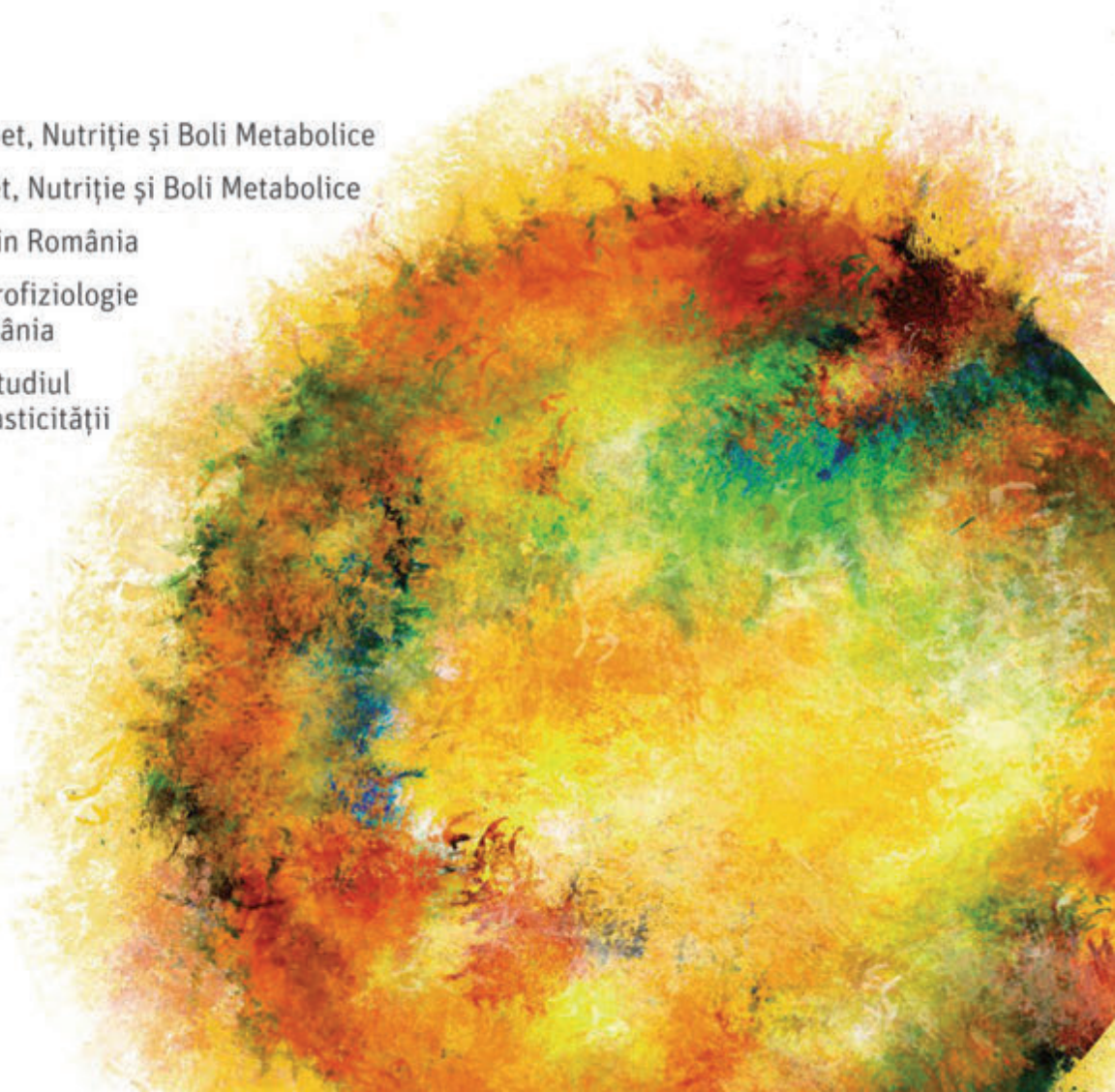

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