Diabetic peripheral neuropathy in the outpatient department – a red-flag for associated risk factors and comorbidities

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ABSTRACT

Objectives. To assess the characteristics of patients with type 2 diabetes mellitus (DM) and diabetic peripheral neuropathy (DPN) as compared to patients with type 2 DM without DPN in an ambulatory setting, given the pandemic size of DM and its challenge for the healthcare systems worldwide in the 21st century. From the chronic complications of DM, DPN has a major impact on the patient’s life quality. DPN risk factors are both modifiable and unmodifiable and represent either other comorbidities per se, or predisposing factors for various comorbidities that alter the patient’s prognosis.

Material and Methods. We conducted a retrospective observational study with 112 patients with type 2 DM treated in an out-patient department, in order to assess the characteristics and associated comorbidities of DPN. The group characteristics are a mean age of 60.28±9.76 years; 62.5% males; 77.67% from urban settlement; a prevalence of DPN of 52.67%.

Outcomes. In the statistical analysis, DPN significantly associated with duration of DM, the need for insulin-therapy, risk factors such as smoking or obesity; with other complications of DM such as retinopathy, chronic kidney disease, atherosclerotic cardiovascular disease or peripheral artery disease; with comorbidities such as heart failure; and with the level of HDL-cholesterol and eGFR.

Conclusions. A patient with DPN is more prone to also present other microvascular complications of type 2 DM, such as chronic kidney disease, retinopathy and, respectively with macrovascular complications of type 2 DM, and with other comorbidities such as heart failure and obesity. Its easily available diagnosis in an ambulatory setting by quantitative sensory testing should offer to DPN the status of a good marker for the presence of other chronic complications or comorbidities in type 2 DM, prompting the patient’s screening and an adequate medical management.

Keywords: diabetes mellitus, complications, outcomes, peripheral neuropathy, prevention

OBJECTIVES

The pandemic of Diabetes Mellitus (DM), a chronic non-transmittable disease, is emerging and is one of the 21st century biggest challenges for the healthcare systems worldwide [1].

The chronic complications of type 2 Diabetes Mellitus (T2DM) arise from chronically increased glycaemic values and are classified in relation to the diameter of the affected blood vessels in microvascular (i.e. microangiopathy, diabetic neuropathy, retinopathy
Diabetic peripheral neuropathy (DPN) has a great impact on the patients with both type 1 DM and T2DM. It decreases the quality of life and increases the morbidity and mortality, secondary to its consequences, such as pain, fall-related injuries, ulcerations, Charcot foot and need of amputation [3,4]. Subsequent pain in DPN can be subjectively assessed by questionnaire, and may be a proper marker for anticipating alteration of sleep and a poorer quality of life [3,5,6].

The risk factors for DPN development and progression are classified as modifiable or nonmodifiable. The first category, the modifiable risk factors, include major risk factors such as poor glycaemic control or other factors such as cardiovascular risk factors (high blood pressure (HBP), obesity, dyslipidaemia, smoking), while the latter, the unmodifiable risk factors, includes major risk factors such as duration of DM and age; or other factors such as prediabetes, education level, gender, height, insulin resistance, hypoinsulinemia [4,7,8].

DPN may be confirmed through invasive technique – skin biopsy; or non-invasive – the novel surrogate imaging markers – corneal confocal microscopy; nerve conduction studies, optical coherence tomography; nevertheless, quantitative sensory testing (QST) represents an easily accessible, inexpensive method for screening for DPN [3,8,10]. In this case, referral to a neurologist for further investigations is recommended when symptoms are atypical or the diagnosis remains uncertain [10].

Given the accessibility of QST on one side, and the challenging management and high economic burden of DPN on the other side, the need for screening and early diagnosis of DPN is constantly reinforced. Active screening and identification of modifiable risk factors is also very important, as well as their management [10,11,12]. Finally, association with other macrovascular complications, respectively, retinopathy and CKD [8,9,13] as well as with traditional cardiovascular risk factors and diseases [13] is of utmost importance.

The aim of the study was to assess the characteristics of patients with T2DM and DPN as compared to patients with T2DM without DPN in an ambulatory setting.

**MATERIAL AND METHODS**

We conducted a retrospective observational study among patients seen in the ambulatory office over a 3-month period, during January and March 2020. The inclusion criteria were the diagnosis of T2DM, recent evaluation (less than 3 months), age of more than 18 years and signed informed consent. Patients with T1DM, secondary DM or other causes of peripheral neuropathy were excluded.

Data collected from the medical records were: demographic – age, settlement; clinical: height, weight, body mass index, smoking status and comorbidities; paraclinical – HbA1c, creatinine, urea, HDL-Cholesterol, total cholesterol, triglycerides, transaminases. Diagnosis of DPN as well as for other diabetes complications or other comorbidities was established by the patient’s medical records. Only patients with complete data were included for the analysis. Data were collected and analysed using the Microsoft Excel and PSPP software. Means (standard deviation) were calculated for continuous variables and frequencies were reported for the categorical variables. Chi square test was used for binary variables and linear regression for continuous variables. The study has met the ethical principles of the Institutional Ethics Committee.

**OUTCOMES**

In the final analysis, 112 T2DM patients met the inclusion criteria. The group characteristics were: mean age of 60.28±9.76 years; 62.5% males and 37.5 females; 77.67% from urban settlement; 12.5% active smokers and 9.82% ex-smokers. Mean age at DM diagnosis was 51.74±12.49 years, the median evolution of DM was 6.5 years with a minimum of 0 years and a maximum of 42 years; the mean HbA1c was 7.375±1.31%; all patients received metformin and 28 patients (25%) required insulin-therapy with only 2 cases of intensive basal-bolus regimen.

Concurrent chronic microvascular complications of DM were as follows: DPN 52.67%, vegetative neuropathy 1.78%, retinopathy 16.96%, CKD 13.39%. Macrovascular complications were ASCVD 34.82%, grade 1 PAD in 18.75% and, respectively, grade 2 PAD in 8.92% of patients, with only 3.57% (4 cases) of history of amputation due to complications secondary to DPN or PAD.

Other presented comorbidities were obesity in 60.71% of cases, HBP in 86.60% of cases, dyslipidaemia (evaluated by the presence of statin treatment) in 83.92%, hepatic steatosis in 41.07% and heart failure in 8.92% of patients.

Patients were subgrouped based on the presence of DPN (59 patients with DPN and, respectively, 53 patients without PDN). Further analysis was conducted and the subgroup characteristics that reached statistical significance are shown in Table 1.

In Table 2 are shown the subgroup characteristics that did not reach a statistically significant difference.
The patients included in our study presented mild glycaemic imbalance (as they were receiving close guidance and constant follow-up in the outpatient department), although no significant difference was found in the A1c haemoglobin between the two study groups. Despite this, DPN had a high prevalence, more than half of the patients being affected. However, the duration of DM evolution since diagnosis, one of the most important unmodifiable risk factors for DPN in T2DM [4,11], was significantly longer in our study (p=0.007) and this finding is in accordance with other reported data [15].

Further, the strong association with smoking (p=0.03), lower HDL cholesterol (p=0.006) (dyslipidaemia diagnosis may not reflect adequate measure of the lipid imbalance as patients had already statin treatment), obesity (p=0.021) (components of an “adverse cardiovascular-metabolic profile” [13]) was obtained, thus enhancing the importance of proper management of the associated modifiable risk factors. Moreover, we obtained significant higher frequency for all other comorbidities in DPN patients versus those without DPN (both microvascular complications – diabetic retinopathy p=0.013, CKD p=0.027; and macrovascular – ASCVD p<0.001, PAD p<0.001). This finding is highly supportive for the idea that DPN diagnosis should trigger close screening for other DM complications and, respectively, comorbidities. Last but not least, HF had higher prevalence in the DPN subgroup (0.001), drawing further attention on this circumstance, as microvascular complications of DM may trigger worse outcomes in HF with reduced ejection fraction compared to uncomplicated DM [16].

The main limitation in our study was the small size of the analysed group and the cross-sectional perspective. Although there are numerous studies evaluating the influence of certain parameters as risk factors for DPN, the majority of them are cross-sectional, or size-limited and causality is hard to probe [11].

**CONCLUSIONS**

DPN is associated with risk factors such as the smoking status, obesity, lower value of HDL cholesterol, longer duration of DM evolution, need for insulin-therapy.

Patients who already had a DPN diagnosis presented with more frequent microvascular complications of T2DM, such as CKD, retinopathy and, respectively with macrovascular complications of T2DM, and with other comorbidities such as HF and obesity as well.

DPN is easy to diagnose even in an ambulatory setting by performing QST and could be considered a good marker for the presence of other chronic com-

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**TABLE 1.** Characteristics comparison after the presence of DPN with statistical significance

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Peripheral Neuropathy present</th>
<th>Diabetic Peripheral Neuropathy absent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active or former smoker (%)</td>
<td>45</td>
<td>22.65</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes Mellitus duration (years)</td>
<td>8 (0, 42)</td>
<td>4 (0, 35)</td>
<td>0.007</td>
</tr>
<tr>
<td>Insulin-therapy (%)</td>
<td>32.3</td>
<td>15.1</td>
<td>0.046</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>25.42</td>
<td>7.54</td>
<td>0.013</td>
</tr>
<tr>
<td>Chronic Kidney Disease* (%)</td>
<td>20.33</td>
<td>5.66</td>
<td>0.027</td>
</tr>
<tr>
<td>Atherosclerotic Cardiovascular Disease** (%)</td>
<td>54.23</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral Artery Disease (%)</td>
<td>45.76</td>
<td>7.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>71.17</td>
<td>49.05</td>
<td>0.021</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>16.94</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>88.77 ±16.54</td>
<td>99.56 ±17.71</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dL)</td>
<td>41.08 ±16.44</td>
<td>46.92 ±13.56</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Diagnosed according to KDIGO criteria using eGFR (estimated Glomerular Filtration Rate) and ACR (albumin to creatinine ratio)

**Is represented by Angina Pectoris, Ischaemic Coronary Disease, Myocardial Infarction and Peripheral Artery Disease**

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Peripheral Neuropathy present</th>
<th>Diabetic Peripheral Neuropathy absent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.86 ±9</td>
<td>59.64 ±10.59</td>
<td>0.472</td>
</tr>
<tr>
<td>Mean age at Diabetes Mellitus diagnosis (years)</td>
<td>50.63 ±11.78</td>
<td>52.97 ±13.25</td>
<td>0.325</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>61.01</td>
<td>64.15</td>
<td>0.845</td>
</tr>
<tr>
<td>Urban environment (%)</td>
<td>72.88</td>
<td>83.01</td>
<td>0.257</td>
</tr>
<tr>
<td>High Blood Pressure (%)</td>
<td>88.13</td>
<td>84.9</td>
<td>0.782</td>
</tr>
<tr>
<td>Dyslipidaemia (%)*</td>
<td>84.74</td>
<td>83.01</td>
<td>0.804</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.41 ±1.1</td>
<td>7.33 ±1.51</td>
<td>0.887</td>
</tr>
</tbody>
</table>

*Evaluated by the presence of a statin in the patient’s medication

**DISCUSSIONS**

DPN is reported to be the most frequent cause of neuropathy worldwide, as well as one of the most frequent chronic complications of DM [11]. The exact prevalence is hard to be determined given the different perspectives in diagnosis criteria and methods used [12].

Our study found an increased prevalence of DPN, that is higher than the one recently reported by an international study, respectively, of 26.71%, although this study result has encountered a large variability between the different countries included [14].
plications or comorbidities in T2DM, prompting the attending physician towards thorough screening and adequate management.

**Ethics approval** – The study has met the ethical principles of the Institutional Ethics Committee.

**REFERENCES**


**Conflict of interest** – I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work.

**Funding** – No funding was received.

**Acknowledgements** – none to be declared.