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DETEKCIJA DIJABETESNE POLINEUROPATIJE U AMBULANTI PORODIČNE MEDICINE KORIŠĆENJEM MONOFILAMENTA

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Abstract

Introduction. Diabetic polyneuropathy (DPN) is the most common microvascular complication of diabetes mellitus (DM), which may be present at the time of disease detection. Screening for DPN is performed for the patients with type 2 diabetes at the time of diagnosis and for type 1 diabetes 5 years after diagnosis. The primary objective of this study was to determine the prevalence of DNP among family medicine patients with diabetes mellitus aged 18 to 70 years using nylon monofilament. Methods. The cross-sectional study estimated the prevalence of DPN among primary care patients with DM in Banja Luka. Seemes-Weinstein nylon 10g monofilament was used to detect DPN. Age, sex, duration of diabetes, type of therapy, symptoms, glycosylated hemoglobin (HbA1c) and risk factors (hypertension, smoking, dyslipidemia, obesity, physical inactivity) were analyzed. Data collection took place from 01/06/2017 to 31/05/2018. Results. The study included 228 patients, 132 (57.9%) men and 96 (42.1%) women. There was a statistically significant difference in the duration of diabetes and the presence of all symptoms of DPN (tingling, burning, light burning and stinging) with respect to the presence of polyneuropathy (p <0.01). Multivariate logistic regression revealed that patients who had hypertension (OR=26.2; 95% CI: 4.070-168.488; p=0.001), used oral antidiabetic therapy (OR=12.3; 95% CI: 1.300 -116.309; p=0.029 ) had tingling (OR=5.2; 95% CI: 1.431-18.571 p=0.012;)and a longer duration (OR=4.27; 95% CI: 1.983-9.175; p=0.000) of diabetes were more likely to have DPN. Conclusion. The prevalence of DPN in patients with diabetes is 24.2%. Determinants of DNP are the presence of symptoms of tingling, duration of diabetes, hypertension, dyslipidemia, and the use of oral antidiabetic therapy alone.

Key words:
diabetic polyneuropathy, diabetes mellitus, patient, prevalence.
Apstrakt

Uvod. Dijabetesna polineuropatija (DPN) je najčešća mikrovaskularna komplikacija dijabetesa melitusa (DM), koja može da bude prisutna i u trenutku samog otkrivanja bolesti. Skrining na DPN se radi svim pacijentima kod tipa 2 dijabetesa u trenutku postavljanja dijagnoze, a kod tipa 1 dijabetesa 5 godina od postavljene dijagnoze. Osnovni cilj ovog istraživanja je utvrditi prevalenciju DPN kod pacijenata sa DM korišćenjem najlonškog monofilamenta u ambulanti porodične medicine. Metode. Istraživanje je studija presjeka kojom je praćena učestalost DPN kod pacijenata sa DM na području Banja Luke. Za detekciju DPN korišten je Seemes - Weinstein najlonski 10g monofilament. Analizirani su: dob, pol, trajanje dijabetesa, simptomi, vrsta terapije, glikozilirani hemoglobin - HbA1c i faktori rizika (hipertenzija, pušenje, dislipidemija, gojaznost, fizička neaktivnost). Podaci su prikupljani u periodu od 01.06 2017.do 31.05.2018. godine. Rezultati. U istraživanje je bilo uključeno 228 pacijenata i to 132 (57,9%) muškarca i 96 (42,1%) žena. Utvrđena je statistički značajna razlika u trajanju dijabetesa i prisustvu svih simptoma DPN (trnjenja, gorenja, peckanja i žarenja) u odnosu na prisustvo polineuropatije (p<0,01). Multivarijantnom logističkom regresijom je utvrđeno da najveću vjerovatnoću pojave DPN ima pacijent koji ima hipertenziju, koristi oralnu antidijabetesnu terapiju, koji ima simptom - trnjenje i duže trajanje dijabetesa. Zaključak. Prevalencija DPN kod pacijenata sa dijabetesom je 24,2%. DPN je udružena sa prisustvom simptoma trnjenja, trajanjem dijabetesa, hipertenzijom, dislipidemijom i upotrebom samo oralne antidijabetesne terapije.

Ključne riječi:
dijabetesna polineuropatija, dijabetes melitus, pacijent, prevalencija.

Introduction

Diabetic polyneuropathy (DPN) is the most common microvascular complication of diabetes mellitus (DM), which may also be present at the time of disease detection. It is mainly distal sensorimotor polyneuropathy, which in 75% of cases is responsible for the early amputation of parts of the extremities and whole extremities in patients with diabetes (1,2,3,4,)


A study conducted in England found the onset of symptoms of painful neuropathy in one-third of the total number of diabetic patients at the community level examined (5).

Small A-delta and C fibers become damaged first. Initially, the disease is asymptomatic in 50% of cases (6), but later there the symptoms such as tingling, burning, loss of sensation of touch, temperature or pain, trophic changes on the skin with the onset of ulcers develop. The intensity of symptoms is greatest when resting - especially at night. DPN is the leading cause of foot ulceration, as well as a prerequisite for the development of Charcot's neuropathy or Charcot's foot, also increasing the risk of falls and fractures (7,8). It was found that 45% -60% of diabetic foot ulcers are of neuropathic origin, and are 3.5 times more likely to develop ulcers than non-diabetic patients.

The American Diabetes Association (ADA) (9) recommends DNP screening for all patients with type 2 diabetes at the time of diagnosis and with type 1 diabetes 5 years after diagnosis. According to the International Diabetes Federation (IDF), every family physician should provide foot examination at least once a year to his patients (10). There are several clinical diagnostic modalities for diagnosing DPN. Quantitative sensory testing (QST) has been available for more than 2 decades using cold and warmth thresholds to detect small fibre neuropathies. Seemes-Weinstein 10 g monofilament test is commonly used to detect DNP in family medicine setting. Further evaluation includes clinical imaging and nerve conduction studies (NCS). The study by Park et al. established the need for simple and non-invasive tests, including a Seemes-Weinstein 10 g monofilament test for DPN in patients with type 2 diabetes (11).

According to previous studies, DPN can develop as early as in pre-diabetes (glucose tolerance impairment - IGT) (12,13). In addition to hyperglycemia, one of the important factors involved in the pathogenetic mechanism of diabetic polyneuropathy is hyperlipidemia (14,15).

Many prospective studies have confirmed that loss of pressure sensitivity by 10-gram monofilament is an important predictor of possible onset ulceration and diabetic foot leading to possible lower limb amputations (16,17). Monofilament test is the best choice for DPN detection because it is portable, fast, non-invasive, inexpensive and patient-friendly.
The epidemiological research found that prevalence of DPN in the world is greater than 50%, when adjusted for diabetes duration and age (18,19,20). However, data for the diabetes patients in the Republic of Srpska are lacking.

The primary objective of this study was to determine the prevalence of DPN among family medicine patients with diabetes mellitus aged 18 to 70 years using nylon monofilament. The secondary objective was to determine the risk factors (hypertension, smoking, dyslipidemia, obesity, physical inactivity), duration of diabetes, type of therapy and regulation of diabetes mellitus (glycosylated hemoglobin - HbA1c) associated with DNP.

**Methods**

The cross-sectional study explored the prevalence of DPN in patients with DM registered with the family practices and affiliated with Primary Health Center Banja Luka. With a population size of 15617 diabetic patients, an error of 5%, confidence level of 95% and confidence interval of 6.44, the estimated sample size was 228. Patients were selected randomly from electronic registry of patients with diabetes. Data collection took place between June 2017 and May 2018.

Inclusion criteria were: age 18 to 70, DM diagnosis according to International Classification of Diseases (ICD) typ 1 and typ 2 DM, and written consent to participate in the study obtained from each respondent. Patients with DM who had ulcers or amputations, associated peripheral arterial disease, and those with multiple complications of diabetes were excluded from the study. Written and electronic records of DM patients were used in the data collection.

For the purpose of the research, a checklist was created for each participant individually. The participants underwent inspection, palpation and physical examination of the foot. Seemers-Weinstein nylon 10g monofilament was used to detect DPN.

The examiner demonstrated first the strength of the monofilament touch on each participant’s arm, then asked them to close their eyes and performed testing on both feet. The examined points included first metatarsal-phalangeal joint of the thumb, the dorsum of the thumb, the plantar side of the thumb, and the plantar side of the heel. The participant should relay when he or she feels the touch. The total score is eight. According to a previous study more than four wrong answers screened positive for DPN (4). Also, data on
subclinical manifestations (tingling, burning, light burning and stinging) of DPN are collected in an interview with each participant (Yes, No).

Age, sex, duration of diabetes, type of therapy, glycemic regulation (glycosylated hemoglobin - HbA1c) and risk factors (hypertension, smoking, dyslipidemia, obesity, physical inactivity) were recorded for each participant.

Participants were divided in 4 age groups: 20-30 years, 31-40 years, 41-50 years and 51-60 years. According to the duration of diabetes, they were also divided into 4 groups: duration of diabetes up to 5 years, 10 years, 20 years and over 20 years.

According to the type of therapy, they were divided into 3 groups: those using oral antidiabetic therapy, insulin therapy and combination therapy. For glycemic control assessment, HbA1c was used. HbA1c levels were evaluated in the central laboratory of the Primary Health Center Banja Luka (bioanalyzer Arhitekt c 8000). HbA1c <7% was considered as good glycemic control, and HbA1c ≥ 7% as poor glycemic control. Blood pressure value value greater than 130/80 considered unregulated hypertension.

Dyslipidemia was diagnosed if total cholesterol value was >4mmol/l, and/or LDL cholesterol > 2.6mmol/l and/or triglyceride > 1.7mmol/l (21,22). Obesity was recorded if participant’s body mass index (BMI) was > 30kg/m2 and waist circumference (WC) > 94 cm for men and 80 cm for women. According to physical activity, participants were rated as inactive, moderately active, and extremely physically active (23).

The consent of the institutional Ethics Committee has been obtained for this research.

Statistical analysis

All analyzes were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). The results were analyzed and presented using descriptive statistics (absolute and relative numbers, measures of central tendency, standard deviation). Demographic data and risk factors in the respondents were analyzed using adequate statistical tests (Hi square / $\chi^2$ test and Student's t test of independent samples). Univariate and multivariate logistic regression were used to determine the association between DNP and risk factors (CI). A probability level or p value of less than 0.05% (p <0.05) was considered statistically significant.

Results
The study included 228 patients, 132 (57.9%) men and 96 (42.1%) women. The average age of our participants was 55.8 ± 9.2 years. The prevalence of DNP among our participants with diabetes mellitus using nylon monofilament was 24.2%.

Participants with longer duration of diabetes and reporting all symptoms of DPN (tingling, burning, burning and burning) were more likely to have DNP in comparison with those without symptoms and short disease duration (p <0.001). The statistically significant difference in the DNP presence was found between patients on insulin therapy and those who used other types of therapy (p =0.012). No statistical significance was found between patients with lower and higher HbA1c than 7%, nor between both types of diabetes with respect to the occurrence of polyneuropathy (Table 1).

Differences in DNP presence were not found in regards to hypertension (p =0.276) and smoking (p=0.607). However, DNP was more frequently found among participants with dyslipidemia in comparison to those without (p=0.046)(Table 2).

The multivariate logistic regression model was adequate for the data available (χ² = 80.794, p < 0.001), with 63.6% of the variability of the dependent variable explained by the selected model. Also, when predicting polyneuropathy using the characteristics of patients who entered the model, 85.9% of cases would be successful.

In univariate regression models, associations were found between DNP and following variables: the presence of symptoms of tingling (8,509), burning (5,415), light burning and stinging (4,906), hypertension (3,380), and the use of insulin therapy (2.075).

Multivariate logistic regression revealed that patients who had hypertension(OR=26.2; 95% CI: 4.070-168.488; p=0.001), used oral antidiabetic therapy (OR=12.3; 95% CI: 1.300 -116.309; p=0.029 ), had tingling (OR=5.2; 95% CI: 1.431-18.571 p=0.012;) and a longer duration of diabetes (OR=4.27; 95% CI: 1.983-9.175; p=0.000)were more likely to have DPN. (Table 3).

**Discussion**

The prevalence of DNP among family medicine patients with diabetes mellitus aged 18 to 70 years using nylon monofilament was 24.2%. The determinants of DNP were hypertension, using oral antidiabetic therapy, having tingling and a longer duration of diabetes.
The prevalence found in the current study was lower than in previously conducted research. Salvotelli et al. investigating DPN in patients with type 2 DM, based on a clinical examination of the foot, detected a prevalence of 30% (24). A study conducted in Tanzania found that more than a half of patients included in that study had neuropathy with the severe form and the main risk factors were increasing age, increasing duration of diabetes, obesity, and hypertension (25).

Age and gender were not associated with the prevalence of DNP, what is in disagreement with study of Gill et al. finding association between prevalence of DPN, age and duration of symptoms (26).

Study of Abbott et al. from North West England showed that type 2 DM patients, women, and the South Asian population have higher incidence of DNP (5). Studies in Jordan and England have found a prevalence of DPN of 30.3% -39.5% in patients with type 2 DM over the age of 18. Also, they detected higher prevalence in the secondary health care versus primary health care setting level of health care, as well as higher occurrence of DPN among patients with type 2 DM in comparison to the patients with type 1 DM (27,28). Our study showed no association between glycemic control via HbA1c and the presence of DPN, although the greater number of patients who had DPN had HbA1c greater than 7% (Avg HbA1c = 7.98 ± 2.07).

Although statistical analyses showed that participants with dyslipidemia have higher prevalence of DNP, no associations between DNP and lipids serum level were found per multivariate regression analysis. A meta-analysis of several observational studies has demonstrated an association between LDL cholesterol fraction and systolic blood pressure with DPN (29). Also, a study done in Jordan (27) found a significant association of dyslipidemia with increased OR for DPN.

Chinese study carried out on patients with type 2 DM, found higher prevalence of DNP among overweight and obese patients (33.1%) in comparison with patients who had optimal BMI (30). On the other hand, recent Indian found no associations between obesity and DNP, what corroborates our findings (31).

Considering the type of therapy, this study found that the use of oral antidiabetic therapy alone was a predictor of DPN together with the duration of diabetes and the present risk
factor - hypertension (OR = 12.296, 95% CI: 1.300-116.309, p <0.05). A cross-sectional study conducted in Peru found that patients who were both on oral and insulin therapy were 40% more likely to have DPN than those with a diabetes duration longer than 10 years (32).

Several limitations need to be considered. Only Seemes-Weinstein nylon 10g monofilament test was used to detect DNP. Although this test presents a good, inexpensive and accessible screening tool, more objective diagnostic procedures are required for confirm the diagnosis of DNP. The study measured HbA1c at single point of the time, what may not reflect the real level of glycemic control. Study was carried out in one region of the Republic of Srpska, and the results may not be generalized to the whole country.

Conclusion

The prevalence of DPN in diabetic patients is 24.2%. DPN was associated with hypertension, the presence of symptoms (tingling), the duration of diabetes, and the use of oral antidiabetic therapy alone. Screening of diabetic polyneuropathy is justified in a family medicine setting. Early and rigorous management of diabetes and associated risk factors may have an essential role in the prevention of diabetic complication development and progression.

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Annex

Table 1. Frequency of DPN with respect to sex, age, HbA1c, duration of diabetes, presence of symptoms (tingling, burning, light burning and stinging) and type of therapy

| Presence of DPN | YES | NO | p    |
|-----------------|-----|----|------|
| **Gender, n (%)** |     |    |      |
| Male            | 38  | 94 | 0.059|
| Female          | 17  | 78 |      |
|                  | 0   | 0  |      |
| **Age, n (%)**  |     |    |      |
| 18 - 30         | 1   | 6  |      |
| 31 - 40         | 2   | 10 |      |
| 41 - 50         | 4   | 21 | 0.712|
| 51 - 60         | 25  | 73 |      |
| 61 - 70         | 23  | 62 |      |
| 71+             | 0   | 0  |      |
| **HbA1c, n (%)** |     |    |      |
| <= 7.00         | 20  | 64 | 0.887|
| 7.01+           | 35  | 107|      |
| 5-10g           | 19  | 106|      |
| **Duration of diabetes, n (%)** |     |    |      |
| 10-15           | 11  | 41 | <0.001|
| 15-20g          | 13  | 18 | 10.5%|
| > 20g           | 12  | 7  | 4.1% |
| **Presence of symptoms - tingling, n (%)** |     |    |      |
| YES             | 44  | 55 | <0.001|
| NO              | 11  | 117|      |
| **Presence of symptoms - burning, n (%)** |     |    |      |
| YES             | 27  | 26 | <0.001|
| NO              | 28  | 146|      |
| **Presence of symptoms - light burning, n (%)** |     |    |      |
| YES             | 32  | 38 | <0.001|
| NO              | 11  | 117|      |
stinging, n (%)  
|   | YES | NO  |
|---|-----|-----|
|   | 13  | 23  |
|   | (23.6%) | (41.8%) |

Oral antidiabetic therapy, n (%)  
|   | YES | NO |
|---|-----|----|
|   | 13  | 42  |
|   | (23.6%) | (76.4%) |

Insulin therapy, n (%)  
|   | YES | NO |
|---|-----|----|
|   | 33  | 22  |
|   | (60.0%) | (40.0%) |

**DPN- diabetic polyneuropathy; HbA1c-glycosylated hemoglobin**

Table 2. Frequency of risk factors in a patient with and without DPN

| Presence of DPN | p     |
|-----------------|-------|
| **Hypertension >130 end >80, n (%)** |       |
| YES             | 19    | 46   | 0.276 |
| NO              | 36    | 125  |       |
| Ex-smoker       | 9     | 35   |       |

| Smoking, n (%) |     |
|----------------|-----|
| Smoker         | 14  | 34  | 0.607 |
| Non-smoker     | 32  | 103 |       |

| Dyslipidaemia, n (%) |     |
|----------------------|-----|
| YES                  | 30  | 111 | 0.046 |
| NO                   | 22  | 42  |       |

| LDL, Avg ± std.dev |     |
|--------------------|-----|
| 2.939 ± 0.95       | 3.353 ± 1.019 | 0.012 |

| HDL, Avg ± std.dev |     |
|--------------------|-----|
| 1.3075 ± 0.397     | 1.293 ± 0.435 | 0.825 |

| CHOL, Avg ± std.dev |     |
|---------------------|-----|
| 5.1172 ± 1.152      | 5.468 ± 1.248 | 0.068 |

| Tg, Avg ± std.dev |     |
|------------------|-----|
| 2.007 ± 1.45     | 2.1605 ± 1.509 | 0.516 |

| Obesity, BMI>30, n (%) |     |
|------------------------|-----|
| YES                    | 24  | 56  | 0.155 |
| NO                     | 30  | 110 |       |
| Inactive               | 13  | 35  |       |

| Physical activity, n (%) |     |
|--------------------------|-----|
| Moderately physically active | 34  | 109 | 0.857 |
| Extremely                | 8   | 28  |       |
physically active

DPN-diabetic polyneuropathy; LDL-low density lipoprotein; Avg- average, std. dev- standard deviation; HDL- high density lipoprotein; CHOL- cholesterol, Tg- triglyceride; BMI: body mass index

Table 3. Univariate and multivariate logistic regression of DPN-related variables

|                  | p   | OR  | 95% C.I. for OR | p   | OR  | 95% C.I. for OR |
|------------------|-----|-----|----------------|-----|-----|----------------|
|                  | Lower | Upper |          | Lower | Upper |          |
| Gender           | 0.061 | 0.539 | 0.283 | 1.029 | 0.790 | 0.850 | 0.257 | 2.813 |
| Duration od diabetes | 0.000 | 2.085 | 1.534 | 2.833 | 0.000 | 4.266 | 1.983 | 9.175 |
| Presence of symptoms - tingling | 0.000 | 8.509 | 4.083 | 17.733 | 0.012 | 5.155 | 1.431 | 18.571 |
| Presence of symptoms - burning | 0.000 | 5.415 | 2.761 | 10.618 | 0.105 | 3.368 | 0.777 | 14.600 |
| Presence of symptoms - light burning, stinging | 0.000 | 4.906 | 2.572 | 9.357 | 0.066 | 4.054 | 0.914 | 17.980 |
| HbA1c            | 0.097 | 1.153 | 0.975 | 1.365 | 0.407 | 1.159 | 0.817 | 1.645 |
| Holesterol       | 0.070 | 0.787 | 0.607 | 1.020 | 0.150 | 0.556 | 0.250 | 1.238 |
| LDL              | 0.013 | 0.641 | 0.450 | 0.912 | 0.077 | 0.440 | 0.177 | 1.093 |
| CCR ml/sec       | 0.107 | 0.637 | 0.368 | 1.103 | 0.133 | 0.516 | 0.218 | 1.222 |
| AvgTAa           | 0.008 | 1.033 | 1.008 | 1.058 | 0.028 | 0.934 | 0.879 | 0.993 |
| Hypertension >130 ili >80 | 0.001 | 3.380 | 1.667 | 6.852 | 0.001 | 26.186 | 4.070 | 168.488 |
| Oral antidiabetic therapy | 0.045 | 0.526 | 0.282 | 0.985 | 0.029 | 12.296 | 1.300 | 116.309 |
| Insulin therapy  | 0.025 | 2.075 | 1.098 | 3.919 | 0.069 | 6.014 | 0.870 | 41.578 |

OR – odds ratio; CI – confidence interval; HbA1c-glycosylated hemoglobin; LDL-low density lipoprotein; CCR- creatinine clearance; AvgTA- average blood pressure
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