A Review: Diabetic Neuropathy

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Abstract- *Diabetes mellitus is the leading cause of end-stage renal disease in the United States. Between 1996 and 2001, the prevalence of diabetes in the Medicare population increased by 31%. Patients with diabetes account for approximately one-third of all cases of end-stage renal disease (ESRD). This number is expected to rise dramatically as a result of the growing incidence of diabetes and the aging population. A major complication of diabetes includes end-stage renal disease as a result from diabetic nephropathy. The earliest clinical evidence that nephropathy exists is the appearance of low, yet abnormal, levels of albumin in the urine, referred to as microalbuminuria. This can progress to proteinuria representing overt diabetic nephropathy. Prevention remains the best way to reduce mortality and maintain a high quality of life in these individuals as recent clinical trials confirm that it is possible to not only slow down the progression of diabetic nephropathy, but even prevent it from becoming a significant problem. This article reviews the pathogenesis, diagnostic screening, and treatment strategies of diabetic nephropathy.*

Keywords- Diabetic complications, Diabetic nephropathy

I. INTRODUCTION

Neuropathy, a common complication of diabetes mellitus, is generally considered to be related to duration and severity of hyperglycemia. However,it may also occur acutely even withhypoglycaemia1-3. Usually more than 50% of patients with duration of diabetes of 25 years or more are affected, making it as one of the most common disease of the nervous system . One of the largest published series reported a prevalence of 7.5% even at the time of diagnosis of diabetes4.The prevalence however, increases progressively without a plateau. Diabetic neuropathy has been defined as presence of symptoms and/or signs of peripheral nerve dysfunction in diabetics after exclusion of other causes, which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic, and secondary to other systemic illnesses. Since the manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinating polyneuropathy, alcoholic neuropathy, and other endocrine neuropathies, hence, before labelling diabetic neuropathy it is mandatory to exclude all other causes of peripheral nerve dysfunction. Oxidative stress plays an important role in the etiology of diabetes and diabetic complications. Diabetics and experimental animal models exhibit high-oxidative stress due to persistent and chronic hyperglycemia, thereby deplete the activity of the ant oxidative defense system and thus promote free radicals generation Such models include alloxan or streptozotocin (STZ) induced diabetic rats and mice.

Experimental Models of Diabetes : Experimental models of diabetes can be divided into two main categories: genetic (spontaneous) and induced syndromes. Many different mammalian species can be used as experimental models of diabetes including monkeys, cats, sheep, rabbits, dogs, pigs, hamsters, guinea pigs, rats and mice. Nevertheless, due to their relatively small size, reduced cost, easy to bread in and maintenance in animal care facilities, rats are the most common animals used in the experimental diabetes investigations. However, the use of mouse models to advance knowledge of physiology, pathology and development is exploding in all areas, mainly due to the availability of genetically manipulated mice. Thus, mice are being introduced as another rodent model for experimental neuropathies studies. Alloxan and streptozotocin (STZ) are the most prominent diabetogenic chemicals used to induce experimental diabetes in animals . Since both are cytotoxic to pancreatic beta-cells, their use to introduce experimental diabetes in rats is convenient and simple. Diabetic-inducing property of alloxan was first identified in 1943 as a result of the observed specific necrosis of pancreatic beta-cells. Alloxan diabetes (state of experimental diabetes resulting in insulinopenia after the alloxan injection) was then successfully induced in rabbits, rats, dogs and other species such as cats, sheep, monkeys, pigs and mouse. Guinea pigs have shown to be resistant .Subsequent decades witnessed a rise in journal articles reports and reviews about alloxan and its diabetogenic properties Alloxan is a hydrophilic and unstable substance with a molecular shape resembling glucose. Its half-life at neutral pH and 37 ºC is about 1.5 min but when a diabetogenic dose is used, its time of decomposition is sufficient to allow pancreas penetration in amounts that are deleterious. Rapid uptake by insulin-secreting cells has been proposed to be one of the important features determining alloxandiabetogenicity. Alloxan exerts its diabetogenic action when administrated

intravenously, intraperitoneally or subcutaneously. The dose required for diabetes induction depends on the animal species, route of administration and animal nutritional status, age and gender. The most frequently used intravenous dose used to induce diabetes in rats is 65mg/kg but the effective dose for intraperitonealy or subcutaneously injections must be 2 to 3 times higher . Fasted animals are more susceptible to alloxan but high blood glucose levels provide partial resistance. Several investigations suggested that the selectivity of alloxan action is not quite satisfactory and alloxan uptake occurs in liver and other tissues The diabetogenic property of STZ was observed 20 years later than alloxan and since then, it has been the agent of choice for the induction of diabetes mellitus in animals). STZ is more efficient and specific to the pancreatic beta-cells than alloxan. STZ synthesized by Strep to my cetesachromogenes and is used to induce both insulin-dependent and non-insulin-dependent diabetes mellitus. As with alloxan, its beta-cell specificity is mainly the result of selective cellular uptake and accumulation. The range of the STZ dose is not as narrow as in the case of alloxan and the frequently used single intravenous injection of 40 to 60 mg/kg in adult rats is enough to induce an insulin-dependent diabetes mellitus state. If given in multiple low doses, predominantly in the mouse, an induction of an insulin-dependent diabetes mellitus state is achieved by activation of immune mechanisms. Due to its chemical properties, particularly greater stability, STZ is the agent of choice for reproducible induction of a diabetic metabolic state in experimental animals. Injections of alloxan and STZ induce the same blood glucose, plasma insulin responses and morphological features of pancreatic beta-cells destruction characteristics of necrotic cell death. When using these chemically induced models of experimental diabetes, one should take into account that this mechanism is clearly at a variance with that which underlies autoimmune type 1 diabetes in humans and rodent models where beta-cell demise is the result of apoptotic cell death .

Diagnosis :

Diabetic neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after other aetiologies have been excluded. Typically, the presence of more symptoms or signs of nerve dysfunction confers higher certainty about the diagnosis, although abnormalities in lower-limb NCV and sensory and motor nerve amplitudes assessed in nerve conduction studies (NCS) provide even further evidence. For the vast majority of patients, the diagnosis of diabetic neuropathy is based solely on the history and examination and no additional testing is needed. Objective confirmatory testing is most commonly used in the research setting or as part of the diagnostic work-up of patients with atypical clinical presentations.

The symptoms of diabetic neuropathy are numbness, tingling, pain and weakness and unsteadiness, starting distally (at the toes) and spreading proximally and then to the upper limb digits when the lower-limb symptoms reach the knees. Patients often have predominantly small-fibre neuropathy early in the course of diabetic neuropathy or when diagnosed with prediabetes, and have distal painful symptoms of burning, lancinating, freezing pain that are greater at rest. Large-fibre injury usually occurs later in the disease course, but this is not always the case.

Clinical findings of diabetic neuropathy are a loss of sensation to pinprick, temperature (mostly cold), vibration and proprioception in a ‘stocking and glove’ distribution. These sensory modalities are tested initially by the application of the sensory stimulus to a region where normal responses are expected, such as the forehead. Following this, the stimulus is applied to the great toe and then moved proximally up the limb to the level where the sensation is felt to be normal. Pinprick sensation is tested using a sharp object, such as a safety pin, that is discarded after each patient, whereas temperature is tested using a cool material, such as a metallic object. Vibration is tested by application of a vibrating tuning fork to the bony prominence at the dorsum of the great toe and then determining when the vibration stops, and proprioception is examined by small movements of the distal interphalangeal joint of the great toe. Pinprick and temperature sensations are mediated via small nerve fibres, whereas vibration sensation and proprioception are mediated by large nerve fibres.

Loss of ankle reflexes occurs early in diabetic neuropathy; thus, initial examination should include reflex testing. Later, weakness of small foot muscles and dorsiflexors is observed. Although many patients notice symptomatic weakness, major weakness on examination is only observed in later stages of advanced diabetic neuropathy. Early neurological dysfunction in the upper limbs should raise suspicion of a mononeuropathy or an alternative diagnosis.

The symptoms and clinical signs of diabetic neuropathy can be combined in scales, such as in the Toronto Clinical Neuropathy Score, the modified Toronto Clinical Neuropathy Score or the Michigan Diabetic Neuropathy Score, which have defined cut-off values for the presence of neuropathy. Other scales include signs only or a combination of signs and ancillary tests.

If a patient with numbness, tingling, pain and/or weakness presents with atypical features, such as acute or subacute presentation of neuropathy, non-length dependence, motor predominance and/or asymmetry of neuropathic signs and/or symptoms, a neurological consult and additional testing

should be prompted. Additional testing depends on clinical presentation but typically includes measuring serum vitamin B_{12} levels, thyroid function tests, serum protein electrophoresis with immunofixation and markers of autoimmune disorders. Cerebrospinal fluid examination using lumbar puncture to assess protein levels, genetic testing and MRI of nerve roots and peripheral nerves is frequently required for the correct diagnosis in atypical clinical presentations. Rarely, sural or radial nerve biopsy is necessary.

Screening :

Screening for diabetic neuropathy using a recommended evidence-based screening algorithm is advised for all patients with diabetes. Current position statements from the American Diabetes Association (ADA) and guidelines from the Canadian Diabetes Association recommend screening for diabetic neuropathy at diagnosis and annually for patients with T2DM and 5 years after diagnosis and then annually for patients with T1DM.The tests for screening need to be rapid, reliable and simple, and advocating for anything other than very simple test paradigms will lead to a lack of screening. Several simple sensory tests can be carried out to detect diabetic neuropath, for example, the 10 g monofilament test can be used to predict incident diabetic neuropathy.The value of this monofilament is that higher insensitivities predict a high risk of foot ulceration; thus, the practitioner needs to use only a single tool for screening for diabetic neuropathy and to assess risk of foot ulceration. Vibration testing with a 128 Hz tuning fork (timed or number of times felt) has similar discriminating abilities to the monofilament test and is also quick and easy to perform. Assessment of deep tendon reflexes has good test characteristics, although not quite as high as monofilament or vibration testing. Other screening methods, such as the Michigan Neuropathy Screening Instrument, that use a questionnaire and simple examination have also been validated and are useful for screening and assessing the severity of neuropathy

Prevention :

The consistent feature between T1DM and T2DM is hyperglycaemia; therefore, treatment of hyperglycaemia logically would be the best preventive treatment for diabetic neuropathy. However, although enhanced glycaemic control effectively reduced the incidence of diabetic neuropathy in patients with T1DM, the effect was much smaller, or in some studies absent, in patients with T2DM .Indeed, the difference in patients with T2DM did not reach statistical significance in either the meta-analysis or in individual studies. The T1DM meta-analysis was dominated primarily by the Diabetes Control and Complications Trial (DCCT), which accounted for 1,186 of the 1,228 patients in the meta-analysis and demonstrated an annualized risk difference of –1.84 (95% CI –2.56 to –1.11) in favour of enhanced glycaemic control .The T2DM meta-analysis was dominated primarily by the ACCORD and VADT studies, which accounted for 6,568 of the 6,669 patients in the meta-analysis and reported an annualized risk difference of –0.58 (95% CI –1.17 to 0.01) in favour of enhanced glucose control, although this value did not reach statistical significance. Since the publication of this systematic review, another study reported no difference in the prevalence of diabetic neuropathy in patients with screen-detected T2DM who received routine care compared with those who received intensive treatment (encompassing goal-directed glycaemia and cholesterol and blood-pressure management) Importantly, the two groups had little to no differences in glycaemic and other metabolic measurements. Taken together, current data indicate that enhanced glucose control has a large effect on the prevention of diabetic neuropathy in patients with T1DM, whereas the effect in T2DM is much less, although it is likely still important.

Exercise is emerging as a promising prevention strategy in diabetic neuropathy. One study demonstrated increased distal leg IENFD by 1.5 fibres mm^{-1} in patients with diabetes (without neuropathy) who received a weekly structured and supervised exercise programme, but IENFD was unchanged in patients who received lifestyle counselling (–0.1 fibres mm^{-1}; $P = 0.03$). This study indicates the potential for exercise to prevent nerve injury and even promote nerve regeneration, although the study was not randomized and the effect on patient-oriented neuropathy outcomes is still not clear. Currently, routine exercise is recommended to all patients with diabetes, but no firm recommendations can be made pertaining to the role of exercise and the prevention of neuropathy.

Managment :

The current approaches to management of diabetic neuropathy focus on improving glycaemic control (mainly in patients with T1DM), lifestyle modifications (mainly in patients with T2DM) and management of neuropathic pain. The optimal therapeutic approach for patients with T2DM includes lifestyle interventions, specifically diet and exercise, coupled with optimal lipid and blood pressure control. Glycaemic control with a HbA_{1c} goal of <6 increases mortality in patients with T2DMand has little effect on diabetic neuropathy, therefore it is not recommended as standard of care. Rather, good glycaemic control as part of a more holistic, personalized approach to the treatment of T2DM is the optimal choice. Many therapeutic interventions have failed; however, several promising therapies are in ongoing clinical trials.

Treatment :

In diabetic patients the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control, and the improvement of lipid and blood pressure indexesand the avoidance of cigarette smoking and excess alcohol consumption are already recommended for the prevention of other complications of diabetes.

Preventive Treatment

Based on the aetiology of diabetic neuropathy several agents have been tested to halt its progression (after the onset of subjective symptoms, only palliative treatments are currently available), thereby improving clinical outcome . An analysis of the literature on experimental peripheral diabetic neuropathy suggests that, to date, all of the pharmacological agents shown to counteract one or several manifestations of painful or insensate neuropathy also have efficacy against nerve conduction velocity deficit . Animal studies using pharmacological and genetic approaches revealed important roles of increased aldose reductase, protein kinase C, poly(ADP-ribose) polymerase activities, advanced glycation end products and their receptors, oxidative-nitrosative stress, growth factor imbalances, and C-peptide deficiency in both painful and insensate neuropathy.

Selective Serotonin Reuptake Inhibitors

The SSRIs are increasingly being used to treat a spectrum of depressed patients, including the elderly. As a class, SSRIs have comparable efficacy to TCAs against depression but are generally better tolerated . Despite their wide use there is still limited evidence for the role of classical SSRIs in the treatment of painful diabetic neuropathy. The class of serotonin and norepinephrine reuptake inhibitors (SNRIs) now comprises three medications: venlafaxine, milnacipran and duloxetine. These drugs block the reuptake of both serotonin (5-HT) and norepinephrine with differing selectivity. Whereas milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity, duloxetine has a 10-fold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT. All three SNRIs are efficacious in treating a variety of anxiety disorders

Antiepileptic Drugs

These have a long history of effectiveness in the treatment of neuropathic pain, dating back to case studies of the treatment of trigeminal neuralgia with phenytoin in 1942 and carbamazepine in 1962 . Since 1993, nine new antiepileptic drugs (felbamate, gabapentin, pregabalin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide) have received FDA approval for the adjunctive treatment of partial seizures . In addition to providing efficacy against epilepsy, these new antiepileptic drugs may also be effective in neuropathic pain. For example, spontaneous activity in regenerating small-calibre primary afferent nerve fibres may be quelled by sodium channel blockade, and hyperexcitability in dorsal horn spinal neurons may be decreased by the inhibition of glutamate release .

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