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Utility of DN4 questionnaire in assessment of neuropathic pain and its clinical correlations in Turkish patients with diabetes mellitus

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ABSTRACT

Aim: We aimed to assess the utility of DN4 questionnaire (Douleur Neuropathique en 4 questions) to define the frequency and severity of neuropathic pain (NP) and also its clinical correlation to daily clinical practice.

Methods: We included 1357 patients with diabetes (56.5% women, 90.4% type 2 diabetes) who were followed up in our diabetes outpatient clinic. Presence of NP was evaluated by performing simultaneous DN4 questionnaires and physical examination. Those who had a DN4 score ≥4 were considered to have NP.

Results: The mean age was 58.2 ± 12.1 years, mean duration was 12.5 ± 7.5; (min–max: 1–45) years, mean HbA_1c level was 7.8 ± 1.6% (min–max: 5–16.2%), (61.7 ± 6.0 mmol/mol; min–max: 31.1–153.6 mmol/mol). Three hundred thirteen patients (23%) were diagnosed with NP using the DN4 tool. Male gender ($p = 0.01$), receiving antihypertensive treatment ($p = 0.01$), presence of retinopathy ($p < 0.001$), cardiovascular disease (CVD) ($p = 0.01$) and previously diagnosed neuropathy ($p < 0.001$) were significantly associated with higher NP scores. Those who had increased DN4 scores were more likely to be on oral hypoglycemic agents (OHA) + insulin combinations ($p < 0.001$), had longer diabetes duration ($p < 0.001$) and higher HbA_1c levels ($p = 0.001$). Logistic regression model revealed that diabetes duration (OR: 1.02, 95% CI: 1.00–1.04, $p = 0.007$), elevated HbA_1c levels (1.11, 1.02–1.21, 0.015), presence of retinopathy (1.41, 1.20–1.64, <0.001), management with at least one OHA (1.47; 1.12–1.92; 0.004) or any insulin regimen (1.62; 1.16–2.27; 0.005) (compared with diet only-regimens) were significantly associated with NP.

Conclusion: Utilization of DN4 questionnaire in daily clinical practice is an effective tool in the identification of pain related with peripheral diabetic polyneuropathy.

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1. Introduction

Diabetes mellitus is an increasing epidemic with the recent reported prevalence estimated to be 8.3% of adult population meaning that 382 million people have diabetes worldwide. [1]. Over 90% of diabetes cases are type 2 diabetes. Diabetes associated microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral and coronary arterial disorders) complications have a great impact on both patients' survival and quality of lives. In the Turkish Diabetes Epidemiology Study II, the prevalence of diabetes in Turkey is reported as 13.7% [2].

Increasing prevalence of both type 1 and type 2 diabetes results with an increase in diabetes related complications, which also severely affect patients' quality of life especially in the developing countries. Diabetic peripheral neuropathy (DPN) is defined as a progressive loss of distal sensation initially effecting the lower extremities [3,4]. Poor glycemic control, aging, long diabetes duration, visceral obesity, height, hypertension, smoking, hypoinsulinemia and dyslipidemia are the most important factors implicated with disease progression [5]. Neuropathic pain also contributes to diminished vibratory, pain and temperature sensations and results with chronic diabetic foot ulcers, which unfortunately, leads to nontraumatic amputations [6].

Although DPN is estimated as the most common complication of diabetes, it is frequently under recognized leading to underdiagnosis [7]. Furthermore, the causal relationship between DPN and pain still lies as a challenging condition for many patients and their physicians rendering them to low levels of realization [8]. This makes periodic clinical examination mandatory in the surveillance of diabetic patients. Moreover it is considered that, development of accurate and sensitive diagnostic modalities would be helpful in the early detection of neuropathic signs and symptoms [7,8].

Painful DPN is described as a superficial burning pain accompanied with other sensorial symptoms, usually affecting lower extremities and progresses by ascending to upper limbs over time [9]. Among patients with diabetes, 10–20% experience pain due to presence of peripheral neuropathy [10]. There are several methods for detection of DPN ranging from quantitative methods, such as nerve conduction velocity, vibration threshold, pinprick test, and thermal tests, to several validated questionnaires. However, there is no agreed gold standard for the detection of DPN and the diagnosis of painful DPN is still challenging, especially as it is hard to differentiate neuropathic pain from nonneuropathic pain.

Several screening questionnaires (i.e., LANSS, NPQ, PainDETECT, ID-pain, StEP) have been developed to identify neuropathic pain since 2001 [11]. Douleur Neuropathique 4 (DN4) is one of these questionnaires, which was originally developed and validated in France. Linguistic validation has also been reported in international studies [7,12,13].

We aimed to assess the utility of DN4 questionnaire in defining the frequency and severity of NP and its clinical correlations in daily practice.

2. Methods

This study is designed as a cross-sectional study. One thousand three hundred fifty-seven patients were included in the study (56.5% women, 90.4% type 2 diabetes). Patients were being followed up at Istanbul University Istanbul Medical Faculty Diabetes Outpatient Clinic between November 2012 and April 2013. All the patients were evaluated for the presence of neuropathic pain by physical examination and DN4. At first, DN4 questionnaires were applied by an experienced nurse, all the patients were referred to the physician with their DN4 scores.

The 5.07/10 g Semmes-Weinstein monofilament test and evaluation of vibration sensation with a 128 Hz tuning fork were used to diagnose diabetic neuropathy. Symptoms related with pain, numbness and burning sensation were investigated as well as the examination of the main arterial pulses. An electromyography (EMG) test was performed when it was considered necessary.

Two distinct forms were used in the evaluation of the patients: Patient Identification Form and DN4 questionnaire.

Patient Identification Form, included data related with age and gender, type and duration of diabetes, HbA_1c levels and the treatment regimens. Concomitant hypertension, retinopathy, nephropathy, neuropathy, cardiovascular disease (CVD), peripheral vascular disease (PVD) and diabetic foot ulcer were also noted.

Douleur Neuropathique 4 (DN4) questionnaire, consisted of 10 items. The first seven items were associated with the patients' subjective complaints related to pain and sensational variations while the last three items were associated with the clinical findings. Those patients who had a DN4 score $\geq$4 were considered to have NP [14]. The DN4 questionnaire has been validated in Turkey by Unal-Cevik [15].

The patients were categorized into two groups based on their DN4 scores (group 1; DN4 score <4; *n*: 1044 and group 2; DN4 score $\geq$4; *n*: 313) and the two groups were compared according to their mean age, gender, type and duration of diabetes, HbA_1c levels, presence of diabetic complications, comorbidities and as well as the treatment regimens to control neuropathic symptoms.

The study was approved by the Academic Board of Endocrinology Division. An informed consent was obtained from all of the participants.

3. Statistical analysis

According to the literature data; NP frequency, type 1, type 2 error and deviation/error ratio were estimated as 14%, 5%, 20% and 3%, respectively and minimum number of patients that should be included in the study was calculated as 1049. In order to minimize potential error related with missing data, approximately 30% more than the initially calculated sample size was included in the study and 1357 patients were included in this study. Data were tested for normality using One sample Kolmogorov and Smirnov test and histogram. Descriptive analysis was performed with mean $\pm$ SD values that were estimated for continuous variables and frequencies