Diabetic neuropathy in Saudi Arabia: a comprehensive review for further actions

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ABSTRACT
Diabetes mellitus prevalence is rising worldwide. Long-term microvascular and macrovascular complications are responsible for the huge morbidity and mortality caused by this disease; they burden patients and healthcare systems. The most reported complication is diabetic neuropathy. It is linked to a long duration of diabetes and poor glycemic control, resulting in significant pain and distress. The Kingdom of Saudi Arabia (KSA) is the largest country in the Middle East that occupies approximately four-fifths of the Arabian Peninsula, supporting more than 33.3 million people. Around one-fourth of the people above the age of 30 years have diabetes. This review discusses the following on diabetic neuropathy in KSA: prevalence, risk factors, testing, management, awareness, and quality of life of neuropathic patients from the recently published studies conducted on the Saudi diabetic population.

Keywords: Microvascular complications, diabetic neuropathy, peripheral neuropathy, neuropathic pain, autonomic neuropathy, Saudi Arabia.

Introduction
Long-term microvascular complications of diabetes mellitus include retinopathy, neuropathy, and nephropathy. The earliest and most common complication is diabetic neuropathy [1]. It is defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” [2]. Multiple factors may contribute to its pathogenesis through different pathways like oxidative stress, glycation end products, and inflammatory processes [3]. There are various types of diabetic neuropathy. Distal symmetric polyneuropathy (DSPN) and autonomic neuropathy are the most common practices [2]. DSPN accounts for three-quarters of diabetic neuropathies. It presents as burning pain, numbness, paresthesia, or deep ache. Autonomic neuropathy affects the digestive tract, genitourinary, and cardiovascular systems [4]. Diabetic neuropathy affects 30%-50% of diabetic patients [5]. 25%-60% of idiopathic peripheral neuropathy patients were reported to have a pre-diabetic state, and about one-half of pre-diabetic patients have peripheral neuropathy or neuropathic pain [6]. In addition to hyperglycemia, the most important risk factors for developing peripheral neuropathy include age, duration of diabetes, hypertension, smoking, obesity, alcohol consumption, and dyslipidemia [5,7]. The American Diabetic Association states that neuropathy assessment should include a careful history, and small and large fiber function testing “temperature, pinprick, and vibration sensation.” Electrophysiological testing is indicated in special situations like atypical features or where a different cause is suspected [2]. In symptomatic treatment of neuropathic pain of diabetes, pregabalin, duloxetine, gabapentin, and amitriptyline should be considered as an initial approach [2,8]. Opioid-like medications, venlafaxine, desvenlafaxine, and topical agents like lidocaine and capsaicin are possible second-line therapies. Isosorbide dinitrate spray and transcutaneous electrical nerve stimulation may provide relief and can be used as add-on therapy [8]. Symptoms of gastroparesis can be controlled by prokinetic agents, like metoclopramide, domperidone, and erythromycin. Gastric electrical stimulation also has shown to improve symptoms [9].
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Prevalence and risk factors

Diabetic peripheral neuropathy (DPN)

The prevalence varies between studies due to differences in study tools, settings, and inclusion criteria as shown in Figure 1. Wang et al.’s study included 552 diabetic participants in Jeddah. DPN was diagnosed based on a combination of neurological symptoms and reduced vibration perception measured by the neurothesiometer and/or reduced light touch perception evaluated by the 10-g monofilament. The prevalence of DPN was 19.9% and correlated with glycemic control, diabetes duration, abdominal obesity, creatinine level, and white blood cell count [10]. In a hospital-based study in Riyadh, 69.2% of type 2 DM participants have DPN through clinical assessment by physicians. The significant risk factors were age, disease duration, and glycated hemoglobin (HbA1c) level [11]. In another study at the same hospital on 184 nephropathy patients, the DPN prevalence was 66.3%. Baseline creatinine clearance and proteinuria, high systolic blood pressure, advanced age, and longer diabetes duration were the most significant risk factors [12].

A prospective study was carried out at King Abdulaziz University Hospital in Jeddah, which included 237 diabetic patients. Patients were assessed for DPN using the Michigan Neuropathy Program. Neurological examination and nerve conduction studies were conducted for asymptomatic patients who scored less than 2 on simple clinical examination. Symptomatic DPN was present in 56%, while subclinical neuropathy was present in 57% of asymptomatic patients. Old age, long duration of type II diabetes, poor control, and smoking were associated with risk factors [13]. A total of 242 type 2 diabetics who attended the National Guard Primary Health Care (PHC) clinics in Riyadh were recruited in the study. Patients were assessed for painful DPN by using the Michigan Neuropathy Screening Instrument. About one-third of the study participants had a painful DPN.

Associated risk factors were poor glycemic control and poor compliance with treatment [14]. The same tool was used in another study in Al-Qassim, which revealed that the prevalence of diabetic neuropathy was 38.2%. Significant DPN associations included low education, hypertension, obesity, insulin use, and/or multidrug for diabetes [15]. In a large study conducted across the Kingdom of Saudi Arabia (KSA), 1,039 patients were enrolled. The Douleur Neuropathique-4 (DN4) questionnaire was used to identify the presence of a painful DPN. An overall prevalence of painful DPN of 65.3 was found. Age, sex, and duration of diabetes were statistically significant factors in neuropathy development [16]. DN4 was also used to assess patients attending PHC clinics in Al-Madinah for painful DPN. Overall, the prevalence was 29.1%, and it was associated significantly with age, duration of diabetes, poor control, and positive family history of diabetes mellitus [17]. On the other hand, another study in Al-Madinah showed that 62.5% of participants had DPN using the diabetic neuropathy index initially. A nerve conduction study was added for asymptomatic patients [18]. Sheshah et al. investigated 125 newly diagnosed diabetic patients for DPN by nerve conduction studies. They found that...
89% of them had either confirmed or subclinical DPN at that early stage of the disease (less than 6 months of the diagnosis) [1]. A case-control study was conducted in Al-Madinah to determine the predictors of DPN. It was found that the predictors include age, duration of diabetes, glycemic control, hypertension, cardiovascular disease, and other micro-vascular diabetic complications [19]. The prevalence of DPN was evaluated in diabetic patients in gulf countries, including KSA, Kuwait, and the United Arab Emirates, wherein the overall prevalence of DPN was 34.9% [20].

**Diabetic autonomic neuropathy**

Four hundred diabetic patients were evaluated for cardiovascular autonomic neuropathy (CAN) and gastroparesis. CAN was present in 15.3% of the participants [7.8% had prolonged QT interval (QT) on Electrocardiography (ECG), 4.5% had resting tachycardia, and 3% had orthostatic hypotension]. The long duration of diabetes and hypertension was independently associated with CAN. Gastroparesis symptoms were present in 6.3% of the participants and were significantly associated with the female gender. Metformin use was an independent predictor of the presence of at least one symptom [21]. Using the same tool for assessing symptoms of gastroparesis - “Gastroparesis Cardinal Symptoms Index,” 147 types 2 diabetics were recruited in another study. Symptoms of gastroparesis were present in 10.8% of the participants. Symptoms were significantly correlated to HbA1c, duration of diabetes, and comorbidities [22]. In university clinics in Riyadh, the prevalence of erectile dysfunction (ED) was 86.7% in diabetic men with a low testosterone level of 8-12 nmol/l. Obesity was an associated factor with low testosterone levels and ED [23]. Another study showed that 75.2% of the diabetic patients suffered from complete or partial ED, affecting their marital relationship [24]. In two more studies, sexual dysfunction was reported by 88.7% of Saudi women with type 2 diabetes [25], while ED was reported by 83% of Saudi male diabetic patients [26]. A significant association was shown between the presence of ED and age and duration of diabetes, but not glycemic control [27]. In two separate studies by El-Sakka, 86.1% of the participants had varying ED degrees, and 40.2% had acquired premature ejaculation. Both were significantly related to poor control, long diabetes duration, and other diabetic complications [27,28].

**Testing**

Many studies were conducted on the Saudi diabetic population to understand better that may help in the diagnosis and management of DPN. Researchers on electrophysiological studies conclude the following from various studies: absence of the sympathetic skin response is a reliable indicator of autonomic neuropathy among patients with diabetes mellitus in KSA [29]. The peroneal and tibial minimal F-latency and average F-duration provide the most sensitive nerve conduction indicators for diagnosing subclinical neuropathy in diabetes [30]. Sudoscan is a simple and objective tool that can detect DPN and the risk of foot ulceration among patients with diabetes [31]. Zakaria carried out two studies which suggested that the rise of vascular endothelial growth factor in diabetic neuropathy may be protective of preserving the nerve blood flow. On the contrary, the significant rise of soluble fatty acid synthase and the lack of adrenomedullin and ghrelin may cause neuropathy advancement [32,33]. Low plasma levels of magnesium and vitamin D were also investigated. Serum magnesium showed an inverse relationship with glycemic parameters; HbA1c, fasting plasma glucose [34], and DPN were significantly associated with vitamin D deficiency [35].

**Management**

Algefari, who found that 34.7% of his study participants had painful DPN, reported that none was taking medication to control the pain [14]. In Halawa et al.’s study, only 42.3% of participants with painful DPN stated that they were receiving treatment for pain [16]. Abou Zeid et al. studied the metabolic effects of pregabalin in diabetic neuropathic patients and found that the lipid profile parameters, Body mass index (BMI), HbA1c, and micro-albumin, were significantly improved after treatment [36]. The use of Sildenafil or Tadalafil showed incredible improvement in ED, orgasmic function, and intercourse satisfaction [37]. Sildenafil showed a positive influence on sperm motility and ejaculate volume [38]. Tadalafil improved nocturnal erections in diabetic patients with peripheral impotence [39]. Short-term oral vitamin D3 supplementation improved neuropathic symptoms in patients with type 2 diabetes [40]. No statistically significant improvement in symptoms of DPN was shown after 4 months of methylcobalamin use [41]. The addition of either magnetic or laser therapy to medications could bring extra benefits to patients with DPN [42].

**Awareness**

In a study comparing the knowledge between the Saudi and Egyptian diabetic populations, Saudis had moderate knowledge regarding diabetic neuropathy [43]. Another study in Al-Ahsa demonstrated that most Saudi diabetic participants lacked awareness about neuropathy [44]. Diabetic patients are unaware of diabetic foot risk factors, and practice of poor foot care was the conclusion of a multi-center hospital-based study [45].

**Satisfaction and quality of life**

Older patients, those who were compliant to diet, controlled diabetes, and no neuropathy, reportedly have higher treatment satisfaction scores and well-being scores [46]. The quality of life of diabetics was less among those who had diabetes complications: neuropathy, retinopathy, and diabetic foot [47].
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Conclusion

Diabetic neuropathy is prevalent among Saudi diabetic patients. Data about the prevalence of both types of neuropathy came from limited cities in KSA. Scarce evidence was found about the practices of symptomatic treatment of painful DPN. Causes of decreased prescriptions of neuropathic pain should be explored and managed in further studies. Few studies discussed the awareness and quality of life in patients with diabetic neuropathy. Educational programs could improve the understanding regarding DPN and its risk factors, which may help prevent neuropathy.

List of Abbreviations

CAN  Cardiovascular Autonomic Neuropathy
DPN  Diabetic Peripheral Neuropathy
DSPN Distal Symmetric Polyneuropathy
ED  Erectile Dysfunction
HbA1c  Glycated hemoglobin
KSA  Kingdom of Saudi Arabia

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