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"Diabetic Neuropathy in the 21st Century : Novel Approaches to Diagnosis, Treatment, Technology and Lifestyle"

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Abstract :

Diabetic neuropathy is a common and debilitating complication of diabetes mellitus that affects sensory, motor and autonomic nerves. It can cause neuropathic pain, foot ulcers, autonomic dysfunction and reduced quality of life. Despite its clinical impact, diabetic neuropathy remains under diagnosed and undertreated. The aim of this paper is to explore the emerging trends in diabetic neuropathy, especially in terms of diagnosis, treatment, technology and lifestyle. We review the current methods and challenges of diagnosing diabetic neuropathy and the novel diagnostic techniques that may improve the early detection and prediction of this condition. We also review the current pharmacological and non-pharmacological options for treating diabetic neuropathy and its associated pain and the emerging trends and innovations in treatment, such as personalized medicine, gene therapy, stem cell therapy and neuro modulation. Furthermore, we review the current role and limitations of technology in managing diabetic neuropathy and the emerging trends and innovations in technology, such as virtual reality, augmented reality and robotics. Finally, we review the current evidence and recommendations on lifestyle interventions for preventing and treating diabetic neuropathy and the emerging trends and innovations in lifestyle interventions, such as digital health coaching, gamification and mindfulness. We conclude that recent years have brought forth a multitude of emerging biomarkers, tools and treatments for diabetic neuropathy that reflect different pathogenic pathways and have the potential of improving the diagnosis, prevention and management of this common and complex condition. We also highlight the gaps and limitations of the current knowledge and practice on diabetic neuropathy and suggest some directions for future research and innovation on this topic.

Introduction :

In the twenty-first century, diabetes mellitus (DM) is one of the most serious global public health crises. By 2040, 642 million more adults than the current 415 million will have DM. There are between 1.5 million and 1.9 million diabetes patients in Romania, with a prevalence of 11.6%.

There are an estimated 193 million diabetics that remain misdiagnosed, putting them at a higher risk of complications. Blood sugar levels that are consistently high can have an impact on the heart, blood vessels, eyes, kidneys, and nerves. Protein glycation and excessive formation of reactive oxygen species are caused by biochemical anomalies, which harm the vascular system and prompt the activation of tissue-specific growth and repair mechanisms.

Clinical features of DPN

The most frequent neuropathic syndrome found in people with diabetes is diabetic peripheral neuropathy. The Toronto Consensus Panel on Diabetic Neuropathy has recently proposed a revised

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definition of diabetic neuropathy, which it describes as a "symmetrical, length- dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates. It appears that the first objective quantitative sign of the disorder is an anomaly of nerve conduction tests, which is typically subclinical. Neuropathies with a specific focus, including proximal motor neuropathy, and cranial mononeuropathies are less frequent neuropathic disorders. DPN eventually gets closer to the body, starting in the toes. As soon as it has developed well in the lower limbs, it starts to affect the upper limbs, causing sensory loss that often occurs in "glove and stocking" fashion. Significant motor impairments are not frequently present in the early stages of DPN. Although the patient rarely expresses complaints of weakness, when they do, they often have sensory-related symptoms.

Muscle weakness that manifests as a symptom usually appears later in the course of the illness. Around one-third of individuals with DPN and 20% of all diabetes patients have painful sensations as burning, tingling ('pins and needles' or paraesthesia), shooting (like an electric shock), or lancing (stabbing). These sensations typically worsen at night and interfere with sleep. This frequently results in a decline in an individual's capacity to carry out everyday tasks along with uncomfortable sensations during the day. According to one study, the burden of painful DPN was significant and led to limits in daily activities, poor satisfaction with treatments, and prolonged discomfort despite poly pharmacy and high resource utilization.

DPN that is chronically painful and persistently painful can be very upsetting and be linked to severe depression and anxiety. Importantly, symptoms may not accurately predict the degree of nerve injury. While some individuals with strong pain sensations have little sensory impairment, others with no painful symptoms have entirely numb feet, which puts them at a very high risk for developing foot ulcers. Foot ulceration and a number of other unintended yet devastating injuries are both caused by insensitivity or lack of pain. Patients who have lost sensation in their hands are unable to feel warmth and frequently burn themselves when, for instance, cooking or ironing. They also struggle to handle small things. Puncture wounds, friction wounds, and burns are common among people who have lost feeling in their feet and can develop into ulcers that require amputation. But many ulcerations may be avoided with the right foot care. DPN, however there are additional risk factors at play as well. DPN was linked to both glycaemic control and disease duration, according to the EURODIAB IDDM Complications Study, which included 3250 patients with type 1 diabetes from 31 centers in 16 different European countries. After data were adjusted for diabetes duration, the prevalence ranged from 17 to 41%, with lower HbA1c levels associated with lower prevalence rates and higher levels associated with higher prevalence rates. Despite the 28% baseline prevalence of DPN being significantly related to glycosylated hemoglobin (HbA1c) (p 0.001), the prevalence varied from 17 to 41% after data were adjusted. However, even individuals with adequate glycaemic control (HbA1c 5.4%, similar to Diabetes Control and Complications Trial HbA1c of 7%) nonetheless acquired microvascular damage, indicating that variables other than glycaemic control and illness duration are implicated .Following-up information on the type 1 diabetic patients in the EURODIAB cohort showed that, during a 7- year period, over one-quarter of these individuals acquired DPN, with age, duration of diabetes, and poor glycaemic control being the main contributing variables.

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Additionally, theoretically modifiable cardiovascular risk factors like obesity, smoking, hypertension, and hyperlipidemia were linked to the development of DPN.. Triglycerides and obesity, two recent cardiovascular risk factors linked to DPN, have also been studied recently. Additionally, Wiggin et al. discovered that higher tryglycerides independently of illness duration, age, and diabetes management linked with myelinated fibre loss. These findings support the emerging hypothesis that hyperlipidaemia may play a role in the development of DPN.

Risk factors for DPN

Poor glycemic control has been identified as a risk factor for rate and HbA1c in studies of individuals with type 1 or type 2 diabetes. An additional risk factor for death in diabetes individuals has been identified as an elevated vibration threshol.

MATERIALS AND METHODS :

The study was done in compliance with the Declaration of Helsinki and was authorized by the ethical committee of Heinrich Heine University, Du¨sseldorf, Germany. A written informed consent was given by each participant. 47 age- and sex-matched controls and 86 patients with type 2 diabetes who had just received a diagnosis were also included. Diabetes patients participated in the German Diabetes Study (Clinical Trials.gov Identifier: NCT01055093), which assesses the long-term course of diabetes and its aftereffects.

Type 1 or type 2 diabetes, known diabetes duration of 1 year, and age of 18 to 69 years at baseline examination are inclusion criteria for enrollment into the GDS. Type 3 diabetes, pregnancy, serious illnesses (such as cancer), psychological problems, immunosuppressive medication, a lack of cooperation, ocular issues, and neuropathy from reasons other than diabetes were excluded criteria from the current study. Age of 18 years and a normal OGTT were the only requirements for inclusion in the control group. Diabetes-related neuropathy and other exclusion criteria applied to the diabetes group. Patients with type 2 diabetes from the GDS who were requested to take part in the current study consented to participate in almost half of those cases. The majority of the volunteers for the control group were found through newspaper and internet advertisements.

CCM examination

CCM was carried out utilizing a Heidelberg Retina Tomograph II (HRT II) and the Rostock Cornea Module-RCM (Heidelberg Engineering, Heidelberg, Germany), as previously mentioned. In a nutshell, the field of vision was 0.16 mm2 and the captured pictures had a resolution of 384 × 384 pixels. The exams were performed by skilled ophthalmologists (AZ and SP), who were blinded to all research data except for CCM. A number of picture stacks (with an axial image distance of 0.5 m) were recorded for each patient using a modified, oscillating volume scan operating mode of the HRT II, in which the focus plane of the microscope is continuously changed back and forth. The size of each stack was customized to the height of the tissue deformations that were visible at the time.

For ridge heights less than 48 mm, a stack size of 96 photos (scan depth: 48 mm) was used, and 120 images (60 mm) for ridge heights greater than 48 mm. Each patient underwent a minimum of three scans, and one or more mosaic pictures of the SNP were created. The entire microscopy process took

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around 15 minutes. The previously reported corneal nerve fiber length (CNFL), which is the sum of all nerve fiber lengths (mm/mm2), the number of nerve fiber segments per mm2, and the number of branching points per mm2 were all determined to be conventional CCM parameters.

Examining spatial point patterns

Spatial dot pattern analysis in diabetic neuropathy is a method to study the spatial arrangement of epidermal nerve fibers (ENFs) in the skin of diabetic patients. ENFs are thin sensory nerve fibers that transmit signals such as heat and pain to the central nervous system. Diabetic neuropathy is a disease that damages ENF, causing loss of sensation and pain. Spatial dot pattern analysis can be used to study how the amount and distribution of ENF change as neuropathy progresses and to identify possible factors influencing the neuronal death process. For example, one study used spatial point pattern analysis to test the hypothesis that isolated neural trees are more likely to be deleted than clustered neural trees.

Another study used the spatial and temporal properties of infrared video to detect diabetic peripheral neuropathy by measuring changes in skin temperature caused by vibration stimulation. Spatial point pattern analysis of diabetic neuropathy may help improve diagnosis and treatment of these common diabetic complications.

Peripheral nerve function

Functional tests of peripheral nerves were performed as previously described. Motor CRV was measured in the median nerve, ulnar nerve, and peroneal nerve. Sensory CRV and sensory nerve action potential (SNAP) were measured in the median nerve, ulnar nerve, and gastrocnemius nerve using surface electrodes at a skin temperature of 33-34°C.. The quantitative sensory test was performed by measuring the vibration threshold (VPT) of the medial malleolus using the threshold method (Vibrameter, Somedic, Stockholm, Sweden) and the heat sensitivity threshold (TDT) including heat and cold thresho ld values at the top of the foot using the threshold method. included measurements. (Neurosensory Analyzer TSA- II, Medoc, Ramat Yishai, Israel). Neurological examination was performed using the Neuropathic Disability Scale (NDS) and Neuropathic Symptom Scale (NSS). These and all other clinical studies were performed by operators blinded to the corneal examination results of all subjects

Statistical Analysis

Comparative differences in the use of different PDN treatment options were analyzed using correlation analysis, unpaired t-test and chi-square. Demographics of the three cohorts were compared using chi-square, unpaired Student's t-test, or one way analysis of variance with Tukey's correction for multiple comparisons. Data were analyzed using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

Corneal Sensation

Corneal esthetics were measured using a Cochet-Bonnet esthetic instrument (Luneau Ophthalmologie, Chartres, France). The nylon monofilament has a diameter of 0.12 mm and a fully expanded length of 60 mm. Starting with a thread length of 60 mm, the central, superior, inferior, nasal and temporal corneas were touched once in each eye. If a positive reaction does not come out, the length of the filament was

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shortened once at an interval of 5 mm, and the process was repeated until a positive reaction was obtained. Corneal sensation was calculated as the average value obtained from 5 corneal regions of each eye.

Treatment and prevention

Prevention

There are no treatments to address the underlying nerve damage that causes DPN. Thus, DPN prevention is a key component of diabetes management. The ADA recommends achieving optimal glucose control in type 1 and type 2 diabetes to prevent or slow the progression of DPN. However, the evidence for improved glycemic control from DPN prophylaxis is much greater in type 1 diabetes than in type 2 diabetes. A meta-analysis of well-conducted large randomized controlled trials found clear benefits of optimizing glucose control in type 1 diabetes The Diabetes Control of Complications Trial (DCCT)/Epidemiology of Diabetic Interventions is one such instance. The Diabetes Control of Complications Trial (DCCT)/Epidemiology of Diabetic Interventions is one such instance and Complications (EDIC) showed that intensive treatment significantly reduced the risk of DPN. However, the benefits of glucose control and multivariate risk factor control in DPN are inconclusive in type 2 diabetes. Large studies such as ADDITION-Denmark, UKPDS, Steno-2 and ACCORD have shown that intensive glucose and multifactor therapy have little effect on the incidence of DPN. However, the presence of multiple comorbidities and risk factors may contribute to discrepancies in the findings of these studies. The type of antidiabetic treatment used may also affect the results of these studies. Recently, patients with type 2 diabetes treated with an insulin-sensitive regimen, such as Pop-Busui, have shown a significantly reduced incidence of DPN compared to patients treated with insulin. In a meta-analysis of eight randomized trials, there was a trend toward intensive treatment to reduce the incidence of DPN in type 2 DM, but it did not reach statistical significance ($p = 0.06$).

Treatment of painful DPN

Current approaches to the treatment of painful DPN focus on achieving and maintaining near- normal blood glucose (HbA1c) at an early stage. However, many diabetics, especially type 2 diabetics, find this difficult. Evaluation and pharmacological treatment of painful DPN has been recently reviewed and readers are encouraged to read this Consensus Report. Based on these trials, duloxetine is the preferred SNRI and pregabalin is the preferred ?-2-? agonist. If pain is not adequately controlled, these first-line drugs can be given concomitantly, subject to contraindications, although this is not supported by trial data If pain is still not adequately controlled, concomitant treatment with opioids such as tramadol and oxycodone Similar agents can be added. Initial selection of primary treatment is influenced by evaluation of contraindications, consideration of comorbidities, and cost. For example, diabetic patients with a history of heart disease, elderly patients taking other concomitant medications such as diuretics and anti hypertensives, and patients with concomitant orthostatic hypotension. TCA has relative contraindications. Duloxetine should not be administered to patients with liver disease, and pregabalin or gabapentin should not be administered to patients with edema.

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Pathogenetic Treatments :

A variety of therapeutic approaches targeting the different etiological mechanisms of diabetic neuropathy have been the subject of clinical trials. These therapies aim to beneficially address the major pathophysiological abnormalities that occur in DPN by targeting various components of the pathway leading to neurovascular dysfunction. A number of therapies have shown promise in trials and early phase 2 trials, but a recurring theme is that there is no "transition" to phase 3 trials. Therefore, there are currently no drugs approved for the treatment of diabetic neuropathy in the United States or United Kingdom. An obvious question is why no single pathogenic treatment for DPN has proven effective enough to warrant regulatory approval. Ziegler and Luft suggested that studies until the mid-1990s were hampered by poor design, short follow-up, and limitations in patients with progressive DPN.

They hypothesized that clinical trials conducted over 3 to 5 years in patients with early DPN were more likely to be successful in delaying or halting the progression of neuropathy rather than reversing it. In 2007 Tesfaye et al. Two randomized controlled trials of luboxistaurine in the DPN reported a placebo group and found significant improvements in signs, symptoms, and quantitative vibration tests. They concluded that studies longer than 12 months were needed to show exacerbations in all placebo groups. In the same year Dyck et al. We examined data from a placebo group, two large-scale interventional trials, and the Rochester Diabetic Neuropathy Study to investigate the issue of selecting appropriate endpoints for clinical trials. They concluded that there were three main reasons these studies failed to demonstrate sustained deterioration of neuropathic endpoints. Strong placebo effect on symptoms and signs.

Measurement noise - The fact that DPN may be more gradual than previously thought. Commentary by Dyck et al. Boulton also suggested a role for concurrent treatment (e.g., ACE inhibitors and lipid-lowering therapy) for comorbid cardiovascular disease in diabetic patients.

These treatments may also have a positive effect on peripheral nerve function and thus may act as a confounding factor in the study. Boulton emphasizes the need to select robust endpoints for future studies that should not be affected by quantitative sensory tests and variability influencing patient-reported outcome rates. This means that skin biopsies and corneal confocal microscopy may be suitable objective endpoints in clinical intervention trials.

Technology

Diabetes's financial toll worldwide

In addition to the human toll caused by diabetes and its complications, the disease has significant economic impacts on the health care System and the economy. In the UK, for example, diabetes costs the NHS £10 billion annually. This is equivalent to £1 million per hour or 10% of the total annual budget. Between 2011 and 2025, the global cost of diabetes and other non-communicable diseases(NCDs) is projected to exceed $7 trillion. According to Professor Namhyun Cho of the International Diabetes Federation, "Diabetes threatens to overwhelm health systems and slow economic growth in many countries."

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Type 1 and Type 2 Diabetes

To understand the role of technology in managing diabetes, it is important to understand the difference between the two main forms of the disease, type 1 and type 2. People with type 1 make up 5 to 10% of those affected. Its cause is unknown and currently cannot be prevented. People with type 1 diabetes do not produce insulin to control blood sugar levels. Symptoms include excessive urination (polyuria), thirst (polydipsia), persistent hunger, weight loss, visual changes, and fatigue. Regular insulin administration is required for survival.

Type 2 affects about 90% of people with diabetes. This is because the body uses insulin inefficiently. Because symptoms can be similar to type 1, but are often less severe, the disease can go undiagnosed for many years and is often only discovered after complications develop. Type 2 is usually the result of being overweight and lacking in physical activity.

In both type 1 and type 2 diabetes, patients can suffer damage to the heart, blood vessels, eyes, kidneys, and nerves. Adults with diabetes are three times more likely to have a heart attack or stroke(5), and diabetes is a leading cause of kidney failure, lower extremity amputations and blindness.

The role of technology

Diabetes control is a top priority for many governments. It is important to prevent type 2 diabetes through educational programs and policies aimed at improving lifestyles, including smoking cessation, physical activity, and improved nutrition. Effective blood sugar control is an important factor in preventing complications and reducing health care costs. Medical technology can play a major role. Options for people with type 1 diabetes who need to monitor their blood sugar levels and inject insulin multiple times a day range from simple test strips to insulin pumps and continuous blood glucose meters. Insulin pumps worn outside the body allow users to program background insulin requirements and provide continuous insulin delivery as needed around the clock and during meals. The advantage over injections is that you can increase or decrease the dose based on your daily changing circumstances.

However, adoption has been slow in some countries, including the UK, despite evidence that it can save millions of dollars in health care costs. Awareness of the value of continuous glucose monitoring (CGM) and rapid glucose monitoring technologies is growing. Both provide more information than a finger stick blood test and allow users to read glucose levels in interstitial fluid and send the results to a reader or smartphone to make more informed treatment decisions.

Point-of-care innovations for type 2 patients include blood glucose meters combined with apps and devices that enable people to manage their medications more effectively. Support for self-care and prevention also comes in the form of mobile health technologies that help people improve their lifestyle or eating habits.

From artificial pancreas to AI

Research teams around the world have been developing artificial pancreas for some time. The technology combines a CGM with an insulin pump using algorithms that mimic the functioning of human organs. Some devices have already been approved and others are still in clinical trials. Originally

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developed for the treatment of type 1 diabetes, work is also underway to find ways this technology could support blood sugar control in people with type 2 diabetes.

Looking to the future, we can expect new developments in microfabrication and implantation devices, as well as 3D printing of tissues that can clone pancreatic cells for transplantation. As machine learning improves blood sugar control with wearable or implantable devices, artificial intelligence (AI) will also become more important.

Lifestyle Changes for Peripheral Neuropathy

Simple lifestyle changes can help manage symptoms of peripheral neuropathy, such as pain, loss of muscle mass, or numbness in a limb.

Get Regular Exercise

Regular exercise can reduce pain or cramps, improve muscle strength, help control blood sugar and prevent muscle loss. Activities, especially walking and swimming, can improve symptoms of neuropathy.

Eat Well

A diet rich in fish, nuts, whole grains, and fresh foods can be part of a healthy weight management plan that can reduce the effects of peripheral neuropathy. A healthy diet can relieve gastrointestinal symptoms such as diarrhea, constipation or urinary incontinence caused by damage to the nerves that control intestinal muscle contractions. A healthy diet also corrects underlying nutritional deficiencies.

Avoid Excess Alcohol

Drinking too much alcohol can worsen certain health conditions that cause neuropathy, such as diabetes and poor eating habits, and can even cause nerve damage. Moderate drinking is defined as no more than one drink per day for women of all ages and men over 65 and no more than two drinks per day for men under 65.

Manage Diabetes

Proper foot care and meticulous debridement are especially important for people experiencing pain problems due to peripheral neuropathy. Good control of diabetes can help stimulate nerve regeneration. Maintaining healthy blood sugar levels has also been shown to reduce symptoms of neuropathy and prevent further nerve damage.

Conclusion :

Diabetic neuropathy is a common and serious complication of diabetes affecting the peripheral and autonomic nervous system. This can result in loss of sensation in the lower extremities, pain, ulceration, infection, and amputation, as well as cardiovascular, gastrointestinal, genitourinary, and diaphoretic dysfunction. The diagnosis of diabetic neuropathy is based on clinical evaluation, nerve conduction studies, quantitative sensory tests, and biomarkers. Treatment of diabetic neuropathy is primarily symptomatic and includes glycemic control, pharmacological agents, non-pharmacological methods, and lifestyle changes. However, current diagnostic and treatment methods are often inadequate, inaccurate, or inaccessible for many patients. Therefore, new trends and innovations in the field of

diabetic neuropathy that can improve early detection, prevention and treatment of diabetic neuropathy are needed. Promising research and development areas include new diagnostics, artificial intelligence, wearable sensors, personalized medicine, gene therapy, stem cell therapy, neuro modulation, virtual reality, augmented reality, and robotics. These technologies could provide more accurate, reliable, convenient and efficient solutions for diabetic neuropathy patients and health care professionals. However, more research is needed to evaluate the safety, efficacy, cost- effectiveness and acceptability of these technologies in different settings and populations. Additionally, greater collaboration and communication between researchers, clinicians, patients, industry and policymakers is required to facilitate the transfer of these technologies from the lab to the bedside. In conclusion, diabetic neuropathy is a complex and complex condition that requires a multidisciplinary and holistic approach to address its various aspects. We hope to harness the power of new trends and technological innovation to improve the diagnosis, treatment and quality of life of diabetic neuropathy patients in the 21st century.

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