ISSN 2515-8260 Volume 08, Issue 04, 2021

Diabetic Peripheral Neuropathy: article review

Ghadeer Mohammed Alaidarous[1], Thamir Abid Y Khayyat[2], Manal Mohammadsadiq S Qnadeli[3], Hameadah Hamed Mohammed AlMalki[4], Turki Mueid Al Buqami[5], Sabah Mutlaq H Alemery[6], Abdullah Mohammed Alwuthaynani[6], Mohammed Masoud AlAhmady[7], Aeshah Zubayr Barnawi[8], Mohammed Abed Abdullah Al-Lahani[9], Ahmad Khalid Ageel Damanhouri[10].

[1]Family Medicine Senior Registrar, Al-Mabdaah Primary Health Care Centre

[2]Nursing technician, Al Malawi primary Health Care Center, Makkah, Saudi Arabia.

[3]Technician Dental Technology, Al Malawi Primary Health Care Center, Makkah, Saudi Arabia.

[4]Clinical Laboratory Sciences, Al Malawi Primary Health Care, Makkah, Saudi Arabia.

[5]Nursing technician, Al Aadl health center, Makkah, Saudi Arabia.

[6]Nursing technician, Malawi Primary Health Care Center, Makkah, Saudi Arabia.

[7]Social worker, King Abdulaziz hospital, Makkah, Saudi Arabia.

[86]Nursing Specialist, Maternity & children hospital, Makkah, Saudi Arabia.

[9]Social worker, maternity and children hospital in Makkah, Saudi Arabia.

[10]Pharmacist technician, Inventory control department in the health assembly in Makkah, Saudi Arabia.

Abstract:

Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and type 2 diabetes affecting over 90% of the diabetic patients. Due to the toxic effects of hyperglycemia there is development of this problem. It is classically characterized by significant deficits in tactile sensitivity, vibration sense, lower-limb proprioception, and kinesthesia. Painful DPN has been shown to be associated with significant reductions in overall quality of life, increased levels of anxiety and depression, sleep impairment, and greater gait variability. Hence DPN is often inadequately treated, and the role of improving glycemic control in diabetes. Major international clinical guidelines for the management of DPN recommend several symptomatic treatments. First-line therapies include tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors, and anti- consultants that act on calcium channels. Other therapies include opioids and topical agents such as capsaicin and lidocaine. The objectives of this paper are to review current guidelines for the pharmacological management of DPN.

Keywords: DPN, hyperglycemia, depression, lidocaine

INTRODUCTION

Diabetic neuropathy comprises the disorder of peripheral nerve in people suffering with diabetes mellitus. Diabetes has become one of the largest global health care problems of the 21st century. It was estimated that around 415 million people worldwide suffered from diabetes in the year 2015, and these value are expected to increase to 642 million people by the year 2040 (Guariguata et al., 2014). Almost 50% of the people suffering through diabetes are expected to develop Diabetic peripheral neuropathy (Zhou& Zhang., 2019). Diabetic peripheral neuropathy is defined as “presence of symptoms and/a sign of peripheral nerve dysfunction in people with diabetes after exclusion of other causes". Diabetic peripheral neuropathy has devastating effect in the day to day life of the patient. Patient with Diabetic neuropathy repay firstly pain in the lower limbs of their body. This pain may be of

different types like sensation of burning, sensation of electric shock, pricking of needle etc. In some cases patient also suffer through loss of sensation. DPN significantly affects the quality of life of the patient and management of wealth (due to disease). Once diagnosed DPN leads to new challenges in the patient management (Knowler et al., 2002).

Review:

The epidemiology and natural history of patients are difficult to describe because of various clinical diagnostic criteria, variable selection of patients i.e. (patients with or without pain) and wide ranging physiological techniques. The EURODIAB complications study identified a prevalence of 28% for DPN at baseline with glycemic control and duration of diabetes being major determinants similar data was observed in the Diabetes Control and Complications Trial (DCCT) (American Diabetes Association., 1988). In a study of 4400 patients, the prevalence of DPN was found to be about 75% of newly diagnosed diabetes increasing to be 45% after 25 years of diabetes (Toeller et al., 1999).

The risk factor for DPN was determined by EURODIAB on 1100 people with type 1 diabetes followed over a period of 7.5 years (Shakher& Stevens., 2011) . These risk factor was similar to macrovascular disease like hypertension, smoking, increased lipid levels, duration of diabetes and body mass index (Ziegler et al., 1992). It was seen that neuropathic pain is also associated with other diseases like peripheral arterial disease (non-diabetic subject). So this is an important factor in diagnosis and treatment of neuropathic pain (Tesfaye et al., 2005).

The signs of diabetic neuropathy are variable. The neuropathic pain includes deep, aching pain with superimposed burning and stabbing pain. From a survey it was found that between 25% and 39% of patients may lack adequate treatment for their pain leading negative impact on quality of life (Dan Ziegler., 2008). The pain has been reported to in with general activity, mood, mobility, work, social relations, sleep, leisure activities, walking ability and enjoyment of life (Kajdasz et al., 2007)

Although exact cause of diabetic neuropathy is not known but it is thought to be caused due to nerve dysfunction and cell break and that results from oxidative stress and inflammation (Harris et al., 2012). Various health condition like hyperglycemia, dsylipidemia and insulin resistance all contribute towards dysfunction of various metabolic pathways like polyol pathway that sum up to cause the excess formation of mitochondrial and cytosolic reactive oxygen species (Sajic., 2014). These reactive oxygen species cause the injury to the axon of the nerve of the PNS hence leading to DPN. Multiple neurotransmitter also affect the pain pathway.

The development of DPN is multifactorial. The harmful metabolic effects of chronic hyperglycemia and effect of ischemia to the peripheral nerves are supposed to be the two mechanisms leading to dysfunction and damage. The pathophysiological effects of hyperglycemia are wide variety and include: activation of polyol pathway, generation of reactive oxygen species (ROS) (Oxidative stress), and reactive nitrogen species (Nitrosative stress) and accumulation of advanced

glycation end products (AGE) (Chokroverty et al., 1977). Excess glucose in the body is metabolized by polyol or sorbitol pathway. In this pathway glucose is reduced to sorbitol by the enzyme aldose reductase, (rate limiting step) before being oxidized by sorbitol dehydrogenase to fructose which is a potent glycating agent. The intracellular accumulation of sorbitol leads to reduction in nerve myoinositol and taurine and disruption of Na + / k + -ATPase membrane activity leading to accumulation of sodium in nerve, dysfunction of axon and structural damage the nerves **(**Ziegler et al., 1992; Shakher& Stevens., 2011**)**. The basement membrane of endothelial cells becomes glycosylated due to glycation of free amino group of protein, lipids and nucleic acid with alteration in their molecular structure and function (Brownlee., 2001). This leads to impaired vasodilation. Additionally the accumulated AGEs bind to receptor of AGE on macrophages with production of inflammatory cytokines (IL-1), tumor necrosis factor, growth factor and adhesion molecules(VCAM-1) (Singh et al., 2001)**.** Another novel pathway that's leads to complications of diabetes is activation of nuclear enzyme poly (ADP ribose) polymerase (PARP). Increased oxidative stress results in DNA damage and PARP 1 activation leading to cellular energy failure which is thought to be important in the pathogenesis of DPN (Vinik et al., 2001).

TREATMENT OF DPN

The DPN represent a great therapeutic challenge in pharmacological aspects. As the exact pathophysiology of the disease is unknown. Hence it can't be cured completely but it can be prevented as the pain can be reduced by the following three main principles: glycemic control, foot care and pain management (Hicks& Selvin., 2019). The glycemic control and foot care efforts are largely preventive. Lifestyle intervention including weight loss and physical activity may also be helpful in treatment of DPN. Pharmacological treatment is indicated. The American diabetes association recommends medication for the relief of pain Andrew symptoms related to diabetic peripheral neuropathy which is known to improve patient quality of life. Drug like Duloxetine and Pregabalin are approved by the US Food and Drug Administration (FDA) for the treatment of diabetic peripheral neuropathy (Onakpoya et al., 2019; Ormseth et al., 2011). Tricyclic antidepressants drugs are also used for treatment of DPN (to reduce pain) but it is not currently approved by FDA due to the risk of major side effects (Kvinesdal et al., 1984; Max et al., 1987)**.** Opioids can also be used to lower neuropathic pain but these are not recommended as they are habit forming drug. Hence they should not be used for first and second line therapy for neuropathic pain.

TREATMENT STRATEGIES

Patients diagnosed with DPN experience painful symptoms as we studied above, tight glucose control, moderate exercise and balanced diet may not be sufficient to reverse disease progression, therefore restoration of function, patient education and pharmacological therapy becoming necessary for treatment. The value of tight glucose control in DPN patients was demonstrated in both the

United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial (DCCT) (Stratton et al., 2000; EDIC., 1999). There are several guidelines recommended the use of pharmacological treatments both approved and off-label to reduce pain and to improve quality of life in DPN patients. These treatments include anti- depressant, anticonvulsant, analgesic, and topical medications. A wide variety of drugs used alone or in combination has been also shown significantly reduce neuropathic pain. Three different agents have regulated approval for the treatment of DPN i.e. Pregabalin, Duloxetine, and Tapentadol (Freeman., 2013; Peltier et al., 2014).

Anticonvulsant

Pregabalin was the first anticonvulsant to receive approval from the Food and Drug Administration (FDA) for the treatment of DPN and neuropathic pain after spinal cord injury (Verma et al., 2014; Blommel, M., & Blommel, A., 2007; Guy et al., 2014). Pregabalin is also proposed to be the result of improved trafficking of α2-δ subunits with a consequent diminishes expression of function Ca 2+ channels (Stahl et al., 2013). In addition to analgesic effects, Pregabalin present anxiolytic ability and it has a beneficial effects on sleep and quality of life (Zilliox, & Russell., 2011; Patel et al., 2014)•. Therefore contributing to improve the general condition of patients. Side effects include dizziness, somnolence, peripheral oedema, headache and weight gain (Tesfaye et al., 2013). Besides Pregabalin, Gabapentin is the only other anticonvulsant drug that is used for treatment of DPN. Some clinical trials have suggested that Gabapentin and Pregabalin present better analgesic efficiency than tricyclic antidepressants or Opioids. Other important aspects of this drug include its tolerability and lack of serious toxicity.

Antidepressants

Anti-depressant represents the first-line of drug in DPN Management. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is rated level A for efficacy and is approved in the United States for the treatment of this condition (Schreiber et al., 2015).The analgesic efficacy of Duloxetine in the treatment of DPN is maintained over a 6 month period (Cameron et al., 2001) .Hence it is a preferred drug for the treatment of DPN. Side effects are nausea, somnolence and dizziness as side effects. Other TCA like Amitriptyline and nortriptyline are found to effective in treatment of DPN. Most common side effects are postural hypotension, arrhythmias, congestive impairment, constipation and urinary retention. These side effects are more frequently observed after amitriptyline than nortriptyline treatment (Saarto & Wiffen., 2010).

Opioids

Opioids are used as second or third line treatment of DPN (Tesfaye et al., 2013; Page et al., 2012). Opioids like morphine and tramadol can be used to lower DPN but they have some side effects like nausea headache and somnolence

(Harati et al., 1998). Tapentadol has been shown to be effective in management of different types of chronic pain, low back pain and DPN with a tolerable safety profile (Afilalo & Morlion., 2013; Taylor et al., 2013). Trials have reported reduction of at least 30% in pain intensity in about 50% of the patients that reserved Tapentadol (Schwartz et al., 2011).

Capsaicin Topical Cream

Use of topical products may lead to less possibility of adverse effects. In addition the possibilities of drug interaction are markedly reduced by the use of topical local treatments which represent good options for patients with multiple medical problems (Peltier et al., 2014). The capsaicin cream has been shown to be effective in the treatment of neuropathic conditions and is approved for topical relief of pain (Peltier et al., 2014; Deli et al., 2013). There are some adverse effects linked with capsaicin cream which include itching, stinging, erythema, transient burning sensation and initial pain at the site of application that diminishes with repeated use (Zilliox& Russell., 2011; Groninger & Schisler., 2012).

Lidocaine Patch

Lidocaine patches acts as peripheral analgesic with minimal systemic absorption and currently used with other analgesic drugs (Zilliox& Russell., 2011;). Lidocaine acts as sodium channel blockers thereby counteracts the hyper excitability of peripheral nociceptors that contributes to neuropathic pain. Adverse effects are local irritation, contact dermatitis and itching (Wolff et al., 2010; Casale& Mattia., 2014).

Alpha Lipoic Acid

Alpha lipoic acid(ALA) acts as an antioxidant thereby it reduces oxidative stress, which is an important factors in pathophysiology of Diabetic neuropathy (Schreiber et al., 2015). Its antioxidant and anti-inflammatory actions may contribute to an all- round improvement of diabetic neuropathy symptoms. ALA has the least side effects among all the various other drugs used for treatment of DPN. The common side effects of ALA is nausea and vomiting (Zilliox& Russell., 2011; Patel et al., 2014).

Discussion:

The most common and debilitating microvascular complication of diabetes is diabetic peripheral neuropathy (DPN), affecting 50-90% of people with diabetes (Almuhannadi et al., 2018). The major manifestations of DPN are painful (pDPN) and painless diabetic peripheral neuropathy. The explosion of diabetes, especially in the South East Asian (SEA) region will result in an increasing prevalence of both painful and painless diabetic peripheral neuropathy. In the United States (US) and Europe, pDPN is estimated to occur in up to one- third of all patients with diabetes (Veves et al., 2008; Davies et al., 2006; Alleman et al., 2015; Sadosky et al., 2008; Gregg et al., 2004). Although diabetes is an increasing problem in Asia studies estimating the prevalence of pDPN are scarce. In a nationwide, observational study of

approximately 4000 patients with type2 diabetes in Korea, the estimated pDPN prevalence was 14.4%, or 43.1% of patients with DPN (Yoon et al., 2006; Ramachandran et al., 2012; Nanditha et al., 2016; Kim et al., 2014). In Japan, 22.1% of 298 diabetic out patients were found to have pDPN (Tsuji et al., 2013).

In a study from 2006 in Bangladesh, the prevalence of DPN was 19.7% in randomly selected patients with Type 2 Diabetes Mellitus (T2DM) aged 50.8±10.6 years and increased with age and duration of diabetes the prevalence increases (Mørkrid et al., 2010). In a study from 2012 in the outpatient department the prevalence of DPN was 35% with was a cross sectional study of 140 patients (Almuhannadi et al., 2018). In another study of 400 patients, neuropathy was diagnosed from the medical records and a prevalence of 16.8% was established (Tilahun et al., 2017).

A cross sectional study in 2013 was undertaken in North India in 586 participants of whom 18.4% were newly diagnosed (< 6 months) and 81.6% had known diabetes with a mean age of 57.1±9.7 years and mean duration of diabetes of 10.8±7.5 years with the help of Semmes-Weinstein monofilament (SWM) and vibration perception threshold (VPT (Almuhannadi et al., 2018). Similarly a study from South India with 1000 diabetic patients underwent biothesiometry and assessment of VPT, the prevalence was found to be 19.1% (Ashok et al., 2002). A retrospective study from Goa of 3261 patients with T2DM established a prevalence of 16.3% (Dias et al., 2016).In another study of 1500 patients with young onset diabetes aged 34.68±4.23 years, the prevalence of advanced neuropathy, the prevalence was found to be 13.1% (Sosale et al., 2016). In a retrospective study of 249 T2DM patients in a tertiary setting, a surprisingly low prevalence of 14.4% was established, but the method of diagnosing neuropathy was not disclosed (Umamahesh et al., 2014). A study of 1319 T2DM patients from 4 centers across India, SWM insensitivity the prevalence was found to be 15% (Viswanathan et al., 2005).

In Sri Lanka**,** a study of 528 diabetic patients of which 191 were newly diagnosed patients, used Diabetic Neuropathy symptom (DNS) score to determine DPN relevance of 48.1% (Almuhannadi et al., 2018). Test on Toronto clinical scoring system (TCSS) the prevalence with known Diabetes was found to be 24% (Katulanda et al., 2012). A most recent study with taking 8401 people was done in a Diabetic centre in Jaffna established as DPN prevalence of 34.1% (Sujanitha et al., 2015). In a further study of 1007 young Diabetic patients aged 36.6±11.17 years with diabetes duration of 4.8±4.2 years, using neurological symptoms the DPN relevance was found to be 30.7% (Almuhannadi et al., 2018).

Within Thailand, study with 899 Thai T2DM patients underwent assessment with the SWM (Semmes-Weinstein monofilament) on seven areas of the foot and 15.9% were diagnosed with advanced neuropathy and deemed at high risk of foot ulceration (Sattaputh et al., 2012). Similarly cross-sectional study of 438 diabetic patients from a tertiary care diabetes clinic, insensitivity to the SWM was found in

19.2% (Kosachunhanun et al., 2012).

A cross sectional study of 1785 people in Indonesia was done between 2008-2009 and the prevalence of DPN was found to be 67.1% (Soewondo et al., 2010) .In similar studies from Surabaya assessed the medical records of 302 T2DM patients and found the prevalence of DPN to be 58.6% (Soewondo et al., 2013) .

CONCLUSION

DPN remains a common and disabling complication of diabetes. The treatment should be focused on identification of risk factors, implementation of diabetic foot care program, symptom relief to improve quality of life and patient education is the key. Approaches like gene therapy and targeted delivery of antioxidant therapy may in the future would offer the best potential to reverse this common and disabling complication of diabetes. Approximately 50% adult with diabetes will be affected by peripheral neuropathy in their lifetime, more diligent screening and management would be the key to reduce complications and health care burden associated with the disease.

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