ORIGINAL ARTICLE

Risk Determinants of Peripheral Neuropathy in Patients with Type II Diabetes Mellitus Attending Follow-Up Clinics at Universiti Kebangsaan Malaysia Medical Center (UKMMC): A Cross-Sectional Study

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ABSTRAK

Neuropati periferi adalah berkait rapat dengan masalah kaki di kalangan penghidap diabetes melitus. Kajian ini bertujuan untuk mengenalpasti tahap neuropati dan faktor-faktor risiko berkaitan dengan keadaan ini. Satu kajian hirisan lintang telah dijalankan di klinik-klinik ulangan Pusat Perubatan UKM (PPUKM) Malaysia, melibatkan 72 pesakit diabetes dan 19 pesakit kawalan. Pesakit yang mempunyai kaki yang bermasalah dan telah mempunyai neuropati tidak dimasukkan dalam kajian. Pesakit kawalan dipilih dari mereka yang tidak mempunyai diabetes, boleh berjalan secara normal, tiada masalah dengan kaki serta menghadiri klinik sebagai peneman kepada pesakit. Kajian kuantitatif dilakukan menggunakan Semmes-Weinstein monofilamen. 'Neuropathy Disability Score' (NDS) digunakan untuk mengukur tahap neuropati diabetes. Ujian 'Spearman rank' dan 'Mann-whitney' dijalankan bagi mengenalpasti hubungkait antara neuropati dan faktor-faktor yang dikaji. Ujian 'logistic regression' dijalankan untuk mengenalpasti faktor risiko keadaan ini. Aras purata HbA1c pada pesakit ialah 8.6 $\pm$ 4.1, dan purata NDS ialah 7.0 $\pm$ 6.0. Sejumlah 79.1% didapati mempunyai neuropati dalam berbagai tahap, dengan faktor kalus kaki dikenalpasti berhubungkait dengan markah NDS yang tinggi. Faktor lanjut usia ($p = 0.02$), berat badan ($p = 0.03$), HbA1c ($p = 0.005$) dan jangkamasa menghidap diabetes ($p = < 0.005$) mempunyai hubungkait positif dengan NDS. Program penjagaan kaki yang teratur untuk pesakit diabetes perlu mengambil kira faktor kalus kaki, dengan keutamaan diberi kepada mereka yang mempunyai berat badan berlebihan dan telah lanjut usia.

Kata kunci: diabetes melitus, neuropati periferi, 'Neuropathy Disability Score (NDS)', 'Semmens-Weinstein monofilamen(SWMF), kalus

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ABSTRACT

Peripheral neuropathy is highly associated with foot complications among diabetics. This study aimed to identify risk factors associated with the development of peripheral neuropathy in diabetic patients and their association with degree of severity of peripheral neuropathy. A cross-sectional study was conducted in follow-up clinics at the Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Malaysia involving 72 diabetic patients and 19 controls. Exclusion criteria were those with amputated limbs, gross foot deformity and existing peripheral neuropathy. Controls were non diabetics who walked normally, had no history of foot problem and attended the clinic as subjects' companion. Quantitative assessment of neuropathy was done using Semmes-Weinstein monofilament. Neuropathy Disability Score (NDS) were used to quantify severity of diabetic neuropathy. Spearman's Rank test and Mann-Whitney test were used to determine correlation between variables and their differences. Logistic regression analysis was used to determine risk factors associated with peripheral neuropathy. The mean HbA1c among diabetics was 8.6% $\pm$ 4.1, and mean NDS was 7.0 $\pm$ 6.0. A total of 79.1% demonstrated various level of neuropathy with presence of callus was associated with higher NDS scores. Older age (P=0.02), body weight (P=0.03), HbA1c (P=0.005) and duration of diabetes (P <0.005) showed positive correlation with NDS. Proper foot care program for diabetics should include recognition of the callus, with special emphasis given to those with heavier weight and increasing age.

Key words: diabetes mellitus, peripheral neuropathy, Neuropathy Disability Score (NDS), Semmes Weinstein monofilament (SWMF), callus

INTRODUCTION

The World Health Organization has declared that the number of people with diabetes mellitus (DM) is rapidly increasing and has become of major public health concern (King & Rewers 1991; WHO 1992). The number of diabetic patients in developing countries is expected to increase by more than two-folds from 84 million in 1995 to 225 million in 2025 (Aboderin et al. 2002). In Malaysia, the prevalence of adult diabetics has doubled over a 10-year period with the prevalence in 2006 reported as 14.9%, the highest among the Asian countries (NHMSIII 2006).

Complications affecting the lower limbs are one of the most common manifestations of diabetes. Approximately 15% of those with diabetes will eventually suffer from foot ulceration during their lifetime (WHO 1992). It is well recognized that diabetic patients experience decreased sensation of their feet because of peripheral neuropathy which is the result of a complex interplay between a number of factors such as limited joint mobility (LJM), altered foot pressures and level of glycaemic control (Boulton et al. 1983; Caputo et al. 1994; Reiber et al. 1999). The loss of sensation caused by poorly controlled diabetes is also thought to reduce the protective sensation of the foot. The repetitive trauma to the plantar areas increases the risks of foot ulceration, which may lead to foot amputation in severe uncontrolled cases.

Factors such as age, gender, diabetic control, presence of vascular disease, and extrinsic sources of trauma were theoretically reported to be associated with the development of peripheral neuropathy amongst diabetic patients (Adler et al. 1997; Tesfaye et al. 1996). To date, there

is limited evidence regarding the risk factors for the development of peripheral neuropathy amongst diabetic patients. Hence, this study aimed to identify risk factors associated with the development of peripheral neuropathy in DM patients and their association with the severity of peripheral neuropathy amongst these patients. The results from this study will be beneficial for the health care providers to initiate early preventive measures to the patients.

MATERIALS AND METHODS

Design

This was a cross-sectional study conducted amongst patients diagnosed with DM attending outpatient clinics in UKM Medical Centre, Kuala Lumpur. The study was conducted from January to August 2008, involving diabetic patients in three out-patient clinics i.e. primary care centre, medical endocrine clinic and orthopaedic clinic.

Subjects

All diabetic patients aged 18 to 70 years old attending the clinics were invited to participate in the study. Written consent was obtained before patients were subjected to assessments for the study. The diagnosis of DM was established from reviews of the patients' medical records. Consented patients were given a checklist documenting duration of diabetes, medical co-morbidities, smoking habits and presence of foot ulceration. Patients were then examined for the presence of clinical peripheral neuropathy. Exclusion criteria included patients with limb amputation, gross foot deformity (e.g: Charcot joints, hallux valgus), and existing peripheral neuropathy in patients. Controls were recruited from non-diabetes mellitus (NDM) subjects that were able to walk normally, had no history of foot problem and attending the clinic as the subjects' accompaniment during the study period.

Study instrument

Neuropathy screening was performed using the Semmes-Weinstein monofilament (SWMF) 5.07/10g that was used as a quantitative assessment of the cutaneous pressure perception. With both eyes closed, the patient informed the investigator when he or she could feel the filament applied to a non-callus site at 8 plantar locations. Neuropathy was confirmed when more than half responses were incorrect (Perkins et al. 2001). The Neuropathy Disability Score (NDS) was used to quantify the severity of the neuropathy. The Achilles tendon reflexes were examined: a score of zero (0) was given if the reflexes were normal, one (1) if the reflexes could be elicited with reinforcement and two (2) if the reflexes were absent. Sensory testing included pin prick using neurotip, vibration using a biothesiometer with a cut-off value of 25 Volts to determine vibration perception and temperature testing using a cold tuning fork at the great toe: a score of zero (0) was given for each normal result and one (1) for each abnormal result. The summation of scores of each modality was entered as the NDS. A score of 1 and 2 was considered normal, whereas score of 3 to 5 indicated mild peripheral neuropathy, 6 to 8 indicated moderate peripheral neuropathy and 9 to 10 indicated severe neuropathy. Finally, the glycosylated haemoglobin (HbA1c) within the past six months was used to ascertain the level of glycaemic control of the patient.

Statistical analysis

Statistical analysis was conducted using the SPSS version 12.0. Descriptive analysis was used for categorical data and analysis of mean, median and variance. The correlation of continuous variables and NDS were analyzed using Spear-

man's Rank order. For the correlation of categorical variables and NDS, Mann-Whitney U test was used to determine the difference. Logistic regression analysis was applied to look for risk factors associated with peripheral neuropathy. A p value of <0.05 was considered significant.

RESULTS

A total of 91 subjects (72 DM patients; 19 NDM volunteers) were recruited. The demographic characteristics are shown in Table 1. For the DM group, 37.5% had DM for more than 15 years, 20.8% between 10 to 15 years, 20.9% between 5 to 10 years while the remaining 20.8% less than five years. There were 49 (41.7%) males.

Among the DM patients, 79.1% demonstrated various levels of peripheral neuropathy (Table 1). Subjects with callus or ulcers had higher NDS than those without (Z: -2.36, p: 0.003). There was a positive correlation between the age of diabetic subjects and the NDS score (r: 0.36, N: 72, p: 0.02), with older DM subjects showing higher NDS. Weight of the DM subjects also demonstrated a positive correlation to the NDS (r: 0.35, N: 72, p: 0.03), with heavier diabetic subjects showing higher NDS. Although NDS seemed to have significant correlation with HbA1c (p: 0.005) and duration of diabetes (p<0.005), it was not significant in the logistic regression analysis. In contrast, NDS was not found to have an association with gender (*P*=0.179), ever smoked (*P*=0.351) and history of ulcer (*P*=0.189).

Table 2 showed the logistic regression analysis of the risk factors associated with peripheral diabetic neuropathy. Age and weight were the only factors found to be significantly associated with peripheral neuropathy (age; p: 0.039; weight; p: 0.005).

DISCUSSION

It is known that although a proportion of people with peripheral neuropathy present with pain and numbness, many are still asymptomatic until much later, hence it is imperative for physicians to identify those who are at risk to develop these complications. This study highlighted the fact that more than half of the DM cohorts demonstrated peripheral neuropathy, with age and body weight significantly associated with neuropathy.

Our results confirm the well-established correlation between age and peripheral neuropathy. This finding could be attributed to two main factors. First, the duration of DM is acknowledged to be associated with the development of complications of diabetes, and peripheral neuropathy is no exception. Secondly, the development of peripheral neuropathy is also known to increase with age, especially after the age of 65 in the general

Table 1: Clinical characteristic of diabetes patients attending outpatient clinics PPUKM (n = 72)

Characteristic	Diabetes N = 72	Percent (%)
Age (years)	56.1±7.5	-
Sex		
Male	30	41.7
Female	42	58.3
Weight (kg)	69.7±18.7	-
HbA1c (%)	8.6±4.1	-
Ever smoked	20	27.8
NDS	[+]7.0 ± 6.0	-
Peripheral neuropathy (NDS Score)		
No evidence	15	20.8
Mild	10	13.9
Moderate	26	36.1
Severe	21	29.2
Presence of callus / ulcer	22	30.6

[+] Median ± interquartile range

Table 2: Logistic regression analysis of risk factors associated with diabetes peripheral neuropathy

Variables	OR	95% CI	P value
Age (year)	1.13	1.01-1.26	0.039
Weight (kg)	1.10	1.03-1.18	0.005
HbA1c (%)	0.206	0.89-1.69	0.206
Duration of diabetes (years)			
< 5 years		1.0	
5 – 10 years	0.04	0.01-1.31	0.020
10 – 15 years	0.20	0.02-1.26	0.870
>15 years	0.37	0.05-2.63	0.318

population with or without diabetes (Cho et al. 2006; Mold et al. 2004). However the mean age for our DM cohorts was much lower than what was reported by Cho and Mold (Cho et al. 2006; Mold et al. 2004). Taking into consideration the high level of HbA1c amongst our DM cohorts, we postulated that the combination of age, duration of diabetes and the poor glycaemic control might have contributed to the accelerating occurrence of peripheral neuropathy amongst our DM patients.

Our findings also demonstrated that heavier patients were more likely to suffer from severe neuropathy compared to those who were less heavy. This finding is consistent with other studies which showed that obese patients achieved poorer results in test of clinical neuropathy compared to those who were less obese (Cavanagh et al. 1991; Straub et al. 1994). Further analysis showed that the amount of visceral fat was proportionally related to the increase of overall insulin resistance. This could explain the findings of severe neuropathy in subjects with heavier body weights. However, this finding was based on the weight alone not the body mass index (BMI) to give an accurate relationship between neuropathy and level of obesity amongst DM patients.

Callus or hyperkeratosis has been implicated in the etiology of neuropathic ulceration. Callus acts like a foreign body which in turn increases the likelihood for tissue breakdown and consequently formation of an ulcer under the callus. Studies have shown that plantar calluses were a strong predictor for ulcers and ulcers recurred mainly at the site of calluses (Murray et al. 1996; Menz et al. 2007). In the present study, the presence of callus was found to be associated with higher NDS. This is important as simple measures like paring of the callus may reduce the risk of plantar ulceration (Young et al. 1992). The fact that calluses were present in approximately 30% of the cohort, suggested that poor foot care was common among our patients and this warrants further intervention in both patients and health practitioners

We were not able to demonstrate any associations of neuropathy with the male gender, ethnicity and duration of diabetes mellitus. Peripheral neuropathy was also not significantly related to smoking, but most of our patients were non-smokers. However it is known that smoking causes the arrest of blood flow in the peripheries which in turn causes tissue hypoxia and neural microvascular damage leading to the development of peripheral neuropathy (Benbow et al. 1997). The glycaemic control was not independently associated with neuropathy; the reason may be the cross sectional design of this study and a single and latest HbA1c result is possibly a poor indicator of the overall diabetic control.

This study provided information to practitioners in identifying potentially reversible factors contributing to the development of peripheral neuropathy, namely the patient's body weight and presence of callus. It supported the deemed importance of weight reduction in Type 2 diabetes patients in preventing progression of neuropathy and consequently the

costly complications of plantar ulceration and lower extremity amputation. This study also underlined the importance of implementing a proper foot care program especially for those who are heavier and older. Although these practices have already been recommended by many clinical guidelines, many practitioners fail to adhere to them and fail to identify those at risk of peripheral neuropathy. So, an increased awareness by primary care providers of the associated risk factors can lead to an early therapeutic intervention and prevention of later neuropathic complications such as infection and foot ulcers, allowing a decrease in patient morbidity.

CONCLUSION

This study demonstrated that age and weight were the risk determinants for the development of peripheral neuropathy. The presence of calluses was also found to be associated with those with peripheral neuropathy. Early detection of these risk factors should be incorporated into any program aiming to reduce diabetic foot complication as to reduce morbidity that is commonly associated with diabetes mellitus. However, the study is limited by its cross-sectional design, we were unable to assess the cause and effect of the study. Likewise, population drawn was from an outpatient setting in a university hospital which in turn causes selection bias in this study. Patients in our cohort might be substantially different from a community-based outpatient setting as our out-patient clinics are mainly referral-based; hence it might not be a true representative of the general population. Nonetheless, despite the limitations, this population-based survey was able to inform us regarding the diabetes foot problems in Malaysia, using inexpensive and simple assessments that can be replicated even in remote settings.

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