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Short Communication

Prevalence and Risk Factors of Diabetic Sensorimotor Polyneuropathy in Diagnosed Diabetes Mellitus Type-2 Individuals in Lahore, Pakistan

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AN, KIK and HR conceptualized and designed the experiment. AN, KIK and ABQ executed experimental work. AN, MSY and HR analyzed the data. AN, MSY, IR, HZ and HR compiled the results and wrote the article.

Key words
Diabetes mellitus type-2, Diabetic sensorimotor polyneuropathy, Prevalence, Risk factors

ABSTRACT

The present study aimed at investigating the prevalence and associated risk factors of diabetic sensorimotor polyneuropathy (DSP) in previously diagnosed Type-2 diabetic subjects in Lahore, Pakistan during April, 2013 to June, 2013. The DSP was diagnosed using the Michigan Neuropathy Screening Instrument Score. Blood was collected during the examination for the determination of various serum biochemical determinants. Prevalence of DSP was found to be 31.48% when 2,290 diabetes mellitus Type-2 subjects were screened. The patients with DSP were older ($p < 0.05$), had longer duration of DMT2 ($p<0.01$), elevated systolic blood pressure ($p<0.05$), blood sugar ($p < 0.05$), HbA_{1c} ($p<0.001$), cholesterol ($p<0.01$), LDL ($p<0.001$), triglycerides ($p<0.05$) and more obese ($p<0.01$) when compared with the diabetic patients without clinical DSP. Occurrence of fatty liver was more ($p<0.01$) frequently seen in the patients with the DSP (87.80%) than having no clinical DSP (83.17%). Multiple logistic regression analysis showed that the DSP was significantly associated with age of the patients (OR:1.40, CI:1.24-1.67), duration of DMT2 (OR:1.24, CI: 1.01-1.35), HbA_{1c} (OR:1.86, CI:1.61-2.05), blood fastening sugar level (OR:1.37, CI: 1.18-1.51) and triglyceride concentrations (OR:1.13, CI: 1.02-1.33). In conclusion, the DSP was considerably higher in DMT2 patients and was significantly associated with age of patients, duration of DMT2, HbA_{1c}, blood fasting sugar and serum triglyceride concentrations. Proper management of DSP needs better management of DMT2.

Diabetes mellitus (DM), a metabolic problem, is associated with defects in insulin secretion and/or action that results in hyperglycemia. Generally, DM has been categorized in two forms. Type-1 DM is a ketosis-prone form resulting due to autoimmune or idiopathic destruction of pancreatic beta-cells. Type-2 DM (DMT2) is primarily due to insulin resistance or a concomitant defect in secretory functions of beta-cell. Prevalence of DM is a worldwide and number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild *et al*., 2004). In Pakistan, nearly 5.0 million peoples are affected with DM that may go up to 13.9% in 2030 (Wild *et al*., 2004). Diabetic sensorimotor polyneuropathy (DSP) is one of the most common forms of diabetic complication affecting nearly 50% patients suffering from DM (Dyck *et al*., 2010).

Prevalence of diabetic neuropathy has wide variation ranging from 2.4 to 61.8% in different populations (Kostev *et al*., 2014). In a previous study conducted in Karachi, Pakistan, the prevalence of DSP was estimated to 39.6% (Shera *et al*., 2004). A body of evidences revealed that gender, age, diabetes duration, diabetes type, glycemic control, dyslipidemia, retinopathy, hypertension, nephropathy smoking status and height are potential risk factors associated with diabetic neuropathy (Franklin *et al*., 1994; Shaw *et al*., 1998). To best of our knowledge, there is no literature available regarding the prevalence of DSP and associated potential risk factors in Lahore, therefore, the current study aimed at determining the prevalence of DSP and DSP linked risk factors in patients of DMT2 in Lahore.

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Materials and methods

This cross-sectional study was conducted at the Diabetes Management Center (DMC), Services Institute of Medical Sciences (SIMS), Lahore, Pakistan. The individuals were recruited for the study that visited the DMC for medical advice during April, 2013 to June, 2013. The patients included in the study were known diabetic and written consent was obtained. The study was approved by the Ethical Committee, SIMS, Lahore. Inclusion criteria for recruiting subjects were DMT2 patients were aged >18 years with no history of any systemic illness related to peripheral neuropathy, neuromuscular disorder, trauma of nerve, neuropathies linked with external toxins, drugs or metals. After obtaining their written consent, a questionnaire that included general information, health status or any other disease, duration of diabetes, type of medication, and history of foot ulcer, angina, hypertension, stroke or smoking were completed. Physical examination was also carried out that included measurement of height, weight, waist and hip circumferences. Blood pressure was measured thrice and then averaged. Subject was declared hypertensive if systolic blood pressure was >140 mmHg and/or diastolic blood pressure was >90 mmHg. Body mass index (BMI) was calculated by dividing weight with height squared (kg/m^2). Venous blood was collected to determine various biochemical determinants. Plasma glucose level was measured by glucose oxidase method. Concentration of glycated hemoglobin (HbA_{1C}) was determined using a high-pressure liquid chromatograph (HLC-723G7, Tosoh Corporation, Japan). Serum urea, creatinine and total lipids profile (cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol) were also determined using commercial kits with a spectrophotometer (Hitachi, 7600).

Diagnosis of the DSP was assessed using the Michigan Neuropathy Screening Instrument (MNSI). The MNSI includes two separate assessments: a 15-item self-administered questionnaire (called history) and a lower extremity examination (physical assessment). The MNSI-questionnaire (part A) includes 15 ''yes'' or ''no'' questions on foot sensation including pain, numbness and temperature sensitivity. A score >7 was considered suggestive of neuropathy. The MNSI examination (part-B) consists of a standardized physical examination including: 1) inspection of the feet for deformities, dry skin, hair or nail abnormalities, calluses or infection, fissures; 2) foot ulceration; 3) the grading of ankle reflexes (normal, reduced, or absent); 4) a semi-quantitative assessment of sensation of vibration at the dorsum of the great toes (normal, reduced, or absent); 5) perception of monofilaments on planter side of the foot.

To examine the differences between DSP patients and DMT2 without clinical neuropathy individuals, several univariate and multivariate analyses were performed using Statistical Packages for Social Science for Window (SPSS for Windows version 12, SPSS Inc., Chicago, IL). The x^2-test was performed for dichotomous variables. Independent Student's *t* test was employed for continuous variables and in case of uneven distribution the Wilcoxon rank-sum test was employed. Multiple logistic regressions were employed to examine the link between dependent variable (DSP) and the independent variables. Results were described as odd ratio with 95% confidence interval (OR, 95%CI) at $p<0.05$.

Results

Of 2,290 DMT2 subjects examined, the prevalence of DSP was 31.48%, being more ($p<0.05$) in females (60.61%) of DSP compared with diabetic females (55.13%) showing no clinical polyneuropathy (Supplementary Table I). The DMT2 individuals with clinical polyneuropathy (51.47±10.78) were older ($p<0.05$) than the individuals without clinical polyneuropathy (50.25±10.69). Diabetic subjects with clinical polyneuropathy had long standing (9.55±6.45 vs. 6.88±5.60 years; $p< 0.01$) DMT2, had more weight ($p=0.0058$), tended to have more waist circumference ($p=0.087$) and more obese ($p<0.01$) compared with the diabetic subjects without clinical polyneuropathy (Table I). Only systolic blood pressure was elevated ($p<0.05$) in the subjects with DSP compared to those without clinical polyneuropathy. The blood glucose concentration was more at fasting phase and also at 2 hours postprandial in subjects with clinical polyneuropathy compared to those without clinical polyneuropathy. Similarly, the individuals with clinical polyneuropathy had higher ($p<0.0001$) HbA_{1c} (8.57±1.51%) compared to those without clinical polyneuropathy (8.25±1.70%). Concentrations of cholesterol ($p<0.01$), LDL ($p <0.0001$) and triglycerides ($p<0.05$) were elevated in the subjects with clinical polyneuropathy compared with those without clinical polyneuropathy. Blood urea and serum creatinine levels were also more disarranged in the subjects with DSP than those without clinical polyneuropathy (Table I). The presence of fatty liver was more ($p<0.01$) in the patients with the DSP (87.80%) compared to those without clinical polyneuropathy (83.17%).

Multiple logistic regression analysis was carried out taking DSP as a dependent variable. The following variables were taken as independent variables to determine their association with DSP: age, sex, duration of diabetes, HbA_{1c}, weight, height, waist and hip circumferences, BMI, systolic and diastolic blood pressures, blood sugar levels at fasting and 2 hours post prandial, lipid profile (cholesterol, TG, LDL and HDL), urea and creatinine. As shown in Table I, the DSP demonstrated a significant association with the

age of the patients (OR:1.40, CI:1.24-1.67), duration of DMT2 (OR:1.24, CI: 1.01-1.35), HbA_{1c}(OR:1.86, CI:1.61-2.05), blood fastening sugar level (OR:1.37, CI: 1.18-1.51) and serum triglycerides concentration (OR:1.13, CI: 1.02-1.33).

Table I. Final multiple logistic regression model using diabetic polyneuropathy as a dependent variable.

Variable	OR (95% CI)	p-value
Age (years)	1.40 (1.24-1.67)	0.003
Duration of diabetes (years)	1.24 (1.01-1.35)	0.033
HbA_{1c} (%)	1.86 (1.61-2.05)	0.002
Blood fastening sugar level (mmol/L)	1.37 (1.18-1.51)	0.005
Serum triglycerides (mmol/L)	1.13 (1.02-1.33)	0.011

OR, Odd ratio; CI, Confidence interval; HbA1c, Glycosylated haemoglobin.

Discussion

To the best of our knowledge, it is the first report demonstrating the prevalence of DSP and associated risk factors in Lahore. In the present study, the prevalence was found to be 31.48%. A previous study described 39.6% prevalence of neuropathy when 500 diabetic patients were screened for the diabetic complications in Karachi, Pakistan (Shera *et al*., 2004). The prevalence of DSP was found to be 33.5-33% in DMT2 patients in Korea which is close to the prevalence rate recorded in the current study (Won *et al*., 2012). In another study conducted in Tehran, Iran, the prevalence of DSP was 31.9% as determined by the MNSI, also used in the current study (Tabatabaei *et al*., 2011). In the Pittsburgh, Epidemiology of Diabetes Complications Study, the prevalence of DSP was 34% which is close to the results of the present study (Maser *et al*., 1989). However, a lower prevalence rate of DSP (26.1%) has also been estimated in Chennai, India (Pradeepa *et al*., 2008). A meta-analysis showed that the prevalence of DSP in the West Pacific–Asia region varied from 9% to 45% (IDF, 2006). For instance, prevalence of neuropathy was in 8.3% in diabetic subjects, being 12.7% in confirmed diabetes and 3.6% in newly diagnosed diabetic subjects in Mauritius (Shaw *et al*., 1998). On the other hand, prevalence of DSP among patients with known diabetes and newly diagnosed subjects was 59.1% and 28.8% respectively in Sri Lanka (Katulanda *et al*., 2012). Prevalence of DSP varies widely ranging from 2.4% to 61.8% in different populations (Kostev *et al*., 2014). It is very difficult to compare the results of various studies as multiple factors like diabetes type, diagnostic criteria used (clinical signs and symptoms, pin-prick perception, quantitative sensory tests or electro-diagnostic tests), design of study, selection of sample, race, study year, sampling period, age and gender influence the occurrence of the DSP (Kiani *et al*., 2013).

In present study, age, duration of diabetes, HbA_{1c} and serum triglycerides had significant association with the DSP (Table II). The association between DSP and independent risks factors indicated that DSP is a heterogeneous disorder that may be caused by the interaction of host susceptibility, vascular factors, metabolic factors and possibly environmental factors (Maser *et al*., 1989).

Presently, we identified ageing as an independent risk factor in the induction of DSP. Various studies also acknowledge age as a significant risk factor linked with diabetic neuropathy (Franklin *et al*., 1994; Pradeepa *et al*., 2008; Liu *et al*., 2010; Won *et al*., 2012). Whereas a few failed to find any such association (Shaw *et al*., 1998; Lu *et al*., 2013).

With regard to glycaemic control status, a body of evidences described that poorly controlled diabetes, in terms of higher HbA_{1c}, is a potential risk factor for DSP (Maser *et al*., 1989; Shaw *et al*., 1998; Pradeepa *et al*., 2008; Lu *et al*., 2010). Our study also confirmed this association with DSP as previously being reported in Pakistan (Shera *et al*., 2004). In the "Shanghai Diabetic Neuropathy Epidemiology and Molecular Genetics Study", a population-based study, it was found that fastening blood glucose level, not HbA_{1c}, is a significant independent risk factor for neuropathy. On the other hand, one report demonstrated that HbA_{1c} had significant inverse association with diabetic polyneuropathy (Won *et al*., 2012).

Results of the current work confirmed the previous reports regarding independent association between diabetic neuropathy and duration of diabetes mellitus (Maser *et al*., 1989; Franklin *et al*., 1994; Pradeepa *et al*., 2008; Won *et al*., 2012; Kiani *et al*., 2013). A previous study described that duration of diabetes was a significant independent risk factor for diabetic neuropathy in both longitudinal and cross sectional studies in Mauritius (Shaw *et al*., 1998). It has been demonstrated that neuropathy prevalence rate at the time of diagnosis was 7.5% with a linear increase of 1.7% per year. After 10–15 years of diagnosis, the rate was between 20 and 30% that reached to 50% after 25 years (Perkins *et al*., 2001). The identification of duration of DM as a risk factor for DSP necessitates the importance of early diagnosis and treatment so that development and progression of diabetic polyneuropathy may be prevented or delayed.

Serum free triglycerides are considered as an alternate marker of endogenous lipid transport pathway. Elevated serum triglycerides represent a valuable biochemical marker for the diagnosis of metabolic disarrangement. In the current report, we also established a relationship between serum triglycerides and DSP. Many studies

revealed that DSP is independently linked with serum triglycerides (Tesfaye *et al*., 1996; Wiggin *et al*., 2009). In the EURODIAB IDDM complications study, higher fastening triglycerides levels were significantly associated with diabetic neuropathy (Tesfaye *et al*., 1996). As early dyslipidemia is one of the major independent risk factors for the progression of DSP, therefore, one could explain why diabetic subjects with type 2 develop the DSP earlier than subjects with DMT1 (Katulanda *et al*., 2012). The delayed development of dyslipidemia in DMT1 and subsequently delay in the abnormal lipid profile coincides with the delayed onset and progression of neuropathy. Hence, correction of triglyceridemia may, at least, delay the development and progression of DSP. However, the study has a few limitations like 1) "duration of diabetes" as measured in this study might not reflect the true duration of the disease but the time since diagnosis and actual diabetes onset might precede diagnosis by several years, 2) results cannot be generalized as the study was conducted only in one diabetes specialized clinic, 3) the study was a cross sectional conducted during 3 months interval involving a small sample size (n=2,290) population. Therefore, there is a need to incorporate more clinic/hospitals and may be a population based study.

Conclusion

In conclusion, we found a comparable prevalence rate of DSP with other Asian countries like Iran, India and Korea. The study also described significant relationship of ageing, duration of diabetes, HbA_{1c}, and serum TG with DSP. However, we are very careful in interpreting the results because of nature of a study (cross-sectional study). Therefore, there is a dire need to extend the study on population and may be multi-centered.

Supplementary material

There is supplementary material associated with this article. Access the material online at: https://dx.doi.org/10.17582/journal.pjz/20160213056633

Statement of conflict of interest

The authors declare there is no conflict of interest.

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