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A STUDY ON PERIPHERAL NEUROPATHY AND ITS RELATED RISK FACTORS ASSOCIATED WITH HbA1c LEVELS

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Abstract

Diabetic peripheral neuropathy (DPN) patients frequently feel persistent pain, which is described as painful diabetic peripheral neuropathy (PDPN), which begins in both feet and frequently spreads to the calves, fingers, and hands. PDPN not only causes pain, but also affects patients' sleep, emotions, mental state, and everyday activities, resulting in a low quality of life and a significant financial burden. The goal of this study was to monitor if there was a link between the prevalence, pattern, and related risk factors of diabetic peripheral neuropathy and hemoglobin A1C (HbA1c) levels. In this cross-sectional study, 150 type-2 diabetic patients were screened for DPN with PDPN and their HbA1c level was measured in every three months. DPN, PDPN and non-painful DPN were confirmed in patients displaying both clinical manifestations of neuropathy and neurological abnormalities assessment. DPN was detected in 24% (n = 36), while PDPN was found at 15% (n = 23) of the total patients. The prevalence of PDPN is 63.88% (n = 23) and non-painful DPN is 36.11% (n = 13) of total DPN (n = 36). Out of total PDPN (n = 23), the prevalence of symmetrical pain is 65% (n = 15), asymmetrical 35% (n = 8), sensory 26% (n = 6), motor 13% (n = 3), mixed (sensorimotor) 61% (n = 14), lower limb involvement 48% (n = 11), upper limb13% (n = 3) and both limb 39% (n = 9). In comparison to patients without DPN, both PDPN and non-painful DPN, patients had greater HbA1c levels ($p<0.05$). Furthermore, advanced age and longer diabetes duration were considerable and significant ($p<0.05$) risk factors for DPN with PDPN and non-painful DPN respectively. Overall, the findings imply that elevated HbA1c levels are closely linked to DPN, PDPN and non-painful DPN in type-2 diabetic patients and that HbA1c might be used as a predictive marker for DPN with PDPN and non-painful DPN in the patients studied.

Key words: Diabetic peripheral neuropathy, Painful diabetic peripheral neuropathy, Type-2 diabetes, HbA1c

Introduction

Diabetes mellitus (DM) is a kind of hyperglycemia that is linked to metabolic syndrome, a condition marked by insulin resistance (Gallagher et al. 2011). Diabetes mellitus has reached epidemic proportions worldwide, with 700 million people expected to have the disease by 2045 (IDF Atlas 2019). Two-thirds of diabetics live in cities, and three out of every four are working age. Diabetes-related deaths are expected to kill almost four million persons aged 20 to 79 in 2019. In Bangladesh, 8.4 million people have diabetes and 4.7 million are undiagnosed (IDF Atlas 2019). Long-term diabetes damages several organs, resulting in serious retinopathy, nephropathy, and neuropathy problems (Gionfriddo et al. 2014). Increased HbA1c concentration is the most

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important risk factor for predicting DM problems (Hossain et al. 2021). HbA1c is plasma glycosylated hemoglobin (HbA1c) that serves as an indication of average glycemic control over the past 2-3 months and signals poor diabetic management. Maintaining an HbA1c level of less than 6.5% is essential for reducing the risk of diabetic complications (International Expert Committee 2009). Diabetic peripheral polyneuropathy, which involves peripheral nerve injury, is one of the most prevalent consequences of diabetes, affecting about 8% of newly diagnosed individuals and more than 50% of long-term DM patients (Deli et al. 2013). Painful diabetic neuropathy (PDN), as well as bothersome autonomic characteristics such as orthostatic hypotension, are clinical symptoms of DPN (Boulton et al. 2005), autonomic neuropathy of the heart (a clinical condition which can result in sudden death) (Vinik and Ziegler 2007), noncardiac autonomic neuropathy causes a variety of different diseases (such as gastro-paresis and erectile dysfunction) (Vinik and Ziegler 2007), and a lack of trauma sensitivity (which can result in ulceration, infections, and lower extremity amputations) (Boulton et al. 2005, Narres et al. 2017).

Diabetic neuropathies are one of the most common long-term effects of diabetes (Dyck et al. 1993, Hossain et al. 2021). Polyneuropathy symptoms range from severe sensory alterations to motor weakness. Painful diabetic neuropathy (PDN) is a prevalent diabetic condition that affects up to one-third of people globally. Because of the diversity of pathophysiological pathways leading to pain, diagnosing, treating, and managing PDN can be difficult for doctors (Bril et al. 2011, Aslam et al. 2014). According to length dependency, the most common symptoms are symmetrical paresthesia and searing sensation in the legs. Foot ulceration and nontraumatic amputation are two severe consequences that can occur (Feng et al. 2011).

The most prevalent form of DPN is chronic sensorimotor distal symmetric polyneuropathy (Boulton et al. 2005), which causes significant sensory loss, muscle weakness, and discomfort. The most common symptom of DPN is a gradual onset of sensory abnormalities in the feet, such as burning and numbness. Indeed, the disease's onset is so slow that it may go untreated for years. Although neuropathic pain can be severe when it occurs, it is only found to occur in 11% to 32% of people with DPN (Vinik et al. 2000). Damage to the dysfunction of the system that conveys pain causes PDPN (National Institute for Health and Care Excellence 2013, Alleman et al. 2015). PDPN patients describe their symptoms as burning, aching, shooting, and stabbing, with nocturnal exacerbations common (Tesfaye 2009, Tesfaye and Selvarajah 2009). PDPN can be found in the arms, hands, legs, and feet (Jensen et al. 2007). DPN (distal symmetrical polyneuropathy) is the most common kind of diabetic neuropathy, affecting up to 50% of patients (Dyck et al. 1993, Tesfaye et al. 2005, Pop-Busui et al. 2017, Hossain et al. 2021). According to a more recent definition of DPN in the American Diabetes Association Position Statement, “the existence of symptoms and/or evidence of peripheral nerve damage in patients with diabetes after the exclusion of alternative causes” (Pop-Busui et al. 2017). The increased number of patients identified with DM-related neuropathic illnesses will have a significant influence on health and social care services (Sadosky et al. 2015). The intensity of the neuropathic pain is variable (Taylor-Stokes et al. 2011). Different clinical symptoms exist in DPN and painful DPN, the most prevalent of which is a mixed large and small fiber neuropathy. Small nerve fibers (SF) are sensory fibers with a small caliber that are responsible for peripheral nociception (Lauria et al. 2012). Regardless of whether or not pain is present, patients may experience numbness, tingling, or pins and needles. Neuropathic pain, especially moderate to severe neuropathic pain, can cause physical impairment, sadness, anxiety, sleeplessness, and a lower quality of life than people with painless-DPN (Gore et al. 2005, Themistocleous et al. 2016, Raputova et al. 2017, ADA 2020, Jensen et al. 2007, O’Connor 2009). Despite

the significant changes in a patient's clinical presentation, the neurological examination of painless and painful-DPN patients are is very similar. On clinical examination, the majority of patients with painful-DPN exhibit sensory loss, while a small percentage of patients with painful-DPN have indicators of "gain of function," such as allodynia and hyperalgesia (Themistocleous et al. 2016). In general, pain relief (as a result of treatment) is linked to an increase in quality of life (Deshpande et al 2006, Attal et al 2010). When compared to diabetic patients without DPN of the same age and sex, painful DPN is said to result in significantly higher healthcare costs. Even after accounting for differences in concomitant medical conditions such as cardiovascular disease, annual healthcare costs in two independent databases were 24% - 38% higher (Dworkin et al. 2010). According to the IDF, overall diabetes health costs were USD 760.3 billion in 2019, and are expected to rise to USD 845.0 billion by 2045. According to one analysis, global GDP losses from 2011 to 2030, including both direct and indirect diabetes costs, will exceed US$ 1.7 trillion, with 900 billion in high-income nations and 800 billion in low- and middle-income countries (Bloom et al. 2012). The exact processes that cause diabetic polyneuropathy are unknown; however, they appear to include systems that are only indirectly related to hyperglycemia (Toth et al. 2008, Obrosova 2009, King and Evcimen 2010). Currently, there is no specific treatment for DPN other than glycemic control which modestly slows the progression of nerve damage but cannot reverse the process (ADA 2021). Many researchers have looked into the link between HbA1c levels and DM complications. A study in Bangladesh reported the prevalence of DPN is 19.7% (Mørkrid et al. 2010). However, little study has been done on the HbA1c level that is crucial in different characteristics of PDPN or non-painful DPN. The aim of this study was to estimate the prevalence of DPN and to identify its risk factors in type 2 diabetic patients, with a view to provide necessary data to identify differential risk factors, which may ensure improved preventive measures and care for diabetic patients.

Material and Methods

This descriptive cross-sectional comparative study has been carried out from July 2017 to June 2018 in the outpatient department of Rajshahi Diabetic Association General Hospital, Rajshahi, Bangladesh. Total 150 diabetic type-2 patients were included randomly with or without DPN with inclusion (age >25, both male and female, patients who fulfilled the WHO criteria of type-2 diabetes mellitus) and exclusion criteria (other known causes of peripheral neuropathy, taking any drug causes peripheral neuropathy, other cusses of pain rather than DPN and also other types of diabetics rather than DM-2). Data was collected by a prescribed data collection sheet with the written consent of all individual patients through a personal interview, anthropometric measurement, investigations, examinations and previous history from the patient's diabetic record book. The HbA1c level was determined using ionic exchange HPLC (IE-HPLC) in the D-10 hemoglobin analysis system (Bio-Rad). In terms of a clinical diagnosis, it is generally agreed that DPN can be diagnosed by the presence of a combination of peripheral symptoms and neurological deficits (Boulton et al. 1998, Hossain et al. 2021). DPN was diagnosed in patients displaying both the presence of neurological symptoms and neuropathic symptoms including numbness, tingling, prickling, or burning pain in the legs and/or feet or upper limbs, symmetrical or asymmetrical. Neuropathic signs were defined as reduced or absent ankle jerk reflexes, knee jerk reflexes, biceps reflex, triceps reflex and supinator jerk reflexes (using an appropriate reflex hammer) and reduced or absent distal sensation, including vibration perception (using a 128-Hz tuning fork), touch sensation (using a 10 g monofilament), thermal discrimination (using cold and warm objects), pinprick sensation (using a pin) and proprioception. Signs were evaluated through careful neurological examinations.

At least one sensory function was impaired in the participant, including vibration sensation, monofilament sensation, touch sensation, pain sensation, thermal sensation, and position sensation, confirming DPN but at least two common symptoms of PDPN, such as burning sensation, numbing sensation, electric shocks, tingling pain, sharp or stabbing pain, or pins and needles. All of the data were articulated as mean ±SD (standard deviation) of the mean. Data have been analyzed using IBM SPSS software (version 20) and compared by Student t-test and p-value <0.05 was considered as statistically significant.

Results

The clinical parameters of all participants are summarized in Table 1. A total of 150 type-2 diabetic patients were recruited randomly, where 36 (24%) had been confirmed with DPN. Among the 150 patients, 81 were female and 69 were male patients. The patients with DPN presented significantly ($p<0.05$) higher age 53.22 ± 6.99 (mean ± SD) years, higher duration of diabetes 8.19 ± 5.11 (mean ± SD) years and higher HbA1c level 10.38 ± 2.12 (mean ± SD) than non-DPN patient's mean age 45.97 ± 9.86 (mean ± SD) years, duration of diabetes 3.77 ± 3.92 (mean ± SD) years and HbA1c level 8.88 ± 1.96 (mean ± SD) respectively. In our study, no significant ($p >0.05$) difference was found in the case of BMI level, systolic and diastolic BP between DPN and non-DPN participants.

Table 1. Clinical characteristics of the participants of DPN

Variables	Type 2 diabetic patients			*P*-value
	Total	Non-DPN	DPN	
n	150	114 (76%)	36 (24%)	-
Male	69 (46%)	47 (68.1%)	22 (31.9%)	-
Female	81 (54%)	67 (72.7%)	14 (17.28%)	-
Age (year)	48.58 ± 9.56	45.97 ± 9.86	53.22 ± 6.99	0.000046
BMI	24.35 ± 3.99	23.91 ± 3.49	25.14 ± 4.69	0.174743
Systolic BP	123.7 ± 14.64	121.88 ± 13.61	126.94 ± 16.00	0.114088
Diastolic BP	75.57 ± 13.26	75.34 ± 15.10	75.97 ± 9.32	0.797649
Duration (year)	5.27 ± 4.77	3.77 ± 3.92	8.19 ± 5.11	0.00003
HbA1c (%)	9.42 ± 2.13	8.88 ± 1.96	10.38 ± 2.12	0.000848

Table 2 shows the distributions of different characteristics (PDPN, non-painful DPN, symmetrical, non-symmetrical, lower limb, upper limb and both limb involvement, sensory, motor and mixed type of pain) of 36 DPN patients (22 males and 14 females). Out of 22 male DPN patients, 11 patients are PDPN and the remaining 11 are non-painful DPN. On the other hand, 12 female patients are PDPN out of 14 DPN while only 2 patients are non-painful DPN. Out of total PDPN (23 patients), symmetrical (15 patients), asymmetrical (8 patients), lower limb, upper limb and both limbs are 11, 3 and 9 respectively. On the other hand sensory, motor and mixed types of pain are 6, 3 and 14 respectively.

Table 2. Different Painful neuropathic signs and/or symptoms of patients with DPN

Type and number of patients		Presence of pain		Pain pattern		Involvement of pain			Pain character		
		Painful	Non-painful	Symmetrical	Asymmetrical	Lower Limb	Upper Limb	Both	Sensory	Motor	Mixed
Male (M)	1	No	Yes	No	No	No	No	No	No	No	No
	2	Yes	No	No	Yes	No	No	Yes	No	No	Yes
	3	Yes	No	Yes	No	Yes	No	Yes	Yes	No	No
	4	No	Yes	No	No	No	No	No	No	No	No
	5	Yes	No	No	Yes	No	Yes	No	No	No	Yes
	6	No	Yes	No	No	No	No	No	No	No	No
	7	No	Yes	No	No	No	No	No	No	No	No
	8	No	Yes	No	No	No	No	No	No	No	No
	9	No	Yes	No	No	No	No	No	No	No	No
	10	Yes	No	Yes	No	No	No	No	Yes	No	No
	11	Yes	No	Yes	No	Yes	No	No	No	Yes	No
	12	No	Yes	No	No	No	No	No	No	No	No
	13	Yes	No	No	Yes	Yes	No	No	No	No	Yes
	14	No	Yes	No	No	No	No	No	No	No	No
	15	Yes	No	Yes	No	No	No	Yes	Yes	No	No
	16	No	Yes	No	No	No	No	No	No	No	No
	17	Yes	No	No	Yes	Yes	No	No	No	No	Yes
	18	No	Yes	No	No	No	No	No	No	No	No
	19	Yes	No	Yes	No	No	Yes	No	No	No	Yes
	20	No	Yes	No	No	No	No	No	No	No	No
	21	Yes	No	Yes	No	No	No	Yes	No	No	Yes
	22	Yes	No	Yes	No	Yes	No	No	No	No	Yes
Sub-total (M)	22	11	11	7	4	5	2	4	3	1	7
Female (F)	1	Yes	No	No	Yes	No	Yes	No	Yes	No	No
	2	No	Yes	No	No	No	No	No	No	No	No
	3	Yes	No	Yes	No	Yes	No	No	No	No	Yes
	4	No	Yes	No	No	No	No	No	No	No	No
	5	Yes	No	Yes	No	Yes	No	No	No	Yes	No
	6	Yes	No	Yes	No	Yes	No	No	Yes	No	No
	7	Yes	No	Yes	No	No	No	Yes	No	No	Yes
	8	Yes	No	No	Yes	No	No	Yes	No	No	Yes
	9	Yes	No	Yes	No	Yes	No	No	No	No	Yes
	10	Yes	No	No	Yes	No	No	Yes	Yes	No	No
	11	Yes	No	Yes	No	Yes	No	No	No	Yes	No
	12	Yes	No	No	Yes	No	No	Yes	No	No	Yes
	13	Yes	No	Yes	No	No	No	Yes	No	No	Yes
	14	Yes	No	Yes	No	Yes	No	No	No	No	Yes
Sub-Total (F)	14	12	2	8	4	6	1	5	3	2	7
Grand Total (M & F)	36	23	13	15	8	11	3	9	6	3	14

Fig. 1 shows prevalence of PDPN is 15% (n = 23) which is higher than non-painful DPN prevalence which is 9% (n = 11) whereas DPN prevalence is 24% (n = 36) patients.

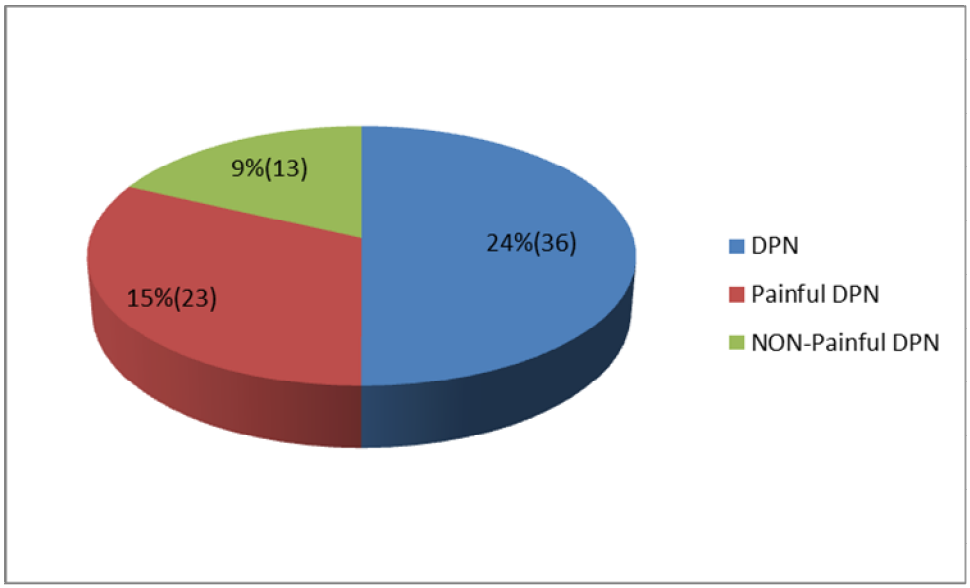

Fig. 1: Prevalence of PDPN, DPN and Non-painful DPN among (150 patients).

Fig. 2 mentioned the prevalence of PDPN and non-painful DPN which are 63.88% and 36.11% respectively among total DPN. Here total DPN indicate 100% (n = 36).

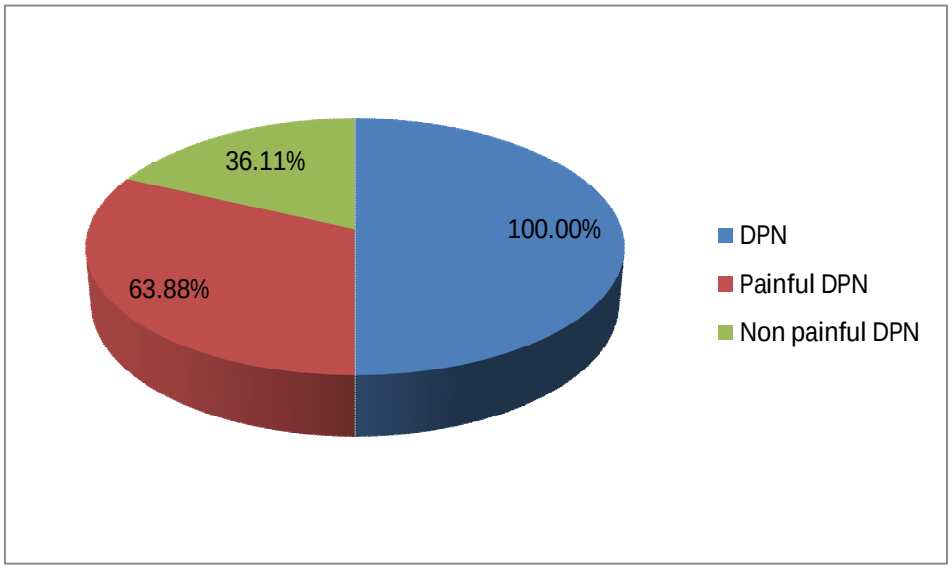

Fig. 2: Prevalence of PDPN, Non-painful DPN among total DPN (36 patients).

Fig. 3 shows the most frequent neurological symptom for 7 males and 8 females was symmetrical involvement of PDPN in limbs whereas the least frequent symptom was found for both upper limb (2 males & 1 female) and motor (1 male & 2 females) involvement. The second most frequent symptom (7 males & 7 females) was mixed (sensorimotor). The third frequent symptom was in lower limb (5 males & 6 females) involvement. Both limbs (4 males & 5 females) involvement were in the fourth position. The fifth and the sixth positions were asymmetrical (4 males & 4 females) and sensory (3 males & 3 females) respectively. These all the frequencies mentioned above, among 23 patients out of total 36 DPN patients who were painful where 11 male and 12 female patients. Females were more sufferers both in the number and frequencies of PDPN.

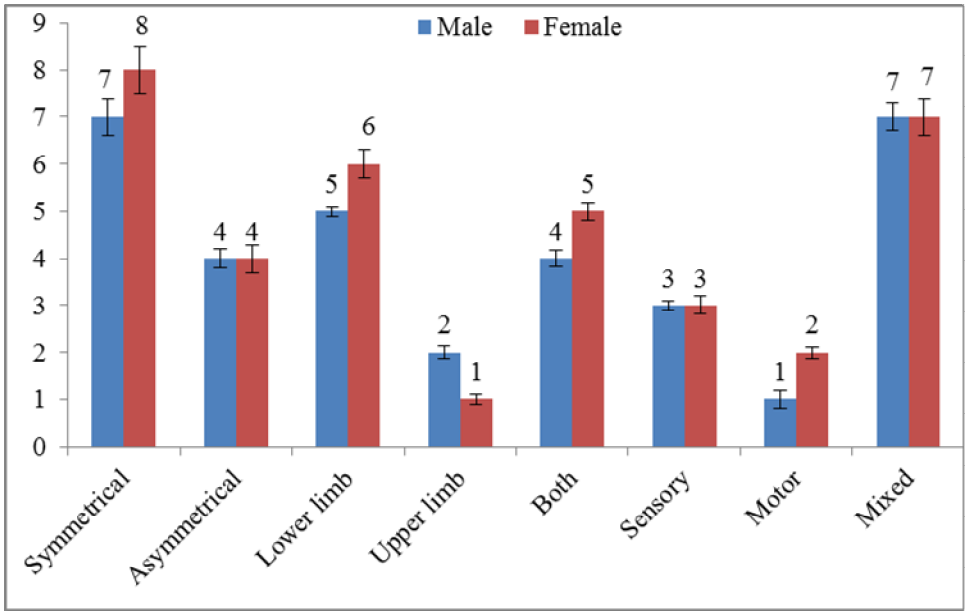

Fig. 3: Frequency of Painful neuropathic signs and/or symptoms of patients with DPN.

Fig. 4 shows the prevalence distribution of different characters, patterns and involvement of pain. The result shows the highest prevalence is 65% that is a symmetrical pattern but the lowest prevalence is 13% both in the case of the upper limb and motor respectively. The second highest prevalence is mixed (sensory motor) type of pain which is 61%. The prevalence of lower limb involvement was 48% which was in the third position. The prevalence of both limbs was 39% and is in the fourth position. 35% and 26% are the prevalence of asymmetrical and sensory respectively and fifth and sixth position also.

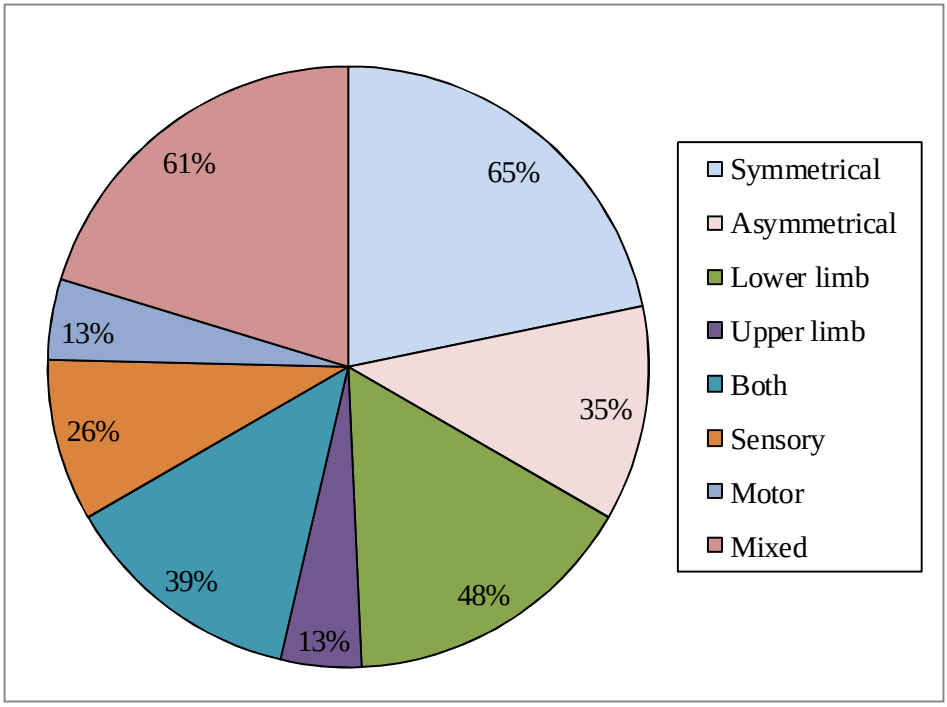

Fig. 4: Prevalence distribution of Painful neuropathic symptoms (among total PDPN) of patients with DPN.

Discussion

In the present study, we investigated the association of HbA1c with the prevalence of different characteristics of DPN in type-2 diabetic patients. The strength of the study is that the increased HbA1c variability was shown to be a significant and independent contributor to DPN with or without pain. In this study, the mean age of the DPN participants was 53.22 ± 6.99 years and the mean duration of diabetes was 8.19 ± 5.11 years. A study in Bangladesh reported by Mørkrid et al (2010) that the prevalence of DPN in type 2 diabetic patients was 19.7% (mean age in the DPN-group: 55.1 ± 10.5 years, mean duration of diabetes: 7.7 ± 1.9 years) (Mørkrid et al. 2010). Whereas the average age of the DPN patients in this study was 53.22 ± 6.99 years, with average diabetes duration of 8.19 ± 5.11 years. This finding suggests that in Bangladesh, the average age for having diabetes is getting younger. A study from an Indian diabetes facility identified a DPN prevalence rate was 19.1% among type 2 diabetic outpatients, which was similar to the current study's prevalence rate (24%) (Mean age in the DPN-group: 62 ± 8 years, mean duration of diabetes: 12 ± 8 years) (Ashok et al. 2002). In comparison to the results from India, diabetic complications in Bangladeshi individuals appeared earlier, both in terms of patient age and diabetes duration. In comparison to European research, Bangladesh has a lower prevalence rate of DPN (Cabezas-Cerrato 1998, BÖRü et al. 2004) with an overall prevalence rate of 32.1% (mean age: 63 years, mean duration of diabetes: six years) (Young et al.1993); 35.4% (mean age: 61.3 years, mean duration of diabetes: 9.7 years) (Cabezas-Cerrato 1998) and 60.0% (mean age: 57.2 ± 10.3, mean duration of diabetes: 8.52 ± 7.13 years) (BÖRü et al.2004) among diabetic hospital outpatients with type 2 diabetes. Even after correcting for age, studies in the UK found a lower DPN prevalence (11.9%) among type 2 diabetic South-Asian patients compared to European patients living in the

UK (Chaturvedi et al. 2002, Abbott et al. 2005). However, this discrepancy could be because the diagnostic criteria utilized in those western studies differ from those used in the current investigation, as stated by Morkid and colleagues (Mørkrid et al. 2010). Our respondents' average age was 48.58 ± 9.56 years, suggesting that the diabetes population in this region of the world is younger than in the West (Hossain et al. 2005, Mørkrid et al. 2010).

In this study, it was found that advanced age and diabetes over a longer period were important risk factors for peripheral neuropathy. These findings were consistent with those of other investigations (Mørkrid et al. 2010, Suljic et al. 2013, Darivemula et al. 2019, Punjot et al. 2021). HbA1c, fasting blood glucose levels, and two hours after breakfast were found to be key risk factors for peripheral neuropathy. These findings were in line with other reports (Chang et al. 2012, Kumar et al. 2012, Agrawal et al. 2014). There was no evidence of a link between systolic and diastolic blood pressure and peripheral neuropathy (Ramchandran et al. 1999) likewise found no substantial link between hypertension and diabetic neuropathy, however, some disagreed with this present study (Knuiman et al. 1986, Agrawal et al. 2014). However, we discovered that systolic and diastolic blood pressures had no significant relationship with peripheral neuropathy in our study.

HbA1c may exhibit a glycaemic threshold with micro and macrovascular consequences of diabetes, according to several studies, suggesting it could be a valuable biomarker to identify those at risk for various vascular issues (Zoungas et al. 2012, Gorst et al. 2015). In this study, it was observed that increasing HbA1c categories above almost 9.0% were significantly associated with increased prevalence of DPN. Results of this study were consistent with those who reported that increasing HbA1c categories (≥8%) had a higher prevalence of peripheral neuropathy (21.2%) (Sabanayagam et al. 2009). Another study also found a similar association of HbA1c with neuropathy (Gorst et al. 2015). The apparent HbA1c level threshold for microvascular events was found to be 6.5% (Zoungas et al. 2012). They also showed that, over certain thresholds, a greater HbA1c level was linked to a higher risk of microvascular events in a log-linear fashion. There was no significant link between mean HbA1c levels and risks below these levels. At HbA1c levels less than 7.0%, there were relatively few DPN episodes seen in the current study.

HbA1c variability, which measures long-term glycemic fluctuation, may induce oxidative stress (Chang et al. 2012), the Enhanced activity of the hexosamine pathway, as well as augmented flux through the polyol pathway, overproduction of precursors of advanced glycation end products, overactivation of protein kinase C isoforms, and overactivation of protein kinase C isoforms, may all contribute to tissue and cell damage. Furthermore, HbA1c fluctuation may boost the expression of a systemic inflammatory marker which is linked to vascular damage (Brownlee 2005). Another way that HbA1c fluctuation plays a role in diabetic complications is through cellular metabolic memory, which differs from short-term glycemic variability (Brownlee 2005). Excessive cellular indicators of DNA damage and hyperactivation of tumor suppressor transcription factors are produced by prolonged exposure to glycemic fluctuation, which may lead to a stronger metabolic memory effect than chronic hyperglycemia (Schisano et al. 2011). These cell damages can affect neurons as well as supporting tissue such as neuroglial cells and capillaries, resulting in nerve dysfunction and neuropathy (Callaghan et al. 2012). Therefore, HbA1c variability may be a potential factor associated with DPN risk.

In the current study, type-2 diabetes patients had a 15% of PDPN and a 24% prevalence of DPN. The prevalence of PDPN is 63.88% among DPN. The prevalence of PDPN in this study was consistent with the prevalence of 14% Turkey (Erbas et al. 2011), and 12% – 18% in Hong Kong, Taiwan, and Thailand, according to physicians (Davies et al. 2006, Sadosky et al. 2008, Veves et al. 2008, Alleman et al. 2015). While physicians in Malaysia and the Philippines estimated PDPN prevalence at 29% and 33%, respectively, similar to that reported in Western countries (Veves et al. 2008, Alleman et al. 2015), which is higher than the

current study. In a nationwide, hospital-based, observational study of type 2 diabetes in Korea, the estimated PDPN prevalence was 14.4%, which is consistent with our study. However, the prevalence of PDPN among DPN of our study is greater than 43.1% (PDPN) of DPN patients in Korea (Kim et al. 2014). In Japan, 22.1% of diabetic outpatients were found to have PDPN (Tsuji et al. 2013), and it is estimated that 15% – 25% of DPN cases are associated with neuropathic pain (Harris et al. 1993, Boulton et al. 2004, Davies et al. 2006, Sadosky et al. 2008), all of which support the findings of this study. Although there were fewer females with clinical neuropathy than males, more females than males reported painful neuropathy symptoms (Abbott et al. 2011) which are consistent with our study where the prevalence of DPN is higher in males (31.9%) compared to females (17.28%) in contrast with PDPN. In our study, old age, longer duration of diabetes and higher HbA1c level are significantly higher in DPN which is consistent with other studies (Darivemula et al. 2019, Punjot et al. 2021). Tesfaye et al. (2005) and Punjot et al. (2021) shown HbA1c and diabetes duration have been identified as risk factors for diabetic peripheral neuropathy (Tesfaye et al. 2005, Punjot et al. 2021). In a study, age and HbA1c levels were found to be independent risk factors for polyneuropathy comorbidity in diabetic patients (Lee et al. 2016, Punjot et al. 2021). According to the study by Zigmond and Snaith (1983), there was no difference in the clinical variables between patients with and without DPN. There was no significant difference in age, sex, diabetes duration, BMI, or glycemic control between patients with and without PDN (Zigmond and Snaith 1983). Therefore, age, sex, duration of diabetes, body mass index and glycemic control are the same as DPN with or without pain because DPN comprises PDPN and non-PDPN which is in favor of our studies. In another study, PDN affects a high number of Japanese diabetic patients (22.1%) (Tsuji et al. 2013). Davies et al. (2006) found a prevalence of PDN of 26% in the United Kingdom (Davies et al. 2006). In a research by Van Acker et al. (2009) in Belgium, 14% of the patients had lower limb neuropathic pain. In another report, 42.2% of diabetics in Eastern Libya had PDN, with age being a risk factor (Garoushi et al. 2019). In Saudi Arabia, 65.3% of people have PDN (Halawa et al. 2010). In the Middle East, 53.7% of people have PDPN (Jambart et al. 2011). As a result, the prevalence of PDPN in this study is somewhat higher than in Belgium but lower than in Japan, Saudi Arabia, and the United Kingdom. The vascular risk factors were found in develops DPN in Type-2 DM (Pop-Busui et al. 2013, Andersen et al. 2018, Callaghan et al. 2018). Increasing age (Van Acker et al. 2009, Ziegler et al. 2009, Aleidan et al. 2020), higher HbA1c (Themistocleous et al. 2016, Algeffari 2018), and duration of DM are all identified risk factors (Van Acker et al. 2009, Aleidan et al. 2020). In chronic pain problems, gender differences are well established, and neuropathic pain intensity has previously been shown to be more severe in females (Sorge and Strath 2018, Shillo et al. 2019). Several research addressing genetic variations related to DPN and painful-DPN have been conducted as a result of recent breakthroughs in gene sequencing technology (Faber et al. 2012, Li et al. 2015, Meng et al. 2015a, Meng et al. 2015b, Blesneac et al. 2018). There has also been a lot of attention to the involvement of voltage-gated sodium channels in neuropathic pain recently. The Nav 1.7 sodium channel is well-known for its role in pain signaling, and mutations in its producing gene, SCN9A, cause unusual pain syndromes. Nav 1.7 mutations have also been found in idiopathic small fiber neuropathy studies (Faber et al. 2012) and painful DPN (Li et al. 2015). Furthermore, despite major disparities in a patient's clinical presentation, the neurological evaluation of PDPN and non-DPN patients is the same. PDPN appears to be associated with the female gender (Shillo et al. 2019), which is in line with our findings. Long-term glycaemic control is necessary to reduce the risk of PDN (Garoushi et al. 2019). A study indicated that 32.5% of people have had chronic pain every day in their distal lower limbs for longer than three months (Bouhassira et al. 2013), Although, in our study, the prevalence and duration of lower limb involvement are higher. In both type-1 and type-2 diabetes, the likelihood of developing distal polyneuropathies- including painful neuropathies- appears to be inversely related to glycaemic control and directly correlated with diabetes duration (Franklin et al. 1990, Harris et al. 1993, The Diabetes Control and Complications Trial Research Group 1993, Tesfaye et al. 2005, Smith and Singleton 2008) which is favorable to our research Controlling your glycemia can help you avoid having DPN (Callaghan et al. 2012) and stifle its progress

(Pop-Busui et al. 2013). With rising pain severity, the burden of PDPN worsens (Gore et al. 2005, Alleman et al. 2015, Sadosky et al. 2015). The only strategy that has been found to reduce the risk of neuropathy in diabetic patients is intensive glucose management (Tesfaye and Selvarajah 2009, The Diabetes Control and Complications Trial Research Group 1993). Aside from having poor glycemic control, those who have had diabetes for a long time and are elderly are more likely to develop diabetic neuropathy (Tesfaye and Selvarajah 2009). Although the duration of diabetes is a well-known risk factor for chronic microvascular issues (Shin et al. 2009), rigorous blood glucose management has been found to reduce diabetic sequelae much more than conventional control for the same disease duration (The Advance Collaborative Group 2008). According to cohort studies, every 1% reduction in HbA1c levels is associated with a 37% reduction in the risk of microvascular complications (Clarke et al. 2004). Intensive glycemic control and lower levels of HbA1c are followed by a reduction in diabetic complications: in HbA1c, <7% is associated with a 60% reduction in the incidence of peripheral neuropathy (Nathan 2013). As a result, HbA1c is an independent risk factor for DPN with PDPN and non-painful DPN.

Conclusion

The present findings of this study suggest that increasing HbA1c level is significantly associated with increased prevalence of DPN as well as PDPN and non-painful DPN and the risk increases markedly at HbA1c levels ≥8.8%. The prevalence and risk of DPN, PDPN and non-painful DPN also increased with the advancement of age and longer duration of diabetes. Careful assessment of the risk factors of DPN, PDPN and non-painful DPN among diabetic patients, and control of HbA1c level and appropriate preventive measures and treatment are thus recommended. This must include effective communication between patients and physicians to maximize patient outcomes.

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