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Prevalence and Characteristics of Painful Diabetic Peripheral Neuropathy in Adult Patients with Type 2 Diabetes Mellitus, And Determine the Effects of This Pain On Their Quality of Life

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Abstract

Diabetes is a common chronic medical condition worldwide. It is becoming more widespread rapidly, because of the changes in behavioural and lifestyle modifications, for example, appropriate healthy eating patterns, and exercise. The complications of type 2 diabetes mellitus (T2DM) create a main public health problem, which is affecting individuals in developed and developing countries that have high rates of mortality and morbidity related to diabetes mellitus (DM).

Keywords: Diabetes Mellitus; Quality of Life; Peripheral Neuropathy; Type 2 Diabetes Mellitus; Painful Diabetic Peripheral Neuropathy

Introduction

As a cost of urbanization, the overall status of DM according to International Diabetic Federation (IDF) estimates in 2017 indicated that there are now four hundred twenty-five million adult patients with DM and three hundred fifty-two million adult patients with impaired glucose tolerance (IGT) worldwide (Ogurtsova et al., 2017). In Jordan, impaired fasting glucose (IFG) and the prevalence of T2DM were 7.8% and 17.1% respectively (Ajlouni et al., 2008). While in the Middle East region, the prevalence of diabetes is rising. In the Kingdom of Saudi Arabia, the prevalence of diabetes was 30% (Alqurashi et al., 2011) ; in Saudi Arabia, Kuwait and Qatar have placed them into the top ten (7^{th}, 8^{th} & 9^{th}) with the prevalence of 24%, 23%, and 23% respectively (Ogurtsova et al., 2017).

Individuals with DM are at raised risk for progressing accelerated complications (microvascular and macrovascular) (Jacovides et al., 2014). One of the most commonly linked complications of diabetes are the development of diabetic peripheral neuropathy (DPN). More recent research carried in Europe to evaluate the prevalence of the DPN range is between 40% and 50% of diabetic individuals (Argoff et al., 2006). Clinically, DPN is described as an appearance of signs or/and symptoms of peripheral nerve dysfunction in individuals with DM (Chawla et al., 2016; Barrett et al., 2017). The damage to peripheral neuropathy can be permanent, with damage of sensation leading to lower limbs amputation, as this condition develops (Barrett et al., 2017 ; Chawla et al., 2016). Also, it is connected with significant mortality and morbidity, and it is a very usual cause of raised hospitalization with health-related costs, lower limbs amputation, and non-traumatic amputations (Halawa et al., 2010 ; Bouhassira et al., 2013; Jacovides et al., 2014).

Painful diabetic peripheral neuropathy (PDPN) is a serious problem among patients who have T2DM (Tesfaye and Kempler , 2005). A 6,779 new cases of PDPN were classified, according to statistics from cohort research among almost 7.5 million persons contributing 38,118,838 personal years of evaluations in the UK, with a prevalence rate of 17.8 per hundred thousand personal years (Reed et al., 2013). Generally, PDPN is described as a direct consequence of deformities in the peripheral nervous system that cause pain for individuals with DM, is the most common manifestation could be aching, burning, or shooting in nature (Halawa et al., 2010 ; Jacovides et al., 2014).

Neuropathic pain usually interferes with activities of daily living (e.g. housework, study, work, leisure, or family activities), mood, work, mobility, and social relations (Abu-Shennar et al., 2020 ; Martino et al., 2020; Say et al., 2020). Additionally, the impaired patients' health could have a negative impact on the patients' quality of life (QoL) and may cause in some cases sleep disruption, discomfort, anxiety, and depression. This latter complication may take the greatest attention due to its dreadful possible outcome of amputation, with its negative consequences on the patient, family, society, and healthcare system (Kiyani et al., 2020). The main problem in adult patients with PDPN management is to prevent microvascular and macrovascular complications and to decrease mortality, economic costs lower limb amputation, and non-traumatic amputations. To achieve these objectives, PDPN patients have to engage in their self-care activities, such as a healthy diet, regular exercise, regular use of medications and blood glucose monitoring. Consequently, the American Diabetes Association (ADA) recommends that patients should undergo regular screening for neuropathy and regular foot investigation which contains annual checks for appropriate pain management, neuropathic symptoms, assessment of peripheral sensation and pulse in order to improve results outcomes in those patients' (American Diabetes Association, 2020).

The mainstay of management for PDPN patients are pain management, while glycemic control is the only disease adjusting therapy. Although there is an enhancing awareness among health care specialists regarding neuropathy, still there's a lack of data that is important for improving PDPN and pain management. Besides, the need for further research on this subject raises because PDPN is an often undertreated and underdiagnosed disease. Thus, early detection in the clinical care settings is necessary to enhance awareness and initiate the appropriate interventions necessary measures in order to delay or/and prevent further complications and improve those patients' QoL. Accordingly, the current research goals are to evaluate the characteristics and prevalence of PDPN in adult patients with T2DM and determine the effects of this pain on their QoL at the MoH hospitals in Jordan.

Designs and Methods

The study was conducted with adult patients (≥ 18 years) with T2DM who had regular follow-up visits at the MoH hospitals for at least six months. Patients with Type 1 Diabetes (T1DM) were excluded from the study because those patients are beyond the purpose

of this study. Adult diabetic patients who had an amputation surgery of the above-knee, whole foot, and below the knee amputations were excluded also from the research due to limited possibilities to examine them physically. The sample size for this study was calculated using the equation: ($n= (Z_{a/2})^2Pq/^2$) with a confidence level (CL) of 95%, expected prevalence of 50% and margin error of 5%, which was found to be (375) participants (Hulley et al., 2013). According to the researchers increased the sample size to 5% to compensate for the attrition rate and missing data. Accordingly, the final estimated sample included 400 participants, during the period from June 2019 - October 2019. An assessment instrument package was used in the current study. This package consisted of four parts including:

1. Socio-demographic data about participants (such as age, gender, smoking status, and education level) were obtained from the patients themselves. Diabetes clinical/laboratory data were gathered from the hospital records (such as HbA1c, weight, height, and treatment modalities). The consent form clearly specified that data regarding clinical health markers were to be extracted directly from each participant's file.

2. The prevalence and characteristics of PDPN were estimated using the Douleur Neuropathique4 (DN4) questionnaire, a truncated version of the International Association for the Research of Pain Questionnaire-Revised (Bouhassira et al., 2005), which determine the combinations of items or discriminate properties of items for the neuropathic pain diagnosis, including numbness, electric shocks, painful cold sensation, burning sensation, itching, pins, needles, tingling, and brushing hypoesthesia to prick, and hypoesthesia to touch. The DN4 Questionnaire is a Likert subscale anchored with 1 (No, definitely not) to 2 (Yes, definitely). It encompasses ten items; higher scores than or equals to three indicating patients with PDPN. Overall, the instrument demonstrated a specificity of 81.2% and a sensitivity of 78% in the psychometric properties analysis study (Bouhassira et al., 2005), and 74.47% of specificity with Cronbach's alpha was 0.67 in Riyadh, Saudi Arabia (Terkawi et al., 2017).

3. The QoL was evaluated using the Quality-of-Life Questionnaire entitled EQ-5D (Grochtdreis et al., 2021). The EQ5D (five-level version) contained five items with each having five response options: 1 (no problems); 2 (slight problems); 3 (moderate problems); 4 (severe problems); and 5 (extreme problems). It has been shown to be a reliable scale with $\alpha = 0.88$ (Abu-Shennar et al., 2020). Domains of the EQ-5D include anxiety/depression, usual activities (e.g., housework, study, work, leisure, or family activities), mobility, self-care, and pain /discomfort (Grochtdreis et al., 2021).

4. The intensity of pain was measured using the Numeric Rating Scale (NRS). This measure of pain intensity and unpleasantness has been shown to be reliable ($\alpha = 0.90$) and valid when used with adult patients (Thong et al., 2018; Atisook et al., 2021). In the current sample, the participants were asked to rate their average pain intensity over the last seven days by selecting a single number from 0 to 10. The scale includes four descriptors that represent four different levels of pain intensity (i.e., 0 "None", 1 to 3 "Mild pain", 4 to 7 "Moderate pain", and 8 to 10 "Severe pain").

In addition to the above measurements, we assessed these instruments with pilot testing on 10% of the sample participants (not included in this study) to ensure the feasibility of the study and to have a clear understanding of the inquiries.

Data Collection

Patients were chosen as a smaller group of the accessible population using the convenience sampling technique (Andrade, 2021). The research was carried on adult diabetic Jordanians diagnosed with T2DM, which that documented in the medical file between June - October 2019. These stages were used for data collection, in the following way:

- Before the data collection procedure, ethical approvals were secured from the Research and Ethics Committee/ Institutional Review Board at the MoH hospitals.

- Medical records were checked to select participants who met the inclusion criteria.
- The researcher contacted the head nurses in the selected center to facilitate the process of data collection.
- The researcher approached all participants who came across the inclusion criteria to invite them to participate in the study.
- A schedule of visits was arranged to meet participants who met the inclusion criteria in the selected center.
- The information sheet attached to the survey was read to each participant. The aim of this survey was explained to the participants and guaranteeing the confidentiality of the responses, and participants were given the required time to fill out the questionnaires.
- A face to face structured interviews were conducted while waiting for participants to turn in the clinic waiting room. The DN4, EQ-5D questionnaires were administered to evaluate PDPN, QoL, and obtain descriptive data. The period of each interview was about 10 minutes.
- After the interview, the participant was examined for the intensity of neuropathy pain using the NRS and lower limbs physical assessment for pain using the second part of the DN4 instrument. The period of each examination was about 5 minutes.

Statistical Analysis

Data were analyzed by using the Statistical Package for Social Sciences (SPSS, version 25). Continuous data were presented using descriptive statistics in the form of frequencies and percentages for qualitative variables and expressed as the mean ±SD when normally distributed, or median and interquartile when not normally distributed. Inter-group differences were evaluated using the Independent-Sample T-tests, Paired-Samples T-tests, and Chi-square or where appropriate. The Shapiro-Wilk test and the Kolmogorov-Smirnov test were used for the assessment of the data distribution. Spearman Rank-Order Correlation Coefficient (*Spearman's Rho*) was used for the assessment of the inter-relationships among quantitative variables and ranked ones. A binary logistic regression model was used to identify independent predictors of peripheral neuropathy after adjusting all other potential confounders. A p-value less than 0.05 was considered statistically significant.

Ethical Aspects

The study was conducted with the approval of the Jordanian Ministry of Health Ethical Board, Amman, Jordan, and the Near East University, Faculty of Nursing, Nicosia, Cyprus. All patients who volunteered for participation in the study gave written informed consent and the confidentiality of the information was assured.

Results

The research included a total of 400 adults diabetic Jordanians with T2DM aged between 32 to 85 years with a mean age of 58.2 years (*SD*= ± 9.4). Their socio-demographic and diabetes clinical/laboratory characteristics are shown in Table 1. More than half of the patients were men, 44.8% were retired unemployed, and 33% were current smokers. The mean BMI of research patients was 31.7 kg/m^2 (*SD*= ±5.4). The mean duration of DM was 9.7 years (*SD*= ±7.3), almost one-third of patients were having DM for less than 5 years and 65% were having controlled DM. Microvascular complications in the form of nephropathy and retinopathy were present in 5.5 and 10%, respectively. The majority of research patients were having dyslipidemia and almost all patients with dyslipidemia were receiving statin treatment. Besides, 85 and 32% were having hypertension and cardiovascular disease respectively.

The overall prevalence of PDPN among adult diabetic Jordanians who obtained scores higher than or equals to three was 47.8% based on the DN4 questionnaire. Regarding the characteristics of neuropathic pain (Table 2), showed that most of the adult diabetic Jordanians had at least one symptom of PDPN. The most commonly revealed symptoms in adult patients with PDPN were burning and tingling which were present in 63.9 and 78.5% of research patients, respectively. While, the least revealed symptoms were itching and painful cold which presented in 16.2 and 15.7% of PDPN, respectively. Using the NRS measurement of neuropathic pain intensity (Table 2), more than half of the patients had mild pain, while, 45% of the patients had moderate pain and 4.7% had severe pain among adult diabetic Jordanians with PDPN.

The prevalence of PDPN for study patients using the DN4 questionnaire according to relevant socio-demographic, and diabetes

Participants' characteristic	*N(%)*	*Mean (±SD)*
Age (year)		58.2 9.4 ±
< 50	56 (14)	
50-69	291 (72.8)	
≥70	53 (13.3)	
Gender		
Male	350 (87.5)	
Female	50 (12.5)	
Marital status		
Single /Divorced /Widowed	27 (6.8)	
Married	373 (93.3)	
Working status		
Unemployed	49 (12.3)	
Employed	172 (43.0)	
Retired	179 (44.8)	
Level of Education		
High school or less	140 (35.0)	
Diploma college	86 (21.5)	
Bachelor degree or higher	174 (43.5)	
Medical insurance		
Not insured	23 (5.8)	
Have any insurance	373 (94.3)	
Smoking status		
Not smoker	231 (53.3)	
Ex-smoker	55 (13.8)	
Current smoker	132 (33.0)	
Duration of diabetes		**9.7 7.3 ±**
< 5 years	149 (37.3)	
5-11 years	128 (32.0)	
≥12 years	123 (30.8)	
Body mass index (BMI) (Kg/ m^2)*		**31.7 (5.4±)**
Normal	32 (8.0)	
Overweight	131 (32.8)	
Obese	237 (59.3)	
Comorbid diseases \ conditions		
Hypertension	340 (85.0)	
Dyslipidemia	351 (87.8)	
Retinopathy	40 (10.0)	
Nephropathy	22 (5.5)	
Cardiovascular diseases	130 (32.5)	
Modality of treatment		
Insulin only	79 (19.8)	
Oral hypoglycemia agents only	207 (51.7)	
Oral hypoglycemia agents & Insulin	114 (28.5)	
HbA1C (%)		**7.6 (1.5±)**
Controlled <7%	140 (35.0)	
Uncontrolled ≥7%	260 (65.0)	

** = Normal: 18.5-24.9 kg/m^2; overweight: 25-29.9 kg/m^2; obese: ≥30 kg/m^2*

Table 1: Socio-demographic, and diabetes clinical/laboratory characteristic of the participants N=400

NRS score	*n (%)*	*P-value*
Mild pain (≤ 3)	96 (50.3)	0.001**
Moderate pain (4-7)	86 (45.0)	
Severe pain (8-10)	9 (4.7)	
Nature of PDPN[1] **n (%)**		
Burning	122 (63.9)	0.001**
Painful cold	30 (15.7)	0.004**
Electric shocks	38 (19.9)	0.001**
Tingling	150 (78.5)	0.001**
Pins and needles	104 (54.5)	0.001**
Numbness	83 (43.5)	0.001**
Itching	31 (16.2)	0.001**

1 = a patient may have more than four characters of pain.
** = significance level 0.05; ** = significance level 0.001.*
Table 2: The intensity, and nature of pain in participants with PDPN (n= 191)

clinical/laboratory data characteristics are shown in Table 3. Of the patients, 36.1% who had DM for longer than twelve years, 31.4% with a duration between five to eleven years, and 32.5% suffering from DM for less than five years revealed experiencing PDPN (p<0.05). The results also showed that 28.8% of the adult diabetic Jordanians with controlled DM and 71.2% of those with uncontrolled DM, suffered from PDPN (p<0.05). 88.5% of the patients with dyslipidemia and hypertension revealed having PDPN, concerning comorbid diseases/conditions. Besides, 24.6%, 34.6%, and 40.8%, of the patients treated with insulin only, oral hypoglycemia agents & insulin and oral hypoglycemia agents only, respectively, also revealed experiencing PDPN, a difference that was shown to be statistically significant (p<0.05).

Data regarding the EQ-5D questionnaire are found in Table 4. The patients who have PDPN revealed a negative impact on QoL and health status imagined compared to patients without PDPN. The overall mean score of the study patients based on the EQ-5D questionnaire was 0.37 (*SD*= ±0.36), while the mean score was 0.45 (*SD*= ±0.34) in adult diabetic Jordanians with PDPN, and the mean score was 0.21 (*SD*= ±0.33) in adult diabetic Jordanians without PDPN (*T-test* = 3.767, p<0.001). Most adult patients with PDPN had no problems in managing self-care (186/191; 98%), with (2/191; 0.8%) reporting severe and extreme problems in this domain. While most patients had no problems performing their usual activities (18/191;77.7%), (35/191; 18.2%) revealed some problems. Approximately half of the patients with PDPN revealed no problems in mobility (189/191; 99.2%), with (2/191; 0.8%) reporting severe and extreme problems due to pain. A large proportion of patients with PDPN revealed having moderate pain or discomfort (109/191; 57.1%), and (60/191;31.6%) reported being in extreme pain or discomfort. Additionally, nearly half of the patients with PDPN had moderate depression and anxiety (14/191; 7.3%), and (59/191; 31.2%) revealed extreme depression and anxiety. The majority of patients without PDPN revealed no problems in each domain of the EQ-5D questionnaire, and in every domain, this number was higher than the corresponding number of adult diabetic Jordanians with PDPN (Table 4).

In order to test the mutual relationship between outcome variables, Spearman's Rho correlation coefficients between PDPN score, EQ-5D score, and the health status imagine score were found to have a statistically important association with the others. The adult diabetic Jordanians with PDPN who revealed having problems in routine activities, mobility, discomfort or/and pain, self-care, and depression and/or anxiety have a negative impact on QoL (*Spearman's Rho* = 0.507, p<0.001); with a poorer self-rated health status (*Spearman's Rho* = -0.404, p<0.001) at a moderate level (50 to 69). Besides, the study patients in homogenate structure and data with a normal distribution, the Shapiro-Wilk, and the Kolmogorov-Smirnov tests revealed that the adult patients with PDPN have a negative impact on QoL and health status imagined, was statistically important (*Degrees of Freedom (df)* = 399, p<0.001) (Table 5).

The binary logistic regression analysis was used to classify the predictors of PDPN using the entry system (Table 6). A combination of demographic, clinical, and laboratory results factors were entered into the binary logistic regression model, including gender (reference: Male), HbA1c result (reference: Controlled <7%), BMI class (reference: Normal), and duration of diabetes (reference: < 5 years). In terms of the unique contribution of the patient factors, the only factor with a statistically significant unique contribution (with a p-value < 0.05) was the HbA1c result.

Variable	Neuropathy status		*P-value*
	With PDPN ***n = 191*** **(100%)**	**Without PDPN** ***n = 209*** **(100%)**	
Gender			
Male	171 (89.5)	179 (85.6)	0.241
Female	20 (10.5)	30 (14.4)	
Age			
<50	25 (13.1)	31 (14.8)	0.869
50-69	141 (73.8)	150 (71.8)	
≥70	25 (13.1)	28 (13.4)	
Employment			
Not employed	26 (13.6)	23 (11.0)	0.249
Employed	74 (38.7)	98 (46.9)	
Retired	91 (47.6)	88 (42.1)	
Smoking status			
Not smoker	98 (51.3)	115 (55.0)	0.690
Ex-smoker	26 (13.6)	29 (13.9)	
Current smoker	67 (35.1)	65 (31.1)	
Body mass index (BMI) (Kg /m²)			
Normal	17 (8.6)	15 (7.2)	0.565
Overweight	58 (30.4)	73 (34.9)	
Obese	116 (60.7)	121 (57.9)	
Duration of diabetes			
< 5 years	62 (32.5)	87 (41.6)	0.057
5-11 years	60 (31.4)	68 (32.5)	
≥ 12 years	69 (36.1)	54 (25.8)	
HbA1c (%)			0.013**
Controlled <7%	55 (28.8)	85 (40.7)	
Uncontrolled ≥7%	136 (71.2)	124 (59.3)	
Marital status			
Single / Divorced /Widowed	16 (8.4)	11 (5.3)	0.215
Married	175 (91.6)	198 (94.7)	
Level of Education			
High school or less than	72 (37.7)	68 (32.5)	0.184
Diploma collage	45 (23.6)	41 (19.6)	
Bachelor degree or higher	74 (38.7)	100 (47.8)	
Comorbid diseases \ conditions			
Hypertension			
Yes	169 (88.5)	171 (81.8)	0.062
No	22 (11.5)	38 (18.2)	
Nephropathy			
Yes	15 (7.9)	7 (3.3)	0.048*
No	176 (92.1)	202 (96.7)	
Cardiovascular disease			
Yes	69 (36.1)	61 (29.2)	0.139
No	122 (63.9)	148 (70.8)	
Dyslipidemia			
Yes	169 (88.5)	182 (87.1)	0.670
No	22 (11.5)	27 (12.9)	
Retinopathy			
Yes	25 (13.1)	15 (7.2)	0.049*
No	166 (86.9)	194 (92.8)	
Type of treatment			
Insulin only	47 (24.6)	32 (15.3)	0.001**
Oral hypoglycemia agents only	78 (40.8)	129 (61.7)	
Oral hypoglycemia agents & Insulin	66 (34.6)	48 (23.0)	

** = significance level 0.05; ** = significance level 0.001.*

Table 3: Prevalence of PDPN for adult patients with T2DM using DN4 questionnaire according to relevant socio-demographic, and diabetes clinical/laboratory characteristics

EQ-5D Item	All Participants (*N= 400*)	Participants with PDPN (*n= 191*)	Participants without PDPN (*n= 209*)	*T-test*	*P-value*
Overall EQ-5D *Mean (±SD)*	**0.37 (±0.36)**	**0.45 (±0.34)**	**0.21 (±0.33)**	**3.767**	**0.002****
Mobility *Mean (±SD)*	**0.02 (±0.25)**	**0.03 (±0.32)**	**0.00 ((±0.00)**	**2.010**	**0.027***
No problem	397 (99.3%)	189 (99%)	209 (100%)		
Some problem	0 (0)	0 (0.2%)	0 (0)		
Severe Problem	1 (0.3%)	1 (0.4%)	0 (0)		
Extreme Problem	1 (0.3%)	1 (0.4%)	0 (0)		
Self-Care *Mean (±SD)*	**0.03 (±0.27)**	**0.04 (±0.34)**	**0.013 (±0.11)**	**2.181**	**0.024***
No problem	393 (98.3%)	186 (98%)	206 (98.7%)		
Some problem	5 (1.3%)	3 (1.2%)	3 (1.3%)		
Severe Problem	1 (0.3%)	1 (0.4%)	0 (0)		
Extreme Problem	1 (0.3%)	1 (0.4%)	0 (0)		
Activity *Mean (±SD)*	**0.24 (±0.51)**	**0.27 (±0.56)**	**0.18 (±0.40)**	**2.974**	**0.004****
No problem	319 (79.8%)	18 (77.7%)	173 (83%)		
Some problem	70 (17.5%)	35 (18.2%)	34 (16.3%)		
Severe Problem	9 (2.3%)	6 (3.2%)	2 (0.7%)		
Extreme Problem	2 (0.5%)	2 (0.8%)	0 (0)		
Pain/discomfort *Mean (±SD)*	**1.21 (±0.76)**	**1.44 (±0.74)**	**0.84 (±0.64)**	**8.589**	**0.001****
No problem	55 (13.8%)	8 (4%)	61 (29.4%)		
Some problem	230 (57.5%)	109 (57.1%)	122 (58.2%)		
Severe Problem	98 (24.5%)	60 (31.6%)	24 (11.8%)		
Extreme Problem	16 (4%)	14 (7.3%)	2 (0.7%)		
Anxiety/Depression *Mean (±SD)*	**0.39 (±0.62)**	**0.48 (±0.67)**	**0.23 (±0.48)**	**4.398**	**0.001****
No problem	271 (67.8%)	116 (60.7%)	165 (79.1%)		
Some problem	107 (26.8%)	59 (31.2%)	40 (19.6%)		
Severe Problem	19 (4.8%)	14 (7.3%)	2 (0.7%)		
Extreme Problem	3 (0.8%)	2 (0.8%)	2 (0.7%)		
The health status imagined *Mean (±SD)*	**78.31 (±12.41)**	**75.71 (±12.49)**	**82.39 (±10.87)**	**5.629**	**0.001****

** = significance level 0.05; ** = significance level 0.001.*

Table 4: Responses in the EQ-5D questionnaire with health status imagined of study participants (N=400)

Item	The correlation coefficient of PDPN	The correlation coefficient of EQ-5D	The correlation coefficient of Health Status Imagine
PDPN score	1.000	0.507*	-0.404*
EQ-5D score	0.507*	1.000	-0.724*
The health status imagine score	-0.404*	-0.724*	1.000

** = Spearman's rho correlation coefficient is significant at the 0.001 level (2-tailed)*

Item	*Kolmogorov-Smirnov*		*Shapiro-Wilk*		*P-value*
	Statistic	*Degrees of Freedom (df)*	*Statistic*	*Degrees of Freedom (df)*	0.001*
Overall PDPN score	0.188	399	0.922	399	

**Lilliefors significance correlation*

Table 5: Spearman's rho correlation coefficient between EQ-5D score with the health status imagined, and PDPN score of the Participants

Uncontrolled DM (≥ 7%) was significantly associated with increased odds ratios (*OR*) for PDPN than those with controlled DM (< 7%) (*OR*=1.48, *CI*; 0.948-2.331; $p< 0.05$). The remaining factors did not show a statistically significant unique contribution in the model (Table 5). However, the overall model was statistically significant (*model Chi-square* = 72.837, *df* = 6, $p<0.001$). The model yielded an *R* of 0.606 and an adjusted R^2 of 0.320. This means that the combination of gender, HbA1c result, BMI class, and duration of diabetes can explain approximately 32% of the variance in PDPN of adult patients with T2DM on the population level; were male patients with uncontrolled HbA1c result (≥ 7%), who were overweight or obese and have had DM for longer than 5 years, are significantly more likely to suffer from PDPN.

P-value	*95% Confidence Interval (Lower – Upper)*	*Odds Ratios (OR)*	Variable
0.319	(0.390-1.358)	1 0.728	**Gender** Male Female
0.015*	(0.948-2.331)	1 1.48	**HbA1c (%)** Controlled <7% Uncontrolled ≥7%
0.406 0.697	(0.324-1.578) (0.406-1.826)	1 0.715 0.861	**Body mass index (BMI) (Kg/ m²)** Normal Overweight Obese
0.738 0.152	1.088 (0.663-1.784) 1.464 (0.870-2.464)	1 1.088 1.464	**Duration of diabetes** < 5 years 5-11 years ≥12 years

*Model Chi-square= 72.837, df = 6, p = 0.001**, R =0 .606, adjusted R^2 = 0.320).*
1 = References group.
** = significance level 0.05; ** = significance level 0.001*

Table 6: Logistic regression analysis of factors associated with PDPN according to DN4 questionnaire in adult patients with T2DM

Discussion

PDPN is a common disease that is challenging to manage due to complications developing from DM. Various studies have found that the PDPN prevalence ranges from 30 to 60% (Argoff et al., 2006 ; Bouhassira et al., 2008; Abbott et al., 2011; Jacovides et al., 2014). The current research intended to evaluate the characteristics and prevalence of PDPN in adult persons with T2DM and determine the effects of this pain on their QoL. The overall prevalence of PDPN in adult diabetic Jordanians with T2DM was 47.8%. There was no significant change according to gender. Based on participants' responses to the DN4 questionnaire: 89.5% of men were having PDPN and 10.5% of women were having PDPN ($p = 0.241$).

The outcomes are consistent with many studies from different regions in which the prevalence of PDPN was 30, 34.5, and 31.7% in South Africa, England, and France, respectively (Bouhassira et al., 2008; Abbott et al., 2011; Jacovides et al., 2014). Halawa et al . (2010), research in Saudi Arabia revealed a higher prevalence of PDPN in patients with T1DM and T2DM, which was 65.3% among 1039 patients (Halawa et al., 2010). The differences in the revealed prevalence rates in the Saudi Arabia research could be related to the differences in the research populations that involved participants with DM (with T1DM, and T2DM), and the discrepancy also could be related to the inter-subject variability in symptoms and signs of PDPN and the differences in the sample selected and methods used to evaluate PDPN.

In the Middle East region (Jambart et al., 2011), an estimated 53.7% of the patients matched the criteria for PDPN (with DN4 scores higher than or equals to four). This research involved different regions in the research like Jordan ($n = 1194$), Egypt ($n = 783$), Lebanon ($n = 1373$) and Gulf States ($n = 639$). Besides, the results revealed that the prevalence of PDPN was 57.5% in Jordan, a value less than the one detected in Egypt (61.3%), however, higher than the result detected in Lebanon and the Gulf States (53.9% and 37.1% respectively) (Jambart et al., 2011). The reason for the difference in the revealed prevalence of PDPN in patients with DM from all over the world can be related to different screening tools, different populations of the studies and different scores for DN4 used to evaluate patients with PDPN. Another possible reason for this association could be the existence of lifestyle differences between patients with PDPN involving less physical activity and weight gain.

Our data revealed that the most commonly revealed symptoms were burning and tingling, and the least reported ones were itching and painful cold in adult diabetic Jordanians. Several researchers assessed the pain nature in adult patients with PDPN, the most commonly revealed symptoms in patients with PDPN were pins, needles, numbness, and burning (Davies et al., 2006; Jambart et al., 2011; Reed et al., 2013). In cross-sectional research conducted in France involving 885 patients with T1DM and T2DM, results showed that the most commonly revealed symptoms in patients with T2DM were burning and numbness. While tingling and numbness were the most commonly revealed ones in patients with T1DM (Bouhassira et al., 2013). On the other hand, numbness, burning, tingling, needles and pins were the most commonly revealed symptoms on the DN4 questionnaire survey among 4097 patients with T2DM in cases of establishing PDPN from various regions in the Middle East involving Jordan (Halawa et al., 2010).

In this study, the neuropathic pain intensity of the 191 patients was evaluated using the NRS measurement of PDPN, participants revealed having pain in various intensities that range from mild to moderate. However, more than half revealed experiencing pain of mild intensity. In cross-sectional research carried with 1111 diabetic patients (776 with T1DM, 344 with T2DM) in Belgium (Van Acker et al., 2009). According to pain intensity, the results have been found that sixty-one percentages of PDPN participants had pain of moderate-intensity (Van Acker et al., 2009). The authors in this trial used a visual analog scale (VAS) for assessment of pain intensity, while in our study 45% of PDPN participants revealed having moderate pain based on the NRS measurement to evaluate pain intensity. The same results were found by another research in the USA, using a different tool for assessment of pain intensity, authors revealed a pain intensity ranging from moderate to severe in 71.4% of PDPN participants, in which pain intensity was evaluated by Brief Pain Inventory (BPI-DPN) scale (Gore et al., 2005).

Regarding the overall mean score of the study, persons based on the EQ-5D questionnaire, the adult persons with PDPN have a negative impact on QoL and health status imagined compared to adult persons without PDPN. These results of this study were

consistent with those from other epidemiological trials, where patients with PDPN had statistically important lower QoL with poorer self-rated health status than those without PDPN. For example, Davies et al evaluated the impact of PDPN in patients with T2DM on their QoL. The outcomes revealed that the patients who developed PDPN had poorer QoL (Bouhassira et al., 2008). Similar outcomes were found in Belgium in 1111 diabetic patients (344 with T1DM and 767 with T2DM). Their outcomes revealed that PDPN patients were more likely to state problems regarding mental alterations and physical activities than those without PDPN patients, a result that may explain their lower QoL (Van Acker et al., 2009). In more recent research carried out in France to evaluate the PDPN patient's impact on the QoL in 766 participants with DM (44.8% with T2DM, 38.7% with T1DM), the outcomes revealed that PDPN patients were related to disturbances in sleep, anxiety, and higher depression levels (Davies et al., 2006). Another recent research that was congruent with the outcomes of our study was carried out in South Africa. In this research, the outcomes revealed that PDPN participants have a negative impact on the QoL of 1036 participants with DM from fifty health care clinics (Jacovides et al., 2014). In conclusion, our data have found that there is a consensus that PDPN participants have a statistically important negative impact on the QoL in adult diabetic Jordanians with T2DM including both mental and physical status, by comparing these outcomes with the current research results.

The outcomes of the present research revealed that the participants with uncontrolled DM were a significant correlation with PDPN. Consistent with this research result is the finding reported in a cross-sectional study that was carried out in the UK, to determine the severity of PDPN and its impact on QOL (Davies et al., 2006), which revealed that the degree of PDPN was correlated with the degree of uncontrolled DM (*OR*: 1.28; *CI*: 1.08-1.52; $p = 0.004$). In Sarajevo, the same results were reported that the higher mean values of HbA1C were more likely in participants with PDPN compared to participants without PDPN (Suljic et al., 2013). These findings can be attributed to the toxic effect of hyperglycemia accumulation of advanced glycation end products (AGEs), oxidative stress, and activation of the polyol pathway (Fowler, 2008 ; Ziegler et al., 2006), which represent the pathophysiological mechanisms underlying microvascular and macro-vascular complications. Also, uncontrolled diabetes will enhance the narrowing of the small blood vessels, ultimately causing nerve ischemia. Furthermore, the anti-hyperglycemic medications and provide them with health education concerning lifestyle could perform a role in attenuation of the impact of HbA1c level on the progress of PDPN (Khawaja et al., 2018). In the meantime, our outcome does not mean that proper HbA1C control has no impact on the progress of chronic diabetes complications as neuropathy pain.

Our research is clinic-based at the MoH hospitals with a large sample size, so our findings may apply to participants receiving care in the community. The use of highly predictive, sensitive and inexpensive screening instrument as NRS scale, DN4, and EQ-5D questionnaires to determine the characteristics and prevalence of PDPN in adult participants with T2DM, and determine the effects of this pain on their QoL; will enhance the validity and reliability of the current research findings. Nevertheless, the research is limited to a cross-sectional design, which could not evaluate the long-term impacts of risk factors on the progress of PDPN as HbA1C control. Furthermore, the lack of detailed data and comparison regarding the documentation of the complications in adult participants with T2DM such as chronic kidney disease (CKD), and the lack of inquiry about, alcohol status and the use of pain treatment through pharmacological and non-pharmacological affecting peripheral neuropathy and causality determination for PDPN as folic acid, and B12 deficiency are another limiting factors that could lead to overestimation of PDPN prevalence.

Conclusion and Recommendations

PDPN is highly prevalent among adult diabetic Jordanians with T2DM, and it has a negative impact on their QoL. Appropriate intervention and early detection are mandatory in participants with uncontrolled diabetes, overweight, and long-standing diabetes. Our data highlighted the requirement for intensive care strategies targeting at early detection of PDPN, enhance patients' awareness, and prompt implementation of health education in participants with uncontrolled DM, overweight, and participants with long-standing DM. Furthermore, initial measures to delay or/and prevent PDPN in the form of implementation of behavioral and lifestyle modifications for example appropriate healthy eating patterns, exercise, and regular visits to the diabetologist, and management should be adopted to prevent the development and/or delay the progression of such a debilitating complication and reduce the burden of the disease. However, we are necessary to keep in mind that initial actions to control the diabetes epidemic is the better solution for preventing and/or delay its complications and improve those patients' QoL.

Declarations

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (national and institutional) and with the Helsinki Declaration of 1975, as revised in 2008.

The study was conducted following the Jordanian Ministry of Health Ethical Board, Jordan, Amman (Ref. No: MoH-2019/131), and the Near East University, Faculty of Nursing, Nicosia, Cyprus (Ref. No: HF-0754/2019).

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

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Authors' contributions

Abu-Shennar J, Bayraktar N, and Hatice B: Study conception and design, data collection, data analysis and interpretation, and preparation of the manuscript. Responsible and accountable for the accuracy or integrity of the work.
Abu-Shennar J, and Bayraktar N: Editing, drafting and critical revision of the manuscript.

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