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Commentary
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Recent Topics on Various Clinical Problems Related with Diabetic Neuropathy

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Abstract

Diabetes has been a crucial disease worldwide, and authors have continued diabetic practice and research. Recent topics on neuropathy are described. For diabetic patients, common symptoms of dysesthesia and loss of protective sensation (LOPS) should be checked annually. Diabetic peripheral neuropathy (DPN) has been treated by pregabalin, duloxetine, gabapentin and tapentadol. Autonomic Neuropathy (AN) includes Orthostatic Hypotension (OH), Cardiac Autonomic Neuropathy (CAN), gastroparesis and genitourinary disturbances. Diabetic foot may be related with Peripheral Arterial Disease (PAD), Diabetic Foot Infection (DFI), diabetic foot osteomyelitis (DFO) and amputation. For those, Hyperbaric Oxygen Therapy (HBOT) may be effective with continuing discussion.

Keywords: Diabetic Peripheral Neuropathy, Loss of Protective Sensation, Cardiac Autonomic Neuropathy, Autonomic Neuropathy, Orthostatic Hypotension, Peripheral Arterial Disease, Hyperbaric Oxygen Therapy.

Abbreviations: DPN: Diabetic Peripheral Neuropathy; LOPS: Loss of Protective Sensation: CAN: Cardiac Autonomic Neuropathy; AN: Autonomic Neuropathy; OH: Orthostatic Hypotension; PAD: Peripheral Arterial Disease; HBOT: Hyperbaric Oxygen Therapy.

Introduction

Across the world, diabetes has been a crucial disease in recent years. To prevent and treat diabetes, various health care and medical care have been necessary(1). The nutritional treatment has been the fundamental therapy for diabetes, metabolic syndrome, and non-communicable diseases (NCDs). Authors and collaborators have continued various research on Low Carbohydrate diet (LCD) and Calorie Restriction (CR) for years(2). Diabetes causes macro- and micro-angiopathy, in which neuropathy has been an important complication to be controlled(3). From neurological and neuropathic points of view, recent topics will be described in this article.

For patients with Type 1 and 2 Diabetes Mellitus (T1DM, T2DM), exams for diabetic peripheral neuropathy (DPN) have to be provided annually by history-taking and simple tests(4). In the earlier period, common symptoms of dysesthesia are from the involvement of small fibers. As to larger fibers, numbness or loss of protective sensation (LOPS) may be present. LOPS suggests the existence of distal sensorimotor polyneuropathy, leading to the risk for diabetic foot problems(5). These examinations can give the screening of the impaired function, as well as the prediction of future complication risk.

Regarding the prevention or delay of DPN or Cardiac Autonomic Neuropathy (CAN) in T1DM, near to normal glucose variability has been known to be effective. In contrast, it is not so effective for T2DM(6). From the study of Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial, the incidence of distal symmetric polyneuropathy was lower in those with insulin sensitizers than those with insulin/sulfonylurea(6,7).

Neuropathic pain may influence the quality of life, depression, mobility limitation, and social dysfunction. For neuropathic pain, pregabalin and duloxetine have been widely used with approval by the FDA, European Medicines Agency, Health Canada(8). Opioid agent tapentadol has also obtained approval in the US and Canada, but its evidence has been not so sufficient(9). As the most extensively studied agent for DPN, pregabalin showed favorable affects about 30-50% decreased pain(10). However, not all studies or not all patients could show satisfactory improvement(11). Consequently, each case complaining of neuropathic pain would be treated with careful attention. Gabapentin has been the related agent and showed the effect of diabetic neuropathy. It may be less expensive to provide, although it has not obtained the approval yet for this indication by the FDA. In the clinical practice, however, it has been provided rather widely(12).

When a physician examines a diabetic patient, symptoms, and signs about diabetic autonomic neuropathy (AN) are carefully checked. They include orthostatic hypotension (OH), resting tachycardia, hypoglycemia unawareness, gastroparesis, diarrhea, constipation, neurogenic bladder, erectile dysfunction, and sudomotor dysfunction. We must pay attention to CAN. It is associated with mortality apart from other cardiovascular risk factors(13). It may be often asymptomatic and found by lower heart rate variability by deep breathing or the presence of OH.

AN includes several genitourinary disturbances, such as bladder dysfunction and sexual dysfunction. In the case of men, erectile dysfunction and retrograde ejaculation may be present(4). It is rather common for females to have some sexual dysfunction, such as reduced sexual desire, decreased sexual arousal, less lubrication, painful intercourse(4). As urinary tract, bladder dysfunction, and urinary incontinence are observed, including frequent urination, nocturia, urgent urination, and weakened urinary stream. There are more episodes of urinary tract infections, incontinence, cystitis, and pyelonephritis. Recent impressive

situations include not only from diabetes itself but also from increased urinary glucose by Sodium-glucose cotransporter 2 inhibitors (SGLT2i) agent(14). The reverse effect of the SGLT2i agent should be recognized in diabetic practice.

Treatment for OH has been rather difficult. The goal is not to normalize but to minimize postural symptoms. It requires both non-pharmacologic measures and pharmacologic agents. Recent topics for the treatment agents include metoprolol or atenolol as before, enalapril as an alternative, and droxidopa and midodrine as approved by FDA(15). Diabetic gastroparesis has been also difficult to treat. Some advice may be effective, such as intake of small particle size, low-fat, low-fiber, frequent meals, a larger ratio of liquid calories, and DPP4i(16). As pharmacologic interventions, some options include metoclopramide, domperidone, erythromycin (only for short-term to tachyphylaxis)(17).

Diabetic foot has been a crucial problem to be prevented and treated. Foot ulcers, infection, and amputation are the results of diabetic neuropathy and peripheral arterial disease (PAD). Early recognition and initiation of treatment would be indispensable(18). Medical staffs should check the risk factors, including i) general, smoking, poor glycemic control, retinopathy, nephropathy, ii) local, peripheral neuropathy with LOPS, foot deformities, pre-ulcerative callus or corn. There is a recommended use of supportive therapeutic footwear, which can lessen the pressure of prevent the worsening or recurrence of the plantar foot ulcer(18). However, the use of the footwear did not show evidence to prevent the first episode of a foot ulcer or heal ischemic lesions(18).

For the prevention of diabetic foot, all diabetic patients should check comprehensive foot evaluation annually. With some positive items, diabetic patients may develop more frequently foot problems(19). To diagnose LOPS, a useful instrument is a 10-g monofilament, as well as a pinprick, ankle reflexes, and vibration sensation by tuning fork(19). During the progress of diabetic patients, initial screening for PAD must be checked for i) history of walking speed, claudication, and assessment of the pedal pulses, ii) ankle-brachial index (ABI) testing(4). If the result of ABI showed ankle pressure <50 mmHg or toe pressure <30 mmHg, the patient should be introduced to the specialist for urgent vascular imaging and revascularization(4,5).

As to diabetic patients with a foot problem, adequate information on footwear would be provided(5). Generally recommended footwear has a broad shape with square toe box, cushioned insole, and lightweight materials(19). The application of these shoes can reduce the risk of foot problems in the future(20). When diabetic foot may exacerbate, diabetic foot infection (DFI) and/or diabetic foot osteomyelitis (DFO) may occur(21). Most diabetic infection cases have polymicrobial, with aerobic gram-positive cocci(5). Among them, the most common causative organisms are staphylococci and streptococci.

Recently, hyperbaric oxygen therapy (HBOT) has been applied to patients with diabetic foot ulcers. It revealed the mixed evidence whether it is useful or not as adjunctive therapy to help healing courses and prevent amputation(22,23). There is a trial for the differentiation between ischemic and non-ischemic diabetic foot ulcers for the application of HBOT(24,25). The discussion concerning the efficacy of HBOT has been continued.

Conclusion

In summary, several problems with diabetic neuropathy were introduced here. They include various pathophysiology, such as DPN, AN, OH, CAN, PAD, DFI, and so on. The information would become a hopefully useful reference for future diabetic practice and research.

Conflict of interest: None.

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