"The prevalence of and risk factors for diabetic peripheral neuropathy among type 2 diabetic outpatients in Bangladesh"

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ABSTRACT

The prevalence of and risk factors for diabetic peripheral neuropathy among type 2 diabetic outpatients in Bangladesh

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Aims/hypothesis: The purpose of the study was to estimate the prevalence and risk factors for diabetic peripheral neuropathy (DPN), and additionally, evaluate the sensory and musculoskeletal lower-leg function, in type 2 diabetic outpatients, attending the BIRDEM hospital in Bangladesh.

Materials and methods: Type 2 diabetic outpatients, diagnosed 5-11 years prior the investigation was randomly drawn. The Neuropathy Symptom Score (NSS) and the Neuropathy Disability Score (NDS) was employed to assess DPN. Data about socio-demographic characters, blood pressure, height, weight, waist and hip circumference, and random blood and urine samples were collected. For the lower-leg function evaluation, the plantar cutaneous sensation (Semmer-Weinstein 5.07 g monofilament), 1st MTP and ankle joint rang of motion (ROM) (goniometry) and muscle function (Kendall's muscle test) in addition to balance (one and two leg static balance, tandem walk) was examined.

Results: Two hundred and ninety four (139 men, 155 women) type 2 diabetic outpatients were studied. The overall DPN prevalence was 19.7 %, male (20.9%) and female (18.7 %). The prevalence rate increased with increasing age (from 11.1% in the 23-40 year-old group to 32.3% in the 60-80 year-old group) and duration of diabetes (from 14.1% in patients with 5 years to 29.2% in patients with 9-11 years duration). Age $\geq$ 60 years (OR 4.2, 95% CI 1.4 – 12.3), low/normal WHR (OR 3.8, 95%CI 1.6-9.3), treatment with insulin (OR 2.0, 95% CI 1.0-4.0) and income $\leq$ 800 TK (OR 3.1, 95% CI 1.1-9.3) were independent, statistically significant risk factors for the occurrence of DPN, longer duration of diabetes (OR 1.2, 95% CI 1.0-1.4) and higher HbA1c (OR 1.1, 95% CI 1.0-1.3) were independent, borderline statistically significant risk factors for DPN. The 1st MTP dorsal (p=0.03) and plantar flexion (p=0.003) joint ROM, the Tibialis anterior (p=0.03) and Flexor hallucis (p=0.02) strength, balance (<0.001) and protective sensation (p<0.001) was statistically significant diminished in the DPN group compared to the non-DPN-group. After controlling for age, protective

sensation, balance, 1st MTP plantar and dorsal flexion ROM, and Tibialis anterior and Flexor hallucis strength in a multivariate logistic regression model, the DPN-group still had reduced balance (OR 1.4, 95% CI 1.1-1.6), diminished protective sensation (OR2.0, 95% CI 1.5-2.6) and Flexor hallucis weakness (OR 3.2, 95% CI 1.1-9.4).

Conclusions/interpretations: We observed a DPN prevalence of 19.7%. Higher age, low socioeconomic status and treatment with insulin were statistically significant risk factors, while longer duration of diabetes and poor glycemic control were borderline statistically significant risk factors for DPN. The DPN subjects preformed worse on all the lower-leg function tests, especially for the protective sensation and balance test. They may therefore be at high risk for developing foot complications. In societies like Bangladesh, where the resources are scare, the awareness among patients and professionals should be raised. Necessary measures ought to be taken to prevent diabetes complication and secure the quality of care to reduce the burden and costs for both the individual family and the society at large.

Key words: Type 2 diabetes, peripheral neuropathy, risk factors, balance, strength, physical therapy techniques, plantar cutaneous sensation

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ABBREVIATIONS

ADL	Activities of daily living
BIRDEM	Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
DAB	Diabetic Association of Bangladesh
DM	Diabetes Mellitus
DPN	Diabetic Peripheral Neuropathy
GOB	Government of Bangladesh
HbA1c	Glycosylated hemoglobin
HPLC	High-performance Liquid Chromatography
ID	Identification number
IP	Interphalangeal
MOHFW	Ministry of Health and Family Welfare
MTP	Metatarsophalangeal
NDS	Neuropathy Disability Score
NGO	Non-governmental Organisation
NSS	Neuropathy Symptom Score
OPD	Out-patient Department
OR	Odds Ratio
PAD	Peripheral arterial disease
RA	Research Assistant
ROM	Range of motion
SPSS	Statistical Package for Social Sciences
TK	Taka (The Bangladeshi monetary unit)
TC	Total Cholesterol
UACR	Urinary Albumin-to-Creatinine Ratio
VGO	Voluntary Social Organisation
WHO	World Health Organisation
WHR	Waist-to-Hip Ratio

Table of content

1. INTRODUCTION

1.1. A brief country profile

1.1.1. Geography

Bangladesh is located on the largest delta in the world and boarders to the Bay of Bengal, Burma and India. The country is flat and low, and only a small area lies more than 12 meters above sea level. Consequently, one third of the country floods during the annual monsoon rainy season. The total area is 144,000 km², with 133,910 km² being land. The climate is for the most of the year tropical and humid with high temperatures.(1)

1.1.2. History

Bangladesh became a part of British India during the 16th century when the British dominated the South-Asian region. India became independent in 1947, and simultaneously West Pakistan and East Bengal, both primary Muslims, separated from India, primary Hindu, and became the new country of Pakistan. East Pakistan (East Bengal) separated from West Pakistan in 1971, and was renamed Bangladesh. Today the official name is People's Republic of Bangladesh, and the capital is Dhaka.(1)

1.1.3. Economy

Bangladesh has done eminent financial and social progress since the independents in 1971. The GDP has been rising the last twenty years. In 2006 the GDP real growth rate was 6.1% (2200 US$ (purchasing power parity) per capita)(1). More than half of GDP is generated through the service sector. The country is now more or less self-sufficient with food. Rice is the single most important product, followed by jute, tea, wheat, sugarcane, potatoes, tobacco, pulses, oilseeds, spices and fruit. Unfortunately, still 45% of the population lives below the poverty line and the disparity between rich and poor are increasing(2). The explanation for the slow growth in Bangladesh is said to be due to the frequent cyclones and floods, a rapidly growing labour force that cannot be absorbed by agriculture, slow implementation of economic reforms and inefficient state-owned enterprises, corruption, inadequate port facilities, delays in exploiting energy resources (natural gas), in addition to insufficient power supplies. The poverty, inequality and overpopulation is therefore maintained(1).

1.1.4. Politics

Bangladesh is governed by a parliamentary democracy with a president chosen by the parliament. There are two major political parties, the Bangladesh Nationalist Party (BNP) and the Awami League (AL). The BNP came to power during the last election in 2001. In accordance with the constitution, a neutral caretaker government undertook the power in October 2006, with the intention to hold an election in January 2007. The political situation has for that reason been very tense with strikes (hartal) and demonstrations since August 2006. The opposition party demanded several measures in order to secure a rightful election. These measures where not made. It resulted in a state of emergency and no election was held. The neutral government gave away the power to a military acting government, who have promised to hold an election in the near future, but not published any date(2).

1.1.5. Population

The total population counted 147.4 millions in 2006, with a population growth rate of 2.09% (1). The urban population grows more rapidly. Today there are approximately 17 million inhabitants in Dhaka, and the number is expected to pass 20 million within 2020(3). Overpopulation and urbanization has resulted in slum formations, and the United Nations human settlements program has stated that immediate, urgent action that need to be taken to slow down or reverse slum trends.

Bangladesh is known to be a moderate Muslim country with 83 % of the population being Muslims and 16 % being Hindus(1). However, several observers have noticed that Muslim fundamentalism is growing(2). The official language is Bangla, which is spoken by 98% of the population. Even though the education system is improving, only 43.1% of the total population aged 15 and over can read and write(1). Two-thirds of Bangladeshis are employed in the agriculture sector, and a great majority works in the informal sector, are unemployed or underemployed(1).

1.1.6. Lifestyle

The food in Bangladesh is spicy and often fried in oil. Rice is the main staple food, and eaten to almost every meal. It is relative cheap compared to vegetables, and very cheap compared to quality meat, chicken and fish. Regional data show that the mean consumption of fruit and vegetables is very low. The daily intake of fibre and protein compared to highly processed carbohydrates is therefore relative small. The food composition and intake is related to the

socioeconomic status(4), which also counts for the type of occupation and activity level. Traditionally, populations of South-Asian countries have been mainly agrarian workers, whose levels of occupational physical activity have been high. Rapid socio-economic transition and urbanization has resulted in more people undertaking industrialized jobs, and a general decline in the physical activity level(5).

Bangladesh is in a stage of demographic transition where the proportion of the elderly population is increasing. In addition, the country is facing an epidemiologic transition, which means that there is a shift from predominantly nutritional deficiencies and infectious diseases, to those classified as degenerative diseases, as the major causes of death(4). The country is therefore facing a double burden of disease. The infant mortality rate is 60.83 deaths per 1000 live births, and the life expectancy age at birth for the total population is 62.46 years(1).

1.1.7. Health care system

The control of the Government of Bangladesh (GOB) health services is highly centralized within the Ministry of health and family welfare (MOHFW), which has the overall responsibility for health sector policy and planning. There MOHFW has been divided into a health services directorate and a family planning directorate, but are now organized into more joint services at the district level. Even though the MOHFW carry the responsibility for the health care services, the non-governmental (NGO) and voluntary social organisations (VGO), which include both for-profit and non-profit organisations, predominates the provisions(6). Therefore the individual's first consultation is largely depending on the symptoms, gender, socioeconomic status and geographic location. The GOB tends to contact the NGO's and VGO's to work in specific areas or to carry out special programs.

The diabetes care is mainly delivered by the Diabetic Association of Bangladesh (DAB), a non-profit medical VGO registered with the Ministry of Social Welfare. It was established in 1956 and started the first out-patient clinic in Dhaka in 1957. Today there are 64 DAB affiliated associative throughout the country. Over the years the clinic in Dhaka has turned into a diabetes care and research complex named the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM)(7).

1.2. Diabetes mellitus

Diabetes mellitus (DM) is a metabolic chronic disease that occurs when the beta cell in the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces(8). The aetiology is multi-factorial. DM may be presented with symptoms like thirst, blurring of vision and weight loss, or with non-specific symptoms like depression and decreased working capacity(9). Hyperglycaemia is a common consequence of uncontrolled diabetes. Over time it will may lead to serious and costly complications to many of the body's systems, especially the nerves and blood vessels(8).

The WHO has estimated that 180 million people have DM today. The total number of people with diabetes and its complications are rising worldwide, and is predicted to rise to 366 million by the year 2030(10). The DM epidemic can partly be explained by increased average life expectancy, obesity, sedentary lifestyle and a changed dietary pattern(9). The highest increase is projected to be found in the urban population in developing countries, especially in South-Asia. Further, this part of the world features a situation where the diabetes population is relative young (45-65 years) compared to the West (above 65 years)(11;12).

The prevalence of DM in Bangladesh is found to be 8.1% in the urban and 2.3% in the rural population(11). Both figures are high compared to the West (1-2%)(13). In the view of the high prevalence rate and low age among diabetic patients it can be assumed that Bangladesh is facing a high number of diabetes complications(12).

1.2.1. Diabetic neuropathy

Diabetic neuropathy is damage to the nerves as a result of DM, and the most common complication of DM. Chronic distal sensorimotor symmetrical neuropathy (diabetes peripheral neuropathy (DPN)) is the most common form and accounts for 75% of the diabetic neuropathy syndromes(14). It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes(15).

The International diabetes federation has estimated that DPN affects 20-50% of people with DM(16). The prevalence rates in the literature varies from 5-100%(17). This diversity may reflect the different diagnostic criteria and diverse study population. In Europe the prevalence is found to be between 20-60 % in patients who have had the DM diagnosis between 4 and 10 years(18-20), but there are few DPN studies from the South-Asian region. A study from India

reported a DPN prevalence of 19.1%(21), and studies from the U.K. have reported lower level of peripheral arterial disease (PAD) and DPN among South-Asians compared to Europeans living in the U.K. (22;23). Age, duration of diabetes and the poor glycaemic control are recognized as risk factors for DPN, while cigarette smoking, retinopathy, hypertension, obesity, hyperlipidaemia and microalbuminuria has been pointed out as potential risk indicators(14).

The primary symptom of DPN is loss of sensation in the toes which extends to involve the feet and leg in a stocking distribution. Some patients complain about numbness and pain, but most frequently the disease progresses insidiously and undetected. Loss of vibratory, tactile, pain and thermal perception, in addition to abnormal distal lower reflexes and pain or tingling feelings are early signs of DPN. It can be detected by means of the 10 gram Semmes-Weinstein monofilament, 128 Hz tuning fork and a reflexes hammer. There is no uniform screening tool or guideline regarding the early evaluation and diagnosis of DPN, but several countries and federation have formulated suggestions. Neuropathy Disability Score (NDS) which includes the examination of the ankle reflex, vibration perception, pin prick sensation, and temperature in combination with the Neuropathy Symptom Score (NSS), which includes questions concerning burning, numbness or tingling feelings in the lower extremities, is recognized as a screening tool(14).

If no appropriate preventive measures are taken and the disease progresses, motor manifestations like wasting of the small muscles in the feet and weakness of the lower extremities become apparent. Deformities and foot callus that can fissure, infect, and ulcerate might develop and further turn into painful and distressing impairments. Of all diabetes related lower extremity amputations, 85% are preceded by foot ulcers, and 70 % of all leg amputations worldwide happen to individuals with DM(15;24). In diabetic patients with severe foot ulcers the mortality figures are as high as 54%(12). Most of the diabetic foot ulcers are considered to be of neuropathic aetiology(14), and therefore eminent preventable. The secondary diabetic neuropathy complications can therefore most likely be avoided, if neuropathy is identified at an early stage(15).

Most of the studies in the field of motor dysfunction and joint mobility are qualitative studies from the West, where expensive testing instruments like e.g. Magnetic Resonance Image and motor nerve conduction velocity apparatus have been used. The results show that diabetic

patients have limited joint mobility, atrophy, additional to gait and balance problems(25-28). Clinical screening tests for mobility and strength are usually preformed by means of a Goniometry and Kendall's muscle test.

1.3. Justification of the study

The prevalence of type 2 diabetes and its complications are predicted to increase extensively in the South-Asian region(10), especially among the urbane population. There are few diabetic neuropathy studies from the South-Asian region and to our knowledge, no published data on the DPN prevalence, or risk factors among type 2 diabetic patients in Bangladesh. Here expensive and modern equipment are less likely to be available, and costly treatment is out of reach for the majority of the people. Therefore the attention should be on easily arranged clinical tests, in addition to preventive measures to avert falls, fractures, work disability and hospitalisation among diabetic patients(12).

Few studies have used objective clinical performance measures to study the relationship between diabetes, DPN and physical function. Considering the motor, sensory and functional impairment caused by DPN, an evaluation of the prevalence and unknown risk factors, in addition to an assessment the patient's physical function become important in order to avert further disability and reduce the enormous medical, economic and social burden for both the individual and the societies.

2. RESEARCH OBJECTIVES

2.1. Objectives

2.1.1. General objective:

To estimate the prevalence of and associated risk factors for diabetic peripheral neuropathy, and additionally, evaluate the sensory and musculoskeletal lower-leg function among type 2 diabetic outpatients in Dhaka, Bangladesh. With a view to provide necessary data to identify differential risk factors, and to identify diabetic patients at risk for developing foot complications in a practical and suitable manner, which may ensure improved preventive measures and the quality care for diabetic patients.

2.1.2. Specific objectives:

1. To determine the diabetic peripheral neuropathy prevalence
2. To identify the associations risk factors for diabetic peripheral neuropathy by
    - Mapping demographics and socioeconomic factors
    - Describing the food habits and physical activity level
    - Analyzing biophysical and biological data in relation to DPN
3. To assess and describe the cutaneous sensation and musculoskeletal lower-leg function

3. METHODS

3.1. Location and Population

The research took place in the out-patient department at BIRDEM hospital in Dhaka, Bangladesh, in the period 8th of August to 18th of September 2006. BIRDEM is a 550-bed general tertiary level hospital with most modern disciplines. The out-patient department (OPD) is largely dedicated to diabetic patients, with a daily turnover of around 3000 patients, including 60 to 70 new patients(7).

3.2. Study design

Due to limited resources and time a cross-sectional design was selected to obtain information regarding the DPN prevalence and associated risk factors, in addition to the assessment of the patients' lower-leg function.

3.3. Sample selection

3.3.1. Inclusion criteria

The inclusion criterion was routine visiting type 2 diabetic outpatients, diagnosed according to the WHO criteria 5-11 years prior to the investigation. The patients were registered at the BIRDEM hospital between the 1st of January 1996 and the 31st of December 2001, and had a registration number in the range 148971 – 238083. The patients with amputations were also included in order to estimate the correct prevalence rate.

3.3.2. Exclusion criteria

The exclusion criteria were any known rheumatic disease, vitamin B12 deficiency, alcoholism, intoxication, hypothyroidism, hyperthyroidism, paraneoplastic disorders, cerebral vascular disease, Parkinson disease, uraemia and acute or chronic musculoskeletal disorders.

3.3.3. Sample size calculation

The determination of an appropriate sample size is most common in clinical trials, but it is also applied in cross sectional studies. The main idea behind a sample size calculation is to have a high chance of detecting a worthwhile difference between groups, if it exists. We wanted to identify associated risk factors for DPN. Therefore we would be interested to detect this difference for a number of variables with 80 % probability and a statistically significant level of 0.05, between the DPN subjects and the non-DPN subjects. We used the assumed proportion for one variable in the DPN group, p1, and the assumed proportion for the same variable in the non-DPN group, p2, to calculate the mutual p= (p1+p2)/2. The standardized difference was calculated with the formula: (p1-p2)/√(p(1-p)). The nomogram was used to calculate the sample size for detecting a difference for the defined variable (29).

Figure 1: Sample size calculation

Sample size from a nomogram	**Proportion in the DPN-group, p1**	**Proportion in the non-DPN-group, p2**	**Mutual p (P1+P2)/2**	**Standardized difference (p2-p1)/root(p*(1-p))**	**Power**	**p-value**
250	0.30	0.15	0.225	0.35921	0.8	0.05
600	0.30	0.20	0.25	0.23094	0.8	0.05
2000	0.30	0.25	0.275	0.11197	0.8	0.05

Taking the WHR variable, we assume that 30% of the DPN-group had a normal WHR, compared to 20% in the non-DPN-group. The proportions to be compared for the WHR variable are thus 0.30 and 0.20, and we would for need 600 patients. In addition to this sample size calculation, we had to match the sample size to the limited time and budget. Therefore we decided to include 400 patients.

3.3.4. Sample collection

Three days before the outpatient's doctor appointment, he/she delivers a blood sample and register with their personal registration number on a patient list in the OPD. The patient list is distributed between ten examination-rooms. There are 2-6 doctors in each examination-room.

Depending on the number of patients allocated for each examination-room, 1-3 examination-room(s) was randomly selected every day, following a simple random procedure. The patient list belonging to the selected examination-room(s) was collected by the researcher, and the personal registration numbers matching the registration range was singled out and clearly marked with a red pen. The doctors were well informed of the research objectives and the inclusion and exclusion criteria. The doctor informed and asked the selected patients (marked with red on the patients list), to make contact with the research department immediately after the doctor appointment. Due to the climatic conditions (heavy rainfall) and the ongoing political unrest, not all the registered patients came to the doctor appointment or to the research department. The number of patient did therefore differ from day to day.

3.4. Data gathering

3.4.1. Preparation

All the theoretical preparation and equipment purchase was done in Norway before the data collection. An academic in the field of community medicine translated the questionnaire, made for this research, and the Neuropathy Symptom Score (NSS) into Bengali.

Training of the assistants

Two research assistants (RA) were recruited for the study. They both had finished their master of science in nutrition. They were introduced to the questionnaire. The Bengali questionnaire and NSS were used as a guide to secure any language misunderstandings. The clinical tests were also introduced, explained and carried out on both of the RAs to make sure that they understood what to put in plain words for the patients.

Pilot testing and Pre-study

The Bengali version of the NSS and the questionnaire were pilot tested on five patients fulfilling the inclusion criterion. There were no remarks or misunderstandings, and therefore no changes were made after pilot-testing. The first examination day was considered as pre-testing session, and seven patients were included. During the session some of the function tests, which included walking and great motions, were conducted and found to be strenuous, time-consuming and not manageable in the small space available. The range of motion (ROM) measurements was initially set to be categorized into limited or normal ROM. We found that all the pre-tested patients ended up in the normal group, which gave little

information regarding the variation. Therefore, the exact ROM measurements were written down and the number of function tests was reduced after the pre-testing session.

3.4.2. Procedure

The patients were referred by the doctors, informed about the project and gave informed consensus to the RA. The patients' medical record book was handed in to the RA. The RA recorded the needed information, gave the patient an ID number, measured the waist and hip circumference, and interviewed the patients. The patients were examined by the researcher and delivered blood and urine to the laboratory technicians. The laboratory staff analysed the blood and urine samples at the BIRDEM hospital. The researcher gathered the blood and urine sample results.

Medical record and Anthropometrics

The medical record book consists of information regarding the patient's DM condition, starting from the registration date up to the present date. Fasting glucose, OGTT levels, lipids, and height in addition to the present day's weight and blood pressure measures were recorded from the patient's medical record book.

In case of any confusion, blood pressure and anthropometrical data was reassessed by the RA. Height was measured to the nearest centimetre and weight in kilograms. Blood pressure was noted by a standard mercury sphygmomanometer while seated with the arm supported on a table.

The waist and hip circumference were measured in nearest centimetre, with a non-stretchable measuring tape. Waist circumference was defined as the midpoint between the iliac crest and lower margin of the ribs. Hip circumference was measured at the symphysis pubis. Both measurements were done with the patient standing and breathing normal. The wais-hip ratio was calculated.

Questionnaire

The questionnaire was made for this study. It was based on the questionnaires used in the revived articles, in addition to the "getting around" part in the World Health Organization Disability Assessment Schedule II. The questionnaire was structured, with clear closed ended questions divided into six sections:

1. Demographic characteristics: age, gender, years of education, occupation (student, housewife, manual work, office work, business, unemployed, retired), average monthly family income and living arrangements (electricity, pipe-water).
2. Patient history: Diabetes duration and medication (diet, tablets, insulin), family diabetes, renal-, vision- and foot complications.
3. Lifestyle.
    a. Smoking: never smoked, ex-smoker, occasionally smoker, <10 per day, 10-20 per day or >20 per day.
    b. Food consumption: Vegetable, rice (<3 units, 3-7 units, >7 units per day), chicken, fish and beef (None or once, <3 times, >3 times per week)
    c. Physical activity level (Never, <30 minutes, 30-60 minutes, 1-2 hours, 2-4 hours, > 4 hours per day,)
    d. Walking and standing difficulties (No, moderate, cannot do)
4. Foot-care awareness: Type of foot-wear, feet cleaning (every week, every day, several times a day) and inspection practices (every day, every week, every month)

Neuropathy Symptom Score

Neuropathy Symptom Score(18) consist of five questions. The RA questioned the patients. If there were any vagueness or remarks the researcher was consulted. Each question was assessed with points in order to calculate the total symptom score. The total symptom score was calculated and converted into grade of symptom. 3-4 points were converted into mild symptoms, 5-6 points into moderate symptoms and 7-9 points into severe symptoms.

1. Burning, numbness and tingling (2p) or Fatigue, cramping and aching (1 p) feelings in the lower extremity
2. The feelings (symptoms) are present in the feet (2p) or calf (1p)
3. There are nocturnal exacerbation of the feelings (symptoms) (2p) or they are equally present during the day and night (1p)
4. The feelings (symptoms) wake the patient up from sleep (1p)
5. Walking (2p) or standing (1p) manoeuvres reduce symptoms

Neuropathy Disability Score

The Neuropathy Disability Score (18) consist of four clinical tests. The RA explained the testing procedure and applied the tests at the patients hand prior to the initiation of the examination. The patient was examined in a supine position with the eyes closed for test

number 1-3. The researcher sat on the edge of the bench facing the patient feet to secure any cheating. Both feet were examined. Each test was assessed with points in order to calculate the total disability score. The total score was converted into grade of disability. 3-4 points were converted into mild disability, 5-6 points into moderate disability and 7-10 into severe disability.

1. Pin-prick – tactile sensation was examined by using the reverse end of the turning fork and tendon hammer, which was sharp and dull respectively. Sharp followed by dull pressure, or in the opposite sequence, was applied at the cuticle of the 1st toe. The patient was asked to tell which application that was sharp or dull, correct answer (0p), incorrect answer (1p).
2. 128 Hz turning fork (Hartmann C128) – vibration was examined by placing the vibrating fork longitudinal on the 1st toe three times. The fork was struck on the examiners knee to create the vibration. In at least one out of three strikes the fork was stopped and not-vibrating prior to the application. The patient was asked to say yes when vibrating, and no when not. Two of three right answers were assessed as correct (0p), whereas one of three right answers was assessed as incorrect (1p).
3. Cold sponge: thermal sensation was examined by using a cold (from the freezer) and a room temperature sponge. Cold followed by normal, or in the opposite sequence, was applied on the dorsum of the foot. The patient was asked to tell which application that was cold and normal, correct answer (0p), incorrect answer (1p).
4. Tendon hammer (Babinski hammer) – Achilles tendon reflex was assessed with the patient in sitting position. The broad end of the hammer was hit at the Achilles tendon. A jerk into dorsal flexion was attained (0p), with reinforcement (1p), and if no jerk (2p).

Lower-leg examination

The screening instruments were clinical. The RA explained the testing procedure prior to the examination. The researcher examined all the patients.

1. Cutanus pressure perception was examined following the practical guidelines on the prevention of diabetic foot, by means of a 10g (5.07 Semmer-Weinstein) monofilament (30). The patient was examined in a supine position with eyes closed. The examiner sat on a chair facing the patient's foot soles. The monofilament was applied perpendicular to the skin surface with sufficient force to cause the filament to bend before it was removed. Both feet were examined on three plantar test sites: the

heel, 1st and 5th metatarsal head(20). The patient was asked to tell if he felt the pressure applied and required to respond (yes/no). The application was repeated three times at the same site with at least one "false" application, in which no filament was applied. Protective sensation was considered to present at each site if the patient had 2 of 3 correct answers (0p), and lost in the patient had 2 out of 3 incorrect answers (1p). The maximum total sum score for both feet was 6 points.

2. Range of motion measure with a goniometry (31). The exact angel measurement was written down. For the ankle joint the normal ROM is 10-20 degrees for dorsal flexion and 20-45 for plantar flexion. For the 1st MTP the normal ROM is 20-45 degrees for both dorsal and plantar flexion.
    a. Ankle dorsal and plantar flexion was examined with the patient in prone position and 90 degrees knee flexion. The stationary arm of the goniometry was placed parallel to the lateral midline of the fibula, projecting towards the fibular head. The axis was 1cm distal to the lateral malleolus of fibula, and the moving arm placed parallel to the lateral midline of the calcareous.
    b. Plantar flexion of the 1st MTP joint was examined with the patient in prone position and 90 degrees knee flexion. The stationary arm of the goniometry was placed over the dorsal aspect of the shaft of the first metatarsal bone. The axis was over the dorsal aspect of the MTP joint Moving arm: placed along the dorsal surface of the shaft of the proximal phalanx.
    c. Extension (dorsal flexion) of the 1st MTP joint was examined with the patient standing and facing the wall. The 1st toe was placed at the wall with the foot in the floor. The stationary arm of the goniometry was placed over the plantar midline shaft of the first metatarsal bone. The axis was over the plantar aspect of the MTP joint, and the moving arm placed along the plantar shaft of the proximal phalanx.
3. Strength graded according to the Kendall's muscle test (32). The researcher supported the patient if there were any balance problems. The grading was 0 if no contraction is palpable, 1 if contraction is palpable with no joint motion, 2 if the subject moves through small motion with gravity minimized, 3 if the subject moves into and holds a test position against gravity, 4 if the subject moves into and holds test position against gravity, against less than maximal resistance (<10 steps) and 5 if the subject moves into and holds test position against gravity, against maximal resistance ($\geq$10 steps).

a. Ankle flexors (Gastrocnemius, Soleus, Plantaris) were evaluated in standing position. The patient was asked to go up on tiptoe 10 times. If the patient did not manage to go up on tiptoe he was asked to do the plantar flexion movement lying prone, then in supine.
b. Ankle extensors (Tibiales anterior) were evaluated in standing position. The patient was asked to walk 10 steps on the heels. If the patient did not manage to go up on heel, he was asked to do the dorsiflexion movement lying supine.
c. Flexor hallucis brevis and longus and Extensor hallucis brevis and longus were evaluated with the patient sitting on the edge of the table with the knees flexed. Resistance was applied beneath the proximal and distal phalanx of the great toe and to the dorsum of the proximal and distal phalanx of the great toe. The patient was asked to keep the normal position, and not let the examiner move the toe. It the patient could not withstand the resistance he/she was asked to do the flexion and extension movement of the 1st MTP and IP joints without any resistance.

4. Balance was examined by use of a modified index for muscle function test for the lower extremity(33). Each test was evaluated on a three point scale, 0 being the best score. The maximum abnormal total sum score for both feet was 8 points.
    a. One leg standing with the eyes open for 30 seconds, both feet was examined. 0 points: > 30 sec, 1 point: 15 – 29 sec, 2 points: 0 – 14 sec.
    b. Narrow two leg standing with the eyes closed for 30 seconds. 0 points: > 30 sec, 1 point: 15 – 29 sec, 2 points: 0 – 14 sec.
    c. Tandem walk on a 2 meter red line with eyes open. 0 points: carry out the test without problems; 1 point: carry out the test with some difficulties; 2 points: not able to carry out the test.
5. Peripheral vascular status(34)
    a. The dorsalis pedis and posterior tibial pulse was palpated with the 2nd and 3rd finger. Each pulse score 0 when present and 1 when absent, on either foot. Max total score for both feet was 2 points.
    b. Capillary refill time of great toe was measured by applying pressure to the plantar side of the 1st MTP. The capillary refill time was timed.
6. Ulcer was assessed by using a Modified Meggit-Wagner Ulcer Classification. No ulcer gave 0 point, superficial ulcer gave 1 point and full-thickness ulcer gave 2 points. The maximum total score for both feet were 4 points.

7. Deformity was assessed by using a scale made for this study. The deformities measured were: Hammer or claw toes (The proximal toe joint is fixed in flexion whiles the distal joint and the MTP joint are extended), Hallux valgus (Prominence of the 1st metatarsal head, the first toe is inclined latteraly and often rotated so the nail faces medially), Charcot arthropathy/Neuropathic arthritis (Form of osteoarthritis, destruction of articular cartilage. The ligament and capsule are lax, and the movements' increased. There is new bone formation that can be felt. Increased fluid.), Pes cavus (The arch is higher than normal, and the heel is in varus position. Often there is claw toes.), and Pes plantus/Flat foot (The arch has collapsed so that the medial boarder of the foot almost touches the ground). Each deformity scored 1 point when present and 0 point when absent. The maximum total score for both feet were 10 points.

Blood and Urine samples

The patients were asked to deliver random blood and urine in the research department after the interview and clinical examination. A water proof resistant marker was used to label the Eppendorf tubes with the patients ID number, one prime and one original.

1. Blood samples. One test tube and one Eppendorf tube (8 ml in total) non-fasting whole blood were drawn. The Eppendorf tube was stored in a refrigerator and send to the laboratory every morning for HbA1c assessment. The test tube with the blood was centrifuged immediately after the examination every afternoon. The serum was collected in two Eppendorf tubes, stored in a freeze and sent to the laboratory for lipid analysis at a convenient (available capacity) time.

2. Urine samples. Every patient was given a sterile test tube and asked to deliver urine. The urine was put in two Eppendorf tubes, stored in the freeze and sent to the laboratory for analysis at a convenient (available capacity) time.

3.5. Variable definition

3.5.1. Diabetic Neuropathy

A total symptom score of 3-4 points was considered as mild symptoms, 5-6 points as moderate symptoms and 7-9 points as severe symptoms. A total disability score of 3-5 points was considered mild disability, 6-8 points as moderate disability and 9-10 points as severe

disability. The minimum acceptable criteria for diagnosis of DPN were moderate disability, with or without symptoms, or mild disability with moderate symptoms. Mild disability alone or with mild symptoms was not considered adequate to make a diagnosis of DPN(18).

3.5.2. Demographic and socioeconomic factors

The exact age and diabetes duration was categorized into three groups being; ≤ 40, 41-59 and ≥ 60 years old and ≤ 6, 7-8 and ≥ 9 years of duration. The monthly household income was divided by number of household members. The monthly income per family member was categorized into three groups; ≤ 800, 801-2 999 and ≥ 3000TK. The patients were asked about their food consumption. Chicken, fish and beef were added, renamed protein intake and categorized into low (0-4 points), middle (5 points) and high (6-9 points) protein intake.

3.5.3. Anthropometrics

Body mass index (BMI) was calculated according to the formula BMI = weight/height^2 (kg/m²). According to the WHO recommended cut-off points underweight was defined as ≤ 18.4, normal weight as 18.5-24.9, overweight as 25-29.9 and obesity as ≥ 30. The wais-hip ratio was calculated by dividing the waist and hip circumference measured in centimetre. A WHR > 0.90 in men and > 0.80 in women is seen as abdominal obesity and a risk factor for developing diabetes(35). Hypertension is defined as systolic blood pressure ≥ l40 mmHg or diastolic pressure ≥ 90 mmHg(36).

3.5.4. Biological specimens

Glycosylated hemoglobin (HbA1c) was analysed by high-performance liquid chromatography (HPLC). Good glucose control was defined as HbA1c ≤ 7.0% (37). The total cholesterol (TC) was measured using conventional laboratory techniques. The urine creatinine level was measured by the Alkaline Picrate (Hitachi 704 Japan) method in the biochemical laboratory, and urine albumin by the Nephelometry (Bn-2 Nephelometer) method in the laboratory(38;39). The detection limit for albumin was 11, 6 mg/l. The urinary albumin-to-creatinine ratio (UACR) was calculated. A value < 2,5 mg/mmol was defined as normal, 2,5-30 mg/mmol as microalbuminuria and >30 mg/mmol as for manifest proteinuria(40).

3.5.5. Sensory and musculoskeletal lower-leg function

Cutanus pressure perception was categorized into present (2 of 3 correct answers (0p)), or lost (1 of 3 correct answers (1p)) for each test site. The scores for each site for both feet were added and categorised into normal (0p), reduced (1p) and absent (2p) protective sensation. In

addition the total protective sensation sum score was calculated, the maximum abnormal score was 6 points. The balance test included 4 tests, each graded on a three point scale and categorised into good (0p), problems (1p) and not able to perform the test (2p). In addition the total balance sum score was calculated, the maximum abnormal score was 8 points. The Kendall's muscle test scales from 0 to 5 points. The points for each muscle group for both feet were added and categorised into strong (10-8 p) and weak (7-0 p). The joint ROM measures for each joint for both feet were added, and the mean value was calculated.

3.6. Ethical issues

Approval was sought and given by the Ethical Committee in Norway and from the BIRDEM hospital, Bangladesh. The study was carried out according to the Helsinki declaration. The patients were informed about the purpose and objective of the study, and that they had the right to withdraw or restrict their data from analysis at any stage of the study. They volunteered and gave informed consent prior to being included in the study.

Ethical difficulties raised in this study included the data collection on the topic of socioeconomic status and behaviour. The findings have been treated with highest possible degree of confidentiality. The uncomfortable feelings were limited, and were done by informing the participant that any question could be refused. The random blood and urine was delivered at the hospital to reduce the discomfort related to fasting and bringing urine to the hospital. The clinical assessment was preformed gentle and with care in order to prevent and limit possible uncomfortable and exhausting feelings. All the tests were explained and showed beforehand in order to secure any unexpected event. The patients' transportation expenditure was covered as a compensation for participating in the study.

3.7. Data handling

The data was entered in the SPSS 14.0 for Windows software, every evening. After arriving Norway the data was transformed into Microsoft Excel 2003. In Excel the raw data was checked. Z-score and XY-plot was prepared in order to acquire an overview of the data material. Subsequently the data was converted again to SPSS 14.0 for Windows software for data analysis.

Descriptive statistics were used in order to identify the DPN prevalence, determined in simple percentages. For comparison of baseline variables between the groups, chi-square (χ^2) test were performed for categorical data, t-test for normally distributed continuous data and Mann-Whitney test for non-normally distributed continuous data. Spearman correlation was used to assess the relationship between variables of interest. Bivariate and multivariate logistic regression analyses were performed in order to identify factors associated with DPN and adjust for potential confounding factors. Odds ratios (OR) with 95 % Confidence Intervals (CI) were provided. Statistical significance set at $p < 0.05$. All tests performed were two tailed.

4. RESULTS

4.1. Main Demographic and socio-economic characteristics

In this cross sectional study a total of 303 patients were interviewed and examined. One patient withdrew in the middle of the examination, one patient was excluded due to duration of diabetes of four years, three patients were excluded due to a history of stroke and four patients were excluded due musculoskeletal disorders (low back (L5) and ankle operations). A total of 294 patients remained for analysis.

There were 155 (52.7%) female and 139 (47.3%) male. The mean age was 50.8 $\pm$ 10.6 years, females being younger (48.7 $\pm$ 10.7) compared to men (53.1 $\pm$ 9.9). The mean diabetes duration was 7.0 $\pm$ 1.8 years, similar in both men and female. There were 82 patients who had a household income per family member of $\leq$ 800 TK, 148 patients between 801-2 999 TK and 64 patients $\geq$ 3 000 TK. The mean education level was 6.8 $\pm$ 5.2 years.

Of the total number of patients, 49.7% were housewives, 13.3% had office work, 8.2% manual work and 11.2% reported business as their occupation, 6.1% were unemployed and 11.6% were retired. Concerning the housing condition, 1 patient had only pipe-water, 78 patients had only electricity, 212 patients had both and 3 patients had either pipe-water or electricity. First degree family diabetes was reported in 48.6% of the cases. Regarding any known diabetes complications only 9 (3.1%) patients reported impaired renal function, whereas 230 (78.2 %) reported vision impairment. There was one toe amputated patient (2^{nd} and 3^{rd} toe), and 46 patients with a foot deformity. A previous foot ulcer was reported in 28

(9.5%) patients and there were 18 patients with either superficial or deep ulcers the present day. Only 11 patients had a mean refill time of more that 3 seconds. In the DPN group17.2 % was not able to walk for one kilometre and 13.8% was not able to stand for half an hour compared to 3.8% for both functions in the non-DPN group. Due to the limited number of patients we decided not to use the data presented in this last paragraph for any further analysis.

4.2. Paper 1

The paper attempts to describe the prevalence of DPN and its associated risk factors for developing DPN among type 2 diabetic outpatients. The overall prevalence of DPN in this study was 19.7 %, which was fairly similar for male (20.9%) and female (18.7 %) patients. There was an increase in the prevalence of DPN with increasing age from 11.1% in those aged 23-40 years to 32.3% in those aged 60-80 years (OR 3.8, 95% CI 1.4-10.4). The prevalence of DPN increased steadily with increasing duration of diabetes per year (OR 1.2, 95% CI 1.0-1.4), from 14.1% in those diagnosed 5 years prior to investigation to 29.2% in those having 9-11 years duration of diabetes

The prevalence rate differed following the treatment procedures for diabetes. The prevalence of DPN was 13.7% in the oral antidiabetic treated group, compared to 29.2 % in the insulin treated group (OR 2.6, 95% CI 1.4-4.7). There were no significant correlation between the treatment procedure and age, or between the treatment procedure and duration of diabetes. There was a significant correlation between the treatment procedure and income ($rSp = 0.00135841$; $p< 0.001$). The prevalence increased with decreasing income from 9.4% in the group earning $\geq$ 3000 TK per month to 25.3% in the group earning $\leq$ 800 TK per month (OR 3.3, 95% CI 1.3-8.8), and with decreasing protein intake from 13.8 % in the group having a high protein intake compared to 32.8% the group having a low protein intake (OR 3.1, 95% CI 1.4-6.9). There was a significant positive correlation between protein intake and HbA1c ($rSp = 0.00052095$; $p< 0.01$), and between the protein intake and income ($rSp = 0.000001$; $p< 0.001$).

After controlling for age, duration of diabetes, HbA1c, treatment procedure, WHR and income in a multivariate logistic regression model, we found age $\geq$ 60 years (OR 4.2, 95% CI 1.4-12.3), low/normal WHR (OR 3.7, 95% CI 1.5-9.3), income $\leq$ 800 TK (OR 3.2, 95% CI

1.1-9.4) and patients treated with insulin (OR 2.0, 95% CI 1.0-4.0) as statistically significant risk factors, and longer duration of diabetes (OR 1.2 95% CI 1.0-1.4) and higher HbA1c level (OR 1.1, 95% CI 1.0-1.3) as borderline, significant risk factors for DPN.

4.3. Paper 2

The aim of this study was to assess the sensory and musculoskeletal lower-leg function among type 2 diabetic outpatients, with and without DPN, in Bangladesh, in a valid and practical manner suitable for low income countries, in order to identify diabetic patients at risk for developing foot complications. We found that the protective sensation was statistically significant reduced for the heel ($p<0.1$), 1st toe ($p<0.001$) and 5th toe ($p<0.001$) in the DPN group compared to the non-DPN group. The statistically significant protective sensation reduction remained after calculating the total sensibility sum score ($p< 0.001$).

The non-DPN group preformed better on the entire balance test, and the difference between the groups was statistically significant even after calculating the total balance sum score ($p< 0.001$). For the tandem walk 92.8% of the non-DPN-group performed the test without problems compared to only 67.2% of the DPN-group. The DPN-group performed worse on both the right and left one-leg standing test. The highest statistically significant difference between the groups was found on the right one-leg ($p<0.001$) compare to the left one-leg ($p<0.01$) standing test.

The joint ROM for both the ankle and 1st MTP joint was reduced in the DPN-group compared to the non-DPN group, but only the dorsal flexion ($p=0.03$) and plantar flexion ($p=0.003$) ROM of the 1st MTP joint was statistically significant reduced. A higher percentage of the DPN-group was weak in all the muscle groups compared to the non-DPN group, but the difference was only statistically significant for the Tibialis anterior ($p=0.03$) and Flexor hallucis ($p=0.02$) muscles.

The results from the multivariate logistic regression analysis revealed that the DPN-group had a higher risk for poor balance (OR 1.4 95% CI 1.1-1.6), reduced protective sensation (OR 2.0, 96% CI 1.5-2.6) and Flexor hallucis weakness (OR 3.2, 95% CI 1.1-9.4) even after controlling for age, balance, sensibility, 1st MTP plantar and dorsal flexion ROM and the Tibialis anterior and Flexor hallucis strength.

5. DISCUSSION

5.1. Findings

The general objective of the study was to estimate the prevalence and associated risk factors for diabetic peripheral neuropathy, and additionally, to evaluate the sensory and musculoskeletal lower-leg function among type 2 diabetic outpatients in Dhaka, Bangladesh. We wanted to do this in a practical manner suitable for low income countries like Bangladesh in order to identify diabetic patients at risk for developing foot complications. Further, we wanted to provide necessary data to identify differential risk factors that may ensure improved preventive measures and care for the diabetic patients.

We found that the overall prevalence of DPN in this population was 19.7 %. European studies using similar diagnostic criteria, have reported prevalence rates of 32.1% (18), 35.4% (19) and 60.0 % (37) among type 2 diabetic patients attending diabetic hospital clinics. The low DPN prevalence in our study could be due to the selection of the study population. We included patients who were diagnosed with DM 5-11 years prior to the investigation, and consequently our subjects had a mean duration of diabetes of 7.03 $\pm$ 1.80 years. The mean age of our subjects was 50.8 $\pm$ 10.55 years, and therefore younger compared to the European subjects. They had a mean duration of diabetes of 6 years and a mean age of 63 years(18), 9.7 years and 61.3 years(19), and 8.5 years and 57.2 years(37) respectively. This may indicate that the diabetes complications in the Bangladeshi subjects have initiated earlier both for the age and duration of diabetes and may confirm that the diabetes population in this part of the world is relative young compared to the West(11;12).

The low DPN prevalence rate in our study corresponds with studies from the UK, showing that the neuropathy prevalence was lower in South-Asians compared with Europeans living in the UK, even after adjusting for age(22;23). It is also similar to the prevalence rate found in a study from a diabetic centre in India, reporting a neuropathy prevalence of 19.1% among type 2 diabetic outpatients(21). The mean duration of diabetes in the Indian subjects with DPN were 12 years, and the mean age was 62 years. However, the Indian study employed different diagnostic criteria and no firm comparison or conclusion can therefore be made.

Population, recruitment, diagnostic criteria and modes of investigation are factors that may influence the differential results reported in various studies. We have used similar diagnostic procedures as those used in Young's study from the UK involving 6487 type 2 diabetic patients(18). They are simple clinical criteria without referring to electrodiagnostic studies, since highly sophisticated and expensive procedure is less suitable to undertake in developing countries like Bangladesh.

Age, duration of diabetes and poor glycemic control are established risk factors(14;18;19;21;36;37;41-43), which we revealed as risk factors for DPN. Duration of diabetes was found to be a marginally independent, statistically significant risk factor for DPN in our population. This may be due to the limited sample size, in addition to the uncertainty between disease onset and time of diagnosis, which may indicate late diagnosis of DM.

The BIRDEM hospital has a welfare system for economically underprivileged patients that provides them with insulin for free, or for a subsidized price. This might have resulted in more insulin treatment among the poorer patients, and explain the statistically significant correlation we found between the treatment regime and income. Although dubious, but in agreement with several other studies(21;37;42), we found more subjects with DPN to be insulin treated. This finding remained even after controlling for the confounding factors age, duration of diabetes, income, WHR and HbA1c in a multivariate logistic regression model.

We also found low income as an independent, statistically significant risk factor for DPN, which is in agreement with the findings from India, demonstrating that poor socioeconomic background contributes to diabetic foot complications(12). A possible explanation could be that the poor people are less likely to use health services(44), which might result in late diagnosis and uncontrolled DM. The statistically significant correlations we identified between protein intake and income, and protein intake and HbA1c may also strengthen the impact of socioeconomic level as a factor. The reason is that proteins and fibre-rich food are expensive and important in order to control the blood sugar level(45). It is reported that members of the higher social classes in Bangladesh are the first once to change from a low-risk to a high-risk way of life, characterized by diets rich in animal proteins and a sedentary lifestyle(4). The socioeconomic status might therefore in turn explain for why low/normal WHR is a risk factor for the development of DPN in our study.

We used several easily arranged and inexpensive clinical tests to assess the sensory and musculoskeletal lower-leg function. The 10 gram monofilament is frequently used to assess the foot ulcer risk status. It is simple to perform, but general agreement is lacking regarding the type of monofilament, number of test sites and procedure. We used the Semmer-Weinstein 5.07 (10 g) monofilament at three plantar sites for detecting loss of cutaneous pressure perception. For the 5th toe, 3.4% of the non-DPN group compared to 20.7% of the DPN group had absent protective sensation, which places them at high risk for developing foot complications. The 5th MTP test site has been reported to have the highest sensitivity compared to the hallux, 1st MTP and 3rd MTP test sites(46).

Besides increasing the foot ulcer risk, loss of plantar cutaneous pressure perception might increase the risk of falling and postural instability (47) due to the lack of accurate proprioceptive feedback (sensory ataxia)(48). In addition to the afferent information from the somatosensory system, balance is controlled on the basis of the visual and vestibular system. As diabetes retinopathy appears to exist frequently with DPN, this will naturally affect the balance performance. We were not able to assess the retinopathy and DPN patients separately. However, large studies have reported that postural control is affected in DPN patient even with normal vision(48-50). Our findings is in agreement with others showing that DPN patients perform worse on a one-leg static balance test, compared to controls(51-53). We found that the difference between the groups for the one-leg standing test was most significant for the right leg compared to the left leg standing test. We did not ask the patients to identify their dominant and non-dominant leg, and can therefore not draw any conclusions. However the finding is interesting seen together with Cimbiz et al. who reported the right leg to be the dominant in the majority of his subjects, and further that the maximal balance reduction in the DPN group was found on the dominant leg(53).

Limited joint ROM can also contribute to reduced balance as well as elevate the foot pressure, and consequently predispose to foot ulceration(54). We did not assess the plantar foot pressure, but studies using plantar pressure analysers have reported that DPN patients have elevated foot pressure in addition to reduced ankle and 1st MTP joint ROM(54;55). Zimney et al. reported the determination of the 1st MTP ROM to be a fairly exact test to identify a foot with elevated plantar pressure(54). Like others we found a statistically significant difference in the 1st MTP joint ROM between the groups(54), but this difference was lost when we

controlled for age, strength, balance and protective sensation. We did not observe any statistically significant difference between the groups for the ankle plantar and dorsal flexion ROM measured with a goniometry, which is in agreement with others(56).

The relation between motor dysfunction and the severity of neuropathy and muscle strength remain largely unknown(57). However, magnetic resonance imaging, electromyography and electrophysiological studies of motor nerve conduction have revealed abnormalities and signs of atrophy, denervation and compensatory reinnervation in DPN patients(27;28;58). Atrophy of the foot muscles has been said to be closely related to the severity of neuropathy(57), and is believed to be the main processes leading to an anatomical foot change and therefore directly related to the development of foot ulceration(28) and postural instability(27). We found a significant difference between the DPN-group and the non-DPN-group for the Flexor hallucis (innervated by the nervus tibiale), but not for the Extensor hallucis (innervated by the nervus peroneal) muscle. This finding is in agreement with van Schie et al., who reported that the Tibial innervated muscles were weaker compared to the Peroneal innervated muscles in DPN subjects(26).

The ability to stand on heels and toes are easily performed test that do not require any technical equipment and are therefore suitable for population based surveys(59). They reflect strength at the ankle and knee. In DPN, motor weakness is believed to result in foot drop and therefore it has been suggested more severe impairment of the ankle extensors (Tibialis anterior) compared to the ankle flexors(Gastrocnemius)(57). However, the findings in the literature are conflicting. Andersen et al. found similar degrees of weakness and atrophy of the ankle extensors and flexors(60), and has suggested that the functional differences between the extensors and the flexors is not caused by selective weakness or atrophy of the ankle extensors, but it is combined with a higher capacity of the ankle flexors and a consequence of the biomechanical properties of the ankle joint(57).

5.2. Methodology

5.2.1. Statistical analysis

This is a cross-sectional study, which means that we have measured the condition, DPN, and the exposure, the associated risk factors, at the same point in time. Therefore we cannot draw

any firm conclusions regarding the risk factors. It is important to be aware that multiple factors may have influenced the dependent factor DPN. One variable may have a significant relationship with the dependent variable, but this association may have been due to the influence of a third variable, called a confounder factor. To control for the confounding factors we have used multivariate logistic regression analyses with DPN as the dependent factor. However, we cannot exclude the possibility that there might be uncontrolled factors that were not included in the study and analysis.

5.2.2. Sample size

We had limited time and recourses to conduct the study, and decided the sample size goal to be 400 patients. We manage to include 294 patients, which we stratified into two or three groups for some of the variables after the data collection. Ideally the number of subjects in each stratified group should have matched the sample size calculation. In theory this is possible, but in real life it is complex. One of the reasons for requiring a large sample size is to secure against a type II error. A type II error means that we run the risk of reaching a conclusion that there are no differences between the groups, even though there is a difference. The small sample size is a possible cause for only being able to identify the established risk factors like HbA1c and duration of diabetes, as borderline statistically significant risk factors. With a bigger sample size, it may be assumed that these risk factors would have become highly statistically significant.

5.2.3. Selection bias

Our sample was drawn from one hospital, the BIRDEM hospital, and the patients were diagnosed with DM 5 -11 years prior to the investigation. BIRDEM is the main diabetic hospital where all the diabetic patients in Dhaka come for diagnosis and follow-up. Since the research team only consisted of one researcher and two assistants, we had a limited capacity and were not able to include all the outpatients every day. To limit the selection bias, which is a distortion resulting from the manner in which the patients are selected, we did a random selection of the examination rooms every day. As we wanted the patients to deliver blood, which most patients find difficult during Ramadan, we decided to finish the sample collection before the start of Ramadan. This was also to secure any bias.

5.2.4. Response rate

We wanted all the patients matching the registration range and fulfilling the inclusion criterion in the selected examination room(s), to make contact with the research department after the doctor appointment. To secure that the doctors asked the patients matching the registration range and fulfilling the inclusion criterion, the researcher personally talked to the doctors and marked the patient list every morning. The number of patients who made contact with the research department varied from day to day. The reasons could have been many. The political situation resulted in several days with transportation strikes and unrest, which made it difficult for many patients and staff to attend the hospital. In addition, the rainy season also resulted in attendance problems. However, this has most unlikely biased the type of patients attending since the climate was similar for the whole city and the unrest took place in different city area almost every time. All the selected patients that turned up in the research department and fulfilled the inclusion criterion were included in the research.

Covering the patients' transportation expenditure, as a compensation for participating in the study, is a standard procedure in the research department at BIRDEM. The welfare system at BIRDEM enables patients from different socioeconomic levels to come to the hospital. To assure patients from all the socioeconomic levels, and ensure that the money was not the reason for the patients' participation in the research, the information regarding financial compensation was not communicated and given before the end of the examination. However, we have no control of what was communicated to the patients and between the patients outside the research examination room.

5.2.5. Validity

Validity refers to whether one is able to measure what he/she intends to measure. It can be divided into internal and external validity. Internal validity is an estimate of how much the measurement is based on clean experimental techniques, which means that it is related to the instruments used. The biological specimens where analysed in the laboratory at the BIRDEM hospital, which is known to be one of the best laboratories in Bangladesh. This increases the internal validity of the study. We chose to use the NSS and the NDS to identify the DPN cases. The reason for choosing this testing instrument was that it is easy to perform and required minimal time. In addition it has been used in several large European studies(18;61), and even among South-Asians living in the U.K.(20). For the sensory and musculoskeletal

lower-leg examination we choose the Semmer-Weinstein 5.07 (10 g) monofilament(61), the goniometry(62) and Kendall's muscle test(32) which has been used several times in previous studies. The index for muscle function test for the lower extremity has not been validated among diabetic patients. However, the balance tests we used have been used in other DPN studies.

The NSS and the questionnaire made for this study was translated to Bengali to prevent any language misinterpretations. To increase the internal validity we pilot tested both the NSS translation and the questionnaire. Nevertheless, we failed to obtain any useful information regarding the patients' physical activity level and foot-care practises. Physical activity is closely related to the occupation in Bangladesh, which were registered. In the Western countries, business this is closely related to a sedentary office work, whereas in Bangladesh, business is related a variety of jobs and can be everything from an office work, to running a small street shop or riding a rickshaw. For that reason we could not make any assumptions regarding the physical activity level. We were not able to evaluate the patients' physical fitness level, since the research had to be limited to clinical tests that could be performed in the small research examination room.

We asked the patients if they washed their feet several times a day, once a day, or once a week, but did not specify and defined what we meant by washing. In a predominantly Muslim country like Bangladesh, a large proportion of the people wash their feet several times a day before praying. Almost all patients replied that they washed their feet several times a day. This may reflect a certain misunderstanding regarding the type of wash, and that this question was unclear, since several of the patients had unclean feet and long toenails. Some patients were also found to have skin-crackers, fungus and prayer marks.

The issue of external validity is the question to what extent one may generalize and apply the conclusion derived from this study to the general population. Since we have only included hospital outpatients with a duration of diabetes between 5 and 11 years, we can not conclude anything regarding the DPN prevalence in Bangladesh at large. However, the BIRDEM hospital controls the diabetic care in Dhaka. Therefore the sample population most likely reflects the diabetic outpatient hospital population in Dhaka. We would have needed a much larger sample size in order to generalise our results to the total diabetes population in Bangladesh.

5.3. Conclusion

Even though this study is relatively small and the findings should be articulated with caution, the data regarding DPN from the South Asian population, where the prevalence of type 2 diabetes is likely to increase substantially in the near future is scare. Therefore, the data is vital in order to develop appropriate preventive measures and improve the quality of care for diabetic patients.

In summary, it can be concluded that the overall DPN prevalence in this population was 19.7%, and thus lower compared with the rates presented in European studies. The risk for the occurrence of DPN is related to increasing age, longer duration of diabetes and poor glycemic control. In addition, we found insulin treatment and low socioeconomic status to be independent risk factors for DPN in this population.

Despite of the importance of DPN investigation in order to provide preventive measures and quality of care, we lack simple accurate and readily reproducible method to measure the rate and extend of DPN in low incoming countries. The inexpensive and feasible tests presented in this study, especially the monofilament and balance test, may be applied in health care services in developing countries to identify patients at high risk of developing foot complications. These risk patients should be identified in time and receive improved care through proper education and training in order to diminish the risk of impairments and disabilities, and further to reduce the burden and cost for both to the individual and society at large.

5.4. Recommendations

In addition to useful experience and observations made during the field work, the data presented in this study generated several questions and issues that warrant further evaluation. First of all is the finding of early age for the onset of diabetes and its complication in Bangladesh. This has been reported in other studies, but no conclusion has been drawn. In a society like Bangladesh, where the resources are already diminutive relative to its population size, the increasing life expectancy and early onset of diabetes and its complications may dramatically raise the burden and expenses of the health care system.

Insulin is thought to be the vital and life saving drug for the diabetic patient. Therefore, the association between DPN and insulin treatment even after controlling for age, duration of diabetes and glycaemic control deserve further attention.

Good physical fitness and muscle strength has been hypothesized to avert diabetes, and may delay the onset of insulin treatment and diabetes complications. In a country where physical activity and exercise is not practised, it is important to identify useful means to increase the physical fitness level. Therefore appropriate physical activity habits suitable for the local cultural context need to be developed and tested, in addition to an assessment of the current physical fitness level.

The last issue is related to the knowledge regarding DM, DPN and diabetic foot. In order to prevent diabetic complications the community needs to be mobilized. The patient is in the end responsible for his own health, and needs to be aware of the risk factors. The attention regarding the diabetic foot problems should be increased to prevent complications and reduce the total burden for the diabetic patient, his family, the community and the country Bangladesh.

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7. PAPER ONE

Risk factors and prevalence of diabetic peripheral neuropathy:

A study among type 2 diabetic outpatients in Bangladesh

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ABSTRACT

Aims/hypothesis The purpose of the study was to estimate the prevalence and risk factors for diabetic peripheral neuropathy (DPN) in type 2 diabetic outpatients attending the BIRDEM hospital, Bangladesh.

Materials and methods Type 2 diabetic outpatients, diagnosed 5-11 years prior to the investigation was randomly drawn. DPN was assessed using the Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS). Data about demographics, blood pressure, height, weight, waist and hip circumference, and random blood and urine samples were collected.

Results Two hundred and ninety four (139 men, 155 women) type 2 diabetic outpatients were studied. The overall DPN prevalence was 19.7 %, male (20.9%), female (18.7 %). The prevalence increased with age (from 11.1% in the 23-40 year-old group to 32.3% in the 60-80 year-old group) and duration of diabetes (from 14.1% in patients with 5 years to 29.2% in patients with 9-11 years duration). Age $\geq$ 60 years (OR 4.2, 95% CI 1.4-12.3), low/normal WHR (OR 3.8, 95% CI 1.6-9.3), income $\leq$ 800 TK (OR 3.1, 95% CI 1.1-9.3) and insulin treatment (OR 2.0, 95% CI 1.0-4.0) were independent, significant risk factors, longer duration of diabetes (OR1.2 95% CI 1.0-1.4), and higher HbA1c OR1.1, 95% CI (1.0-1.3) were marginally independent, significant risk factors for DPN.

Conclusions/interpretations We observed a DPN prevalence of 19.7%. Higher age, low socioeconomic status, treatment with insulin, longer duration of diabetes and poor glycemic control were risk factors for DPN. Necessary measures should be taken to control diabetes complication and secure quality of care.

Key words Type 2 diabetes, peripheral neuropathy, risk factors

Introduction

Chronic peripheral sensorimotor symmetrical neuropathy (DPN) accounts for approximately 75% of the diabetic neuropathies(1). It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes mellitus (DM), after exclusion of other causes(2). The primary symptom of DPN is loss of sensation in the toes which extends to involve the feet and leg in a stocking distribution. Some patients complain about numbness and pain, but most frequently the disease progresses insidiously and undetected. If no action is taken, foot callus, ulceration and infection might develop and further turn into distressing and painful impairments.The foot ulcers among diabetic patients are mostly of neuropathic origin, and therefore eminent preventable. Up to 85% of amputations among diabetic patients are preceded by foot ulcers(3). The prevalence of DPN varies in the literature from 5-100%(4), which may reflect the different diagnostic criteria and diverse study populations. The International diabetes federation has estimated that it affects 20-50% of people with DM(5). Age, duration of diabetes and poor glycaemic control are recognized as risk factors for DPN, while cigarette smoking, retinopathy, hypertension, obesity, hyperlipidaemia and microalbuminuria has been pointed out as potential risk indicators(1).

It has been reported that the risk of diabetes related amputations and the prevalence of diabetic foot ulcers is significantly lower in Asians compared to Europeans in the U.K.(6-8). The reduced risk in Asians was found to be related to the lower levels of peripheral arterial disease (PAD) and DPN, but the reason is not fully understood. Ethnic differences and unknown risk factors in different populations have been proposed. There are few DPN studies from the South-Asian region, where the prevalence of type 2 diabetes and its complications are predicted to rise extensively in the coming years(9). To the best of our knowledge, there are no published data regarding the DPN prevalence in Bangladesh where the prevalence of type 2 diabetes has been reported to be 8,1% in the urban areas(10). The aim of this study was to estimate the prevalence of DPN and to identify its risk factors in type 2 diabetic patients attending the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), with a view to provide necessary data to identify differential risk factors which may ensure improved preventive measures and care for diabetic patients.

Subjects and methods

A cross-sectional study was carried out from July 2006 to September 2006 in the outpatient department (OPD) at the BIRDEM hospital, located in Dhaka, Bangladesh. BIRDEM is a

550-bed general tertiary level hospital with the most modern disciplines. The OPD is mainly dedicated to diabetic patients, the turnover is approximately 3000 patients, including 60 to 70 new patients, per day(11). All the subjects for investigation were recruited from BIRDEM. The inclusion criterion was type 2 diabetic outpatients diagnosed in accordance with the WHO criteria within 5-11 years prior to the investigation. The exclusion criteria were any known rheumatic disease, vitamin B12 deficiency, alcoholism, intoxication, hypothyroidism, paraneoplastic disorders, cerebral vascular disease, Parkinson disease, uraemia and acute or chronic musculoskeletal disorders.

The patient list for the OPD was made three days prior to the doctor appointment. The list was then distributed among ten investigation rooms, with two to six doctors in each room. In order to match the investigating team members' (the researcher and two assistants) capacity, one, two or three examination room(s), depending on the number of doctors attending, was randomly drawn every day. The doctors were well informed of the research objectives, the procedures and the inclusion and exclusion criteria. The doctors informed and requested the appropriate patients to make contact with the research department after the initial examination. The patients were informed about their right to withdraw and restrict their data from analysis at any stage. Informed consent was secured prior to inclusion in the study, which was carried out according to the Helsinki declaration. The Ethical Committee of Medical Research in Norway and the BIRDEM hospital approved the protocol.

A total of 303 patients were examined. One patient withdrew from the study, and seven patients were excluded due to complications related to stroke, ankle and low back operations. One patient was excluded due to diabetes duration of less than 4 years. Subsequently, a total of 294 patients remained for analyses.

The laboratory analyses were done at the BIRDEM hospital. Eight ml whole blood was drawn from each patient, and urine was collected in a glass test tube (6ml). Glycosylated hemoglobin (HbA1c) was analysed by high-performance liquid chromatography (HPLC). Good glucose control was defined as HbA1c $\leq$ 7.0 (12). The total cholesterol (TC) was measured using conventional laboratory techniques. The urine creatinine level was measured by the Alkaline Picrate (Hitachi 704 Japan) method in the biochemical laboratory, and urine albumin by the Nephelometry (Bn-2 Nephelometer) method in the immunology laboratory(13;14). The detection limit for albumin was 11.6 mg/l. The urinary albumin-to-creatinine ratio (UACR)

was calculated. A value < 2.5 mg/mmol was defined as normal, 2.5-30 mg/mmol as microalbuminuria and >30 mg/mmol as manifest proteinuria(15).

Information regarding diagnosis, registration date, medication, height and the present day's blood pressure (BP) and weight was collected from the patients' medical record book. High BP was defined as systolic blood pressure $\geq$ l40 mmHg or diastolic pressure $\geq$ 90 mmHg(16). The body mass index (BMI) was calculated according to the formula BMI = weight/height^2 (kg/m^2). Waist and hip circumference was measured with a non-stretchable measuring tape. Waist girth was measured through the midway between the lower border of the ribs and the iliac crest on the mid-axillary line. Hip circumference was measured to the nearest centimetre at the greatest protrusion of the buttocks just below the iliac crest. Both measurements were done with the patient standing and breathing normal. A WHR > 0.90 in men and > 0.80 in women was defined as abdominal obesity(10).

A structured questionnaire with clear and simple questions was made for this study. An academic in the field of community medicine translated the questionnaire into Bengali. It was used to prevent any language misinterpretation between the researcher and the participants. The Bengali version was pilot tested on five patients fulfilling the inclusion criteria. There were no remarks or misunderstandings, and no changes were made.

Information regarding demographic and socioeconomic factors (age, gender, average monthly income per family member, years of education) and lifestyle characteristics (smoking history, protein intake) was obtained by interview. The Neuropathy Symptom Score (NSS) was recorded by interview following the standard guidelines(17). The NSS consist of five questions; each assigning points in order to calculate the total symptom score. The total maximum abnormal symptom score was 9 points.

5. Burning/numbness/tingling (2 p) or Fatigue/ Cramping /Aching feelings (1 p) in the lower extremity
6. Symptoms present in the feet(2 p) or in the calf (1p)
7. Nocturnal exacerbation of the symptoms (2 p) or present equally at day and night (1 p)
8. The Symptoms awake the patient from sleep (1 p)
9. Walking (2 p) or standing (1 p) manoeuvres reduce the symptoms

The Neuropathy Disability Score (NDS) consists of four clinical tests on both feet(17). The procedure was explained and the tests applied on the patient's hand prior to the examination. The patient had to close the eyes during the examination. Each test was assessed with points to calculate the total disability score. The total maximum abnormal disability score was 10 points.

8. Achilles tendon reflex: The broad end of the reflex hammer (Babinski) was applied at the Achilles tendon. Jerk with reinforcement (1p), no jerk (2p).
9. Vibration perception: A 128-Hz vibrating fork (Hartmann C128) was applied longitudinally on the 1st toe three times with at least one false application (not-vibrating fork). The patient was required to tell which application that was vibrating or not. Two of three right responds were set to be a correct answer (0p), two of three wrong responds were an incorrect answer (1p).
10. Thermal sensation (cold sponge): One cold and one room temperature sponge was applied on the dorsum of the foot. The patients were required to tell which application that was cold or normal, correct answer (0p), incorrect answer (1p).
11. Tactile sensation (pin-prick): The reverse end of the turning fork and tendon hammer, sharp and dull respectively, was applied at the cuticle of the 1st toe. The patients were required to tell which application that was sharp or dull, correct answer (0p), incorrect answer (1p).

A total symptom score of 3-4 points was considered as mild symptoms, 5-6 points as moderate symptoms and 7-9 points as severe symptoms. A total disability score 3-5 points was considered mild disability, 6-8 points as moderate disability and 9-10 points as severe disability. The minimum acceptable criteria for diagnosis of DPN were moderate disability, with or without symptoms, or mild disability with moderate symptoms. Mild disability alone or with mild symptoms was not considered adequate to make a diagnosis of DPN(17).

The data was entered in the SPSS 14.0 for Windows software. The variables age, diabetes duration and income were categorised. Descriptive statistics were used in order to identify the DPN prevalence, determined in simple percentages. For comparison of baseline variables between the groups, the Chi-Square (χ^2) or Fisher's exact test was preformed for categorical data, the t-test for normally distributed continuous data and the Mann-Whitney test for non-normally distributed continuous data. Spearman correlation was used to assess the relationship between variables of interest. Bivariate and multivariate logistic regression analyses were preformed in order to identify factors associated with DPN and adjust for

potential confounding factors. Odds ratios (OR) with 95 % confidence interval (CI) were provided. Statistical significance was set at $p < 0.05$. All tests performed were two tailed.

Results

There were 155 (52.7%) female and 139 (47.3%) male subjects (Table 1). The mean age was 50.8 ± 10.6 years, females being significantly younger (48.7 ± 10.7) than men (53.1 ± 9.9). The mean duration of diabetes was 7.0 ± 1.8 years (Table 1), and was similar in males and females. The overall prevalence of DPN in this population was 19.7 %, and fairly comparable for male (n=29, 20.9%) and female (n=29, 18.7 %) patients.

Table 1 *Demographics and clinical variables related to DPN, Dhaka, Bangladesh, 2006*

Characteristics	**n**	**Total sample** (n=294)	**DPN subjects** (n=58)	**Non DPN subjects** (n=236)	**p-value for the difference**
		Mean ± SD			t-test
Age (years)	293	50.8 ± 10.6	55.1 ± 10.5	49.7 ± 10.3	<0.001
Diabetes duration (years)	294	7.0 ± 1.8	7.7 ± 1.9	6.9 ± 1.8	0.05
Waist/hip ratio	289	0.93± 0.06	0.9333 ± 0.0599	0.9324 ± 0.0603	NS
BMI (kg/m²)	294	24.43 ± 3.35	24.16 ± 3.60	24.50 ± 3.29	NS
HbA1c (%)	293	8.75 ± 2.20	9.54 ± 2.52	8.56 ± 2.08	<0.01
Total cholesterol (mg/dl)	293	190.45 ± 31.83	191.63 ± 34.29	190.17 ± 31.27	NS
		Median (Interquartile Range)			**Mann-Whitney test**
Monthly income pr family member (TK)	294	1345.24 (1866.67)	1081.17 (1535.71)	1408.33 (2024.68)	< 0.02
Education (years)	294	6.5 (12)	5.0 (12)	8.0 (12)	NS
Systolic BP (mmHg)	294	120 (10)	130 (20)	120 (10)	NS
Diastolic BP (mmHg)	294	80 (0)	80 (0)	80 (0)	NS
Albumin creatinin ratio (mg/mmol)	287	0.00 (0)	0.00 (15.3)	0.00 (0)	< 0.05
		% (n)			**Pearson Chi-Square test**
Insulin treatment	120	40.8 % (120)	60.3 % (35)	36.0 % (85)	< 0.001
Oral treatment	153	52.0 % (153)	36.2 % (21)	55.9 % (132)	< 0.01
No medication	21	7.2 % (21)	3.5 % (2)	8.1% (19)	NS *
Low protein intake	61	20.7 % (61)	34.5 % (20)	17.4 % (41)	< 0.01
Middle protein intake	146	49.7 % (146)	44.8 % (26)	50.8 % (120)	NS
High protein intake	87	29.6 % (87)	20.7 % (12)	31.8 % (75)	NS
Never smoked	217	73.8 % (217)	65.5 % (38)	75.8 % (179)	NS
Ex-smoker	44	15.0 % (44)	19.0 % (11)	14.0 % (33)	NS
Smoker	33	11.2 % (33)	15.5 % (9)	10.2 % (24)	NS

* Fisher's Exact Test

An increasing trend in prevalence of DPN with increasing age was observed, from 11.1% in those aged 23-40 years to 32.3% in those aged 60-80 years (OR 3.8, 95% CI 1.4-10.4) (Table 2). The prevalence of DPN increased steadily with increasing duration of diabetes (OR1.2, 95% CI 1.0-1.4) (Table 2), from 14.1% in those diagnosed 5 years prior to the investigation to 29.2% in those having 9-11 years duration of diabetes. The prevalence rate also differed following the treatment procedures for diabetes. The prevalence of DPN was 13.7% in the oral antidiabetic treated group, compared to 29.2 % in the insulin treated group (OR 2.6, 95% CI 1.4-4.7) (Table 2). There were no significant correlation between the treatment procedure and age, or between the treatment procedure and duration of diabetes. There was detected a significant correlation between the treatment procedure and income (rSp = 0.00135841; p< 0.001). The prevalence increased with decreasing income from 9.4% in the group earning ≥ 3000 TK per month to 25.3% in the group earning ≤ 800 TK per month (OR 3.3, 95% CI 1.3-8.8), and with decreasing protein intake from 13.8 % in the group having a high protein intake compared to 32.8% the group having a low protein intake (OR 3.1, 95% CI 1.4-6.9) (Table 2). There was a significant positive correlation between protein intake and HbA1c (rSp = 0.00052095; p< 0.01), and between the protein intake and income (rSp = 0.000001; p< 0.001).

Table 2 *Univariate analysis of risk factors for DPN with 95% CI, Dhaka, Bangladesh 2006*

Variable	**n**	**p-values for the differences**	**p-value for the specific range**	**Odds ratio (95 % CI)**
Female	155	NS		1.0
Male	139		NS	1.1 (0.65-2.04)
Age ≤ 40 years	54	0,014		1.0
Age 41-59 years	172		NS	1.8 (0.70-4.48)
Age ≥ 60 years	61		< 0.01	3.8 (1.40- 10.38)
Diabetes duration (continuous)	294	0.04	0.04	1.2 (1.01-1.36)
Income ≥ 3000 TK	63	0.053		1.0
Income 801-2 999 TK	145		< 0.05	2.6 (1.01-6.49)
Income ≤ 800 TK	79		< 0.02	3.3 (1.25-8.83)
High protein intake	87	0.015		1.0
Middle protein intake	146		NS	1.3 (0.65-2.85)
Low protein intake	61		< 0.01	3.1 (1.36-6.86)
Overweight (WHR)	255	0.036		1.0
Normal (WHR)	32		< 0.05	2.3 (1.06-5.18)
HbA1c (continuous)	293	0.003	< 0.01	1.2 (1.06-1.37)
Oral treatment	150	0.004		1.0
No medication (diet)	18		NS	0.7 (0.14-3.05)

Insulin treatment	119		< 0.01	2.6 (1.41-4.74)
Normal BP High BP	220 74	0,070	 0.07	1.0 1.8 (0.95-3.30)
UACR < 2,5 mg/mmol UACR 2,5-3,0 mg/mmol UACR > 3,0 mg/mmol	234 26 27	0,063	 NS < 0.02	1.0 1.1 (0.40-3.15) 2.8 (1.18-6.48)

Table 3 *Odds ratio (OR) and 95% CI of DPN by the following risk factors in a multivariate model, Dhaka, Bangladesh 2006*

Factors	**p-value for the entire variable**	**p-value for the specific range**	**Odds Ratio (95% CI)**
Age ≤ 40 years Age 41-59 years Age ≥ 60 years	0.030	 NS <0.01	1.0 2.3 (0.83-6.22) 4.2 (1.41-12.28)
Oral treatment No medication (diet) Insulin treatment	0.063	 NS < 0.05	1.0 0.3 (0.03-2.82) 2.0 (1.00-4.03)
Overweight (WHR) Low/Normal (WHR)	0.006	<0.01	1.0 3.7 (1.47-9.34)
Income ≥ 3000 TK Income 801-2 999 TK Income ≤ 800 TK	0.093	 <0.05 <0.05	1.0 2.8 (1.01-7.67) 3.2 (1.09-9.42)
Diabetes duration (continuous)	0.07	0.07	1.2 (0.99-1.40)
HbA1c (continuous)	0.09	0.09	1.1 (0.98-1.31)

Age ≥ 60 years (OR 4.2, 95% CI 1.4-12.3), treated with insulin (OR 2.0, 95% CI 1.0-4.0), low/normal WHR (OR 3.7, 95% CI 1.5-9.3), and income ≤ 800 TK (OR 3.2, 95% CI 1.1-9.4), remained as statistically significant risk factors, whereas duration of diabetes (OR1.2, 95% CI 1.0-1.4), and HbA1c (OR 1.1, 95% CI 1.0-1.3), remained as borderline, statistically significant risk factors for DPN after controlling for potential confounding factors included in the multivariate logistic regression model (Table 3).

Discussion

The overall prevalence of DPN in this study was 19.7 %. It is lower compared to European studies using similar diagnostic criteria(12;17;18), which have reported an overall DPN prevalence of 32.1% (mean age: 63 years, mean duration of diabetes: 6 years)(17), 35.4% (mean age: 61.3 years, mean duration of diabetes: 9.7 years)(18) and 60.0 % (mean age: 57.2 ± 10.3, mean duration of diabetes: 8.52 ± 7.13 years)(12) among type 2 diabetic hospital outpatients. The prevalence rate in our study was similar to the prevalence rate found in a

study from a diabetic centre in India, reporting a neuropathy prevalence of 19.1% among type 2 diabetic outpatients (mean age in the DPN-group: 62 $\pm$ 8 years, mean duration of diabetes: 12 $\pm$ 8 years)(19). The results from India may indicate that the diabetes complication in Bangladeshi subjects have initiated earlier both with respect to the age of the patient and duration of diabetes. However, the diagnostic criteria used in the study from India differ from ours and therefore no firm conclusions can be made.

We used similar diagnostic criteria as studies from the U.K. showing a lower DPN prevalence among type 2 diabetic South-Asian patients compared with European patients living in the U.K. even after adjusting for age(6;7). However, the observed lower DPN prevalence rate in our study compared to the European studies may be explained by the duration of diabetes selection of the study population. The mean age of our subjects was 50.8 $\pm$ 10.55 years, which may confirm that the diabetes population in this part of the world is relative young compared to the West(10;20).

The results from the multiple logistic regression analysis revealed that age and duration of diabetes(1;12;16-19;21;22) are statistically significant risk factors for DPN. Duration of diabetes was only a marginally, statistically significant risk factor in our study, and may be explained by possible late diagnosis. We found no difference in the DPN rate between the genders which also has been confirmed by others(12;16-19;21;22). Our figures showed an numerical higher occurrence of DPN among smokers and patients with high BP, hypercholesorelemina and potential mikroalbuminuri/proteinuri, but like others(12;16), we could not identify them as statistically significant risk factors. This is in contrast with other reports(21;23;24), and may have been due to the limited sample size.

We found a significant correlation between the treatment procedure and income, and between the treatment procedure and DPN. This is in agreement with several other studies showing that subjects treated with insulin are at increased risk for DPN(12;19;21). This may also be a possible consequence of the welfare system provided by the BIRDEM hospital. Insulin is supplied free or at a subsidized cost to those who can not afford to pay, which may have resulted in more insulin treatment among the poorer patients. We found low income and low/normal WHR to be significant risk factors for DPN, in addition to a significant correlation between protein intake and income and between protein intake and HbA1c. This is in agreement with findings from India indicating that poor socioeconomic background contributes to diabetic foot complications(20). Possible explanations for the phenomenon

could be that poor people are less likely to use health services(25), which might result in late diagnosis and uncontrolled DM.

Despite of the importance of DPN investigation for the quality of care provided to the diabetic patients, we lack a simple accurate and readily reproducible method of measuring DPN. Population, recruitment, diagnostic criteria and modes of investigation are factors that may influence the differential results reported in various studies. We have used similar diagnostic procedures as those used in Young's study from the U.K. involving 6487 type 2 diabetic patients(17). The method provide simple clinical criteria without referring to electrodiagnostic studies, as highly sophisticated and expensive procedure is less suitable to put into practice in developing countries like Bangladesh.

Our data suggest that the prevalence of DPN increases with age, poverty and type of treatment provided and subtly by the duration of diabetes and poor glycemic control. Our results were generated from a relatively small study, the DPN prevalence rate should therefore be interpreted with some caution. However, the findings of early age for the onset of diabetes and its complication in Bangladesh, and that insulin treatment may lead to increased risk for DPN deserve further attention. Moreover, the data of DPN from the South Asian population, where the prevalence of type 2 diabetes is likely to increase substantially in the near future, is scarce. Therefore the data on DPN from this population is vital in order to improve the preventive measures and the quality of care related to foot complication among type 2 diabetic patients.

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Duality of interest The authors declare that there is no duality of interest for this study.

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8. PAPER TWO

Sensory and musculoskeletal lower-leg function in type 2 diabetic outpatients in Bangladesh

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ABSTRACT

Aims/hypothesis The purpose of this study was to assess the sensory and musculoskeletal lower-leg function among type 2 diabetic outpatients, with and without DPN, in Bangladesh, in a valid and practical manner suitable for low income countries, in order to identify diabetic patients at risk for developing foot complications.

Materials and methods We randomly recruited 58 (19.7%) DPN subjects and 236 non-DPN subjects. The plantar protective sensation (Semmer-Weinstein 5.07 g monofilament), 1st MTP and ankle joint rang of motion (ROM) (Goniomery), muscle strength (Kendall's muscle test) and balance (one and two leg static balance, tandem walk) was evaluated.

Results The joint range of motion (ROM) for the 1st MTP dorsal (p=0.03) and plantar flexion (p=0.003), the Tibiales anterior (p=0.03) and Flexor hallucis (p=0.02) strength, balance (<0.001) and protective sensation (p<0.001) was statistically significant reduced in the DPN-group. The difference remained for the balance (OR1.4, 95% CI 1.1-1.6), protective sensation (OR 2.0, 95% CI 1.5-2.6) and Flexor hallusis (OR 3.2, 95% CI 1.1-9.4) after controlling for age, sensibility, balance, 1st MTP plantar and dorsal flexion ROM, and Tibiales anterior and Flexor hallucis strength in a multivariate logistic regression model.

Conclusions/interpretations The DPN subjects preformed worse on all the tests, especially for the protective sensation and balance test. The inexpensive and feasible tests presented, may be applied in health care services in developing countries to identify diabetic patients at high risk for developing foot-complications. These patients should receive improved care to prevent and reduce the burden and cost for both the individual and the society.

Key words Type 2 diabetes, peripheral neuropathy, balance, strength, physical therapy techniques, plantar cutaneous sensation

Introduction

Chronic peripheral sensorimotor symmetrical neuropathy (DPN) is the most common form of diabetic neuropathy, and accounts for 75% of the diabetic neuropathy syndromes(1). The primary symptom is loss of sensation in the toes which extends to involve the feet and leg in a stocking distribution. Callus formation, numbness and pain may affect some patients, but most frequently the disease progresses insidiously and undetected. Sural nerve biopsy has revealed that patients with DPN have a 30% reduction in the Sural nerve fibre density compared with patients who have no evidence of DPN(2). As the disease progresses, motor manifestations, reduced joint range of motion (ROM) decreased proprioception and increased reflex time may become apparent(1;3-6). Partial restriction of daily activities has been reported in 74% of type 2 diabetic patients with DPN(7), in addition to decreased physical fitness(5), increased risk of falling(8), mobility impairments and activities of daily living (ADL) disability(9). Up to 85% of the diabetes related amputations are preceded by foot ulcers(10), and the foot ulcers are more likely to be of neuropathic origin(11).

Considering the motor, sensory and functional impairment caused by DPN, an evaluation of the patient's level of functioning become important in order to avert further disability and reduce the enormous medical, economic and social burden for both the individual and the societies Few studies have used clinical performance measures to study the relationship between diabetes, DPN and physical function. There are hardly any DPN studies conducted in Asia and to the best of our knowledge no published data from Bangladesh. Here the prevalence of type 2 diabetes and its complications are predicted to increase extensively in the near future(12), and expensive and modern equipment are less likely to be available. The attention should be on preventive measures(13), since costly treatment is out of reach for the majority of the people.

We have shown that the overall DPN prevalence among type 2 diabetic patients attending the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) was 19.7%. The prevalence of DPN increased with age, poverty and type of treatment for diabetes and subtly with the duration of diabetes and poor glycemic control (submitted). The purpose of this study was to assess the sensory and musculoskeletal lower-leg function among type 2 diabetic outpatients, with and without DPN, in Bangladesh,

in a valid and practical manner suitable for low income countries, in order to identify diabetic patients at risk for developing foot complications.

Methods

A cross-sectional study was carried out from July 2006 to September 2006. All the subjects for investigation were randomly recruited from BIRDEM. The inclusion criterion was type 2 diabetic outpatients diagnosed in accordance with the WHO criteria within 5-11 years prior to the investigation. The exclusion criteria were any known rheumatic disease, vitamin B12 deficiency, alcoholism, intoxication, hypothyroidism, paraneoplastic disorders, cerebral vascular disease, Parkinson disease, uraemia and acute or chronic musculoskeletal disorders. A detailed description of the selection has been described previously (submitted). The patients were informed of the research objectives, the procedure and their right to withdraw at any stage. They gave informed consent prior to inclusion in the study, which was carried out in accordance with the Helsinki declaration. The Ethical Committee for medical research in Norway and the BIRDEM hospital approved the protocol.

A total of 303 patients were examined. One patient withdrew from the study, and seven patients were excluded due to complications related to stroke, ankle and low back operations. One patient was excluded due to diabetes duration of less than 4 years. Subsequently, a total of 294, 155 female and 139 male patients remained for analysis.

DPN was diagnosed by means of the Neuropathy Symptom Score (NSS) and the Neuropathy Disability Score (NDS)(14). NSS was used to identify the severity of neuropathic symptoms, the patients were asked about their experience of pain and discomfort in the lower extremities. NDS was used to determine the level of disability, derived by examination of the Achilles tendon reflex, Vibration perception (128 Hz tuning fork), Thermal sensation (cold sponge) and Tactile sensation (pin-prick). The minimum acceptable criteria for diagnosis of DPN were moderate disability of neuropathy, with or without symptoms, or mild disability with moderate symptoms. The NSS and NDS, in addition to the various demographic, medical and social variables recorded for all patients have been described in depth elsewhere (submitted).

The clinical sensory and musculoskeletal lower-leg examination was carried out by the researcher. Both feet were assessed for each test. The cutaneous pressure perception (protective sensation) was assed using a 10g monofilament (5.07 Semmer-Weinstein)(15) at

three validated plantar sites (the heel, 1st and 5th metatarsal heads)(16). It was applied perpendicular to the skin surface with sufficient force to cause the filament to bend before it was removed. The application was repeated three times at the same site with at least one "false" application, in which no filament was applied(17). In prone position with eyes closed the patient was asked if he felt the pressure, and was required to respond "yes/no". 2 of 3 correct answers gave 0 points, and 2 out of 3 incorrect answers gave 1 point. The points for each test site for both feet were added and categorised into normal (0 points), reduced (1 point) and absent (2 points) protective sensation. In addition, sum score were calculated.

Balance was assessed by means of a modified index for muscle function test for the lower extremity(18). Each test was performed without socks and shoes. The one-leg standing test was assessed on both legs, one at the time with eyes open, and the narrow two-leg standing test with the feet together and eyes closed. The tests was timed and graded on a three point scale. > 30 seconds scored 0 points, 15 – 29 sec: 1 point and 0 – 14 sec: 2 points. For the tandem walk the patients walked heel-to-toe on a 2 metre red line with the eyes open. To carry out the test without problems scored 0 points, with some problems 1 point and not able to carry out the test scored 2 points. In addition, sum score were calculated.

Passive joint range of motion (ROM) was measure with a goniometry(19). Dorsal and plantar flexion of the ankle and plantar flexion of the 1st MTP joint was assessed with the patient in prone position and 90 degrees knee flexion. For the ankle ROM measurement the stationary arm of the goniometry was placed parallel to the lateral midline of the fibula (projecting towards the fibular head), and the moving arm parallel to the lateral midline of the calcareous. The axis was 1cm distal to the lateral malleoli of fibula. For the 1st MTP the stationary arm of the goniometry was placed over the dorsal aspect of the shaft of the first metatarsal bone, and the moving arm along the dorsal surface of the shaft of the proximal phalanx. The axis was over the dorsal aspect of the MTP joint. Dorsal flexion (extension) of the 1st MTP was assessed with the patient standing facing the wall. The 1st toe was placed at the wall, and the 1st MTP joint and foot in the floor. The stationary arm of the goniometry was placed over the planter midline shaft of the first metatarsal bone. The axis was over the plantar aspect of the MTP joint, and the moving arm placed along the plantar shaft of the proximal phalanx. The ROM measurements for each joint on both feet were added.

The leg muscles were assessed with the patient in standing position without socks and shoes, supported by the researcher. For the ankle plantar flexors (Gastrocnemius, Soleus and Plantaris) the patient was asked to go up on tiptoe 10 times, and for the ankle extensors (Tibialis anterior) the patient was asked to walk 10 steps on the heels. The Flexor and the Extensor hallucis muscles were assessed with that patient in sitting position. Resistance was applied beneath the proximal and distal phalanx and dorsum of the proximal and distal phalanx of the great toe. The patient was asked to keep the toe in the normal position, and not let the examiner move the toe in the cranial nor the caudal direction. If the patient was not able to do the movement with resistance, he/she was asked to lie down and do the movement without resistance according to Kendall's muscle test(20). The patient was graded on a five point scale, five being top score per test. Less than 10 steps/minimal resistance: 4 points, holds the test position against gravity: 3 points, moves through a small motion with gravity minimized: 2 points and palpable contraction with no joint motion: 1 point. The points for each muscle group for both feet were added and categorised into strong (10-8 points) and weak (7-0 points).

The data was entered in the SPSS 14.0 for Windows software. Descriptive statistics was used. For comparison between the groups, Chi-Square (χ^2) test was preformed for categorical data and Mann-Whitney test for non-normally distributed continuous data. Spearman correlation was used to assess the relationship between lower-leg function variables and the risk factors for DPN. A multivariate logistic regression model was build with the DNP-group versus the non-DNP-group as the dependent variable, and analyses were preformed in order to adjust for potential confounding factors. Odds ratios (OR) with 95 % confidence interval (CI) were provided. Statistical significance set at $p < 0.05$. All tests performed were two tailed.

Results

Table 1: *Protective sensation and Balance measures for the DPN-group and the non-DPN-group, Dhaka, Bangladesh, 2006*

	Non-DPN-group % (n)	**DPN- group % (n)**	**Chi-Square Tests, p-value**
Sensibility test (n=294)			
Heel			<0.01
Normal	38.3 % (90)	19.0 % (11)	
Reduced	32.8 % (77)	29.3 % (17)	
Absent	28.9 % (68)	51.7 % (30)	
First toe sensitivity			< 0.001

Normal Reduced Absent	93.6 % (220) 6.0 % (14) 0.4 % (1)	70.7 % (41) 19.0 % (11) 10.3 % (6)	
Fifth toe sensitivity Normal Reduced Absent	 85.1 % (200) 11.5 % (27) 3.4 % (8)	 55.2 % (32) 24.1 % (14) 20.7 % (12)	< 0.001
Balance test (n=294)			
Left one-leg standing Good Problems Not able to	 59.3% (140) 14.0% (33) 26.7% (63)	 37.9% (22) 17.2% (10) 44.8% (26)	<0.01
Right one-leg standing Good Problems Not able to	 61.9% (146) 17.4% (41) 20.8% (49)	 34.5% (20) 25.9% (15) 39.7% (23)	<0.001
Narrow two-leg standing Good Problems Not able to	 91.9% (217) 6.8% (16) 1.3 %(3)	 82.8% (48) 10.3% (6) 6.9% (4)	<0.05
Tandem Walk Good Problems Not able to	 92.8% (219) 5.9% (14) 1.3% (3)	 67.2% (39) 31.0% (18) 1.7% (1)	< 0.001

The protective sensation for all test sites were statistically significant diminished in the DPN-group compared to the non-DPN-group, especially for the fifth toe ($p< 0.001$) (Table 1). The non-DPN-group preformed better on all parts of the balance test. The right one-leg standing test was most statistically significant diminished compared to the left one-leg standing test (Table 1).

Table 2: *Joint ROM, protective sensation, balance and strength characteristics for the DPN-group and the non-DPN-group, Dhaka, Bangladesh, 2006*

	Non-DPN-group		**DPN-group**		***p-value***
	Median	IR	Median	IR	*Mann-Whitney test*
Sensibility test (sum score)	1.0	2.0	2.0	2.25	< 0.001
Balance test (sum score)	1	3	2.5	4	< 0.001
ROM (n=288)					
Ankle Dorsal flexion	20	10	15.5	5	NS (0.13)
Ankle Plantar flexion	40	5	40	5	NS (0.25)
1st MTP Dorsal flexion	55	10	50	15	<0.05
1st MTP Plantar flexion	50	10	45	15	<0.01
	% (n)		*% (n)*		*Chi-Square test*
Strength (n=294)					
Gastrocnemius (ankle flex.)					NS (0.65)

Strong Weak	95.3% (225) 4.7 % (11)	93.1% (54) 6.9% (4)	
Tibialis anterior (ankle ext.) Strong Weak	 94.5% (223) 5.5% (13)	 86.2% (50) 13.8% (8)	<0.05
Flexor Hallucis Strong Weak	 94.9% (224) 5.1% (12)	 86.2% (50) 13.8% (8)	<0.05
Extensor Hallucis Strong Weak	 85.6% (202) 14.4% (34)	 75.9% (44) 24,1% (14)	NS (0.07)

The joint ROM for both the ankle and 1st MTP joint was reduced in the DPN-group compared to the non-DPN group, but only the dorsal flexion (p=0.03) and plantar flexion (p=0.003) of the 1st MTP joint was statistically significant reduced (Table 2). A higher percentage of the DPN-group was weak in all the muscle groups compared to the non-DPN group, but the difference was only statistically significant for the Tibialis anterior (p=0.03) and Flexor hallucis (p=0.02) (Table 2). The sum score for the protective sensation and for the balance test was statistically significant diminished in the DPN-group (p<0.001) compared to the non-DPN-group (Table 2).

Table 3 *Odds ratio (OR) and 95% CI of DPN-group versus the non-DPN-group in a multivariate logistic regression model , Dhaka, Bangladesh, 2006*

Variable	**p-values for the differences**	**p-value for the specific range**	**OR (95% CI)**
≤ 40 years 41-59 years ≥ 60 years	NS	 NS NS	1.0 1.4 (0.39-4.79) 1.2 (0.49-2.73)
Balance test		0.002	1.4 (1.12-1.64)
Sensibility test		< 0.001	2.0 (1.50-2.55)
MTP Plantar flexion	NS	NS	1.0 (0.94-1.01)
MTP Dorsal flexion	NS	NS	1.0 (0.98-1.10)
Strong Tibiales anterior Weak Tibiales anterior	NS	 NS	1.0 1.3 (0.39-4.07)
Strong Flexor hallucis Weak Flexor hallucis	0.037	 0.04	1.0 3.2 (1.08-9.37)

The results from the multivariate logistic regression analysis revealed that the DPN-group have a higher risk for having poor balance (OR 1.4, 95% CI 1.1-1.6), reduced protective sensation (OR 2.0, 95% CI 1.5-2.6) and Flexor hallusis weakness (OR 3.2, 95% CI 1.1-9.4) even after controlling for potential confounding factors included in the model (Table 3).

Discussion

The monofilament test has been used frequently to detect loss of protective sensation and to assess the foot ulcer risk status. We assessed the cutaneous pressure perception by means of the Semmer-Weinstein 5.07 g monofilament. We found that the DPN group had significant diminished cutaneous pressure perception for the entire protective sensation test even after adjusting for age. We found the fifth MTP test site to be the most important test site. This is in agreement with Miranda-Palma et al. who reported that the 5th MTP test site had the highest sensitivity compared to the hallux, 1st MTP and 3rd MTP test sites(21).

Loss of plantar cutaneous pressure perception contributes to lack of afferent information from the somatosensory system(22), which in addition to information from the visual and vestibular system, controls the balance. We were not able to assess the DPN and retinopathy patients separately. However, large studies have reported that postural control is affected in DPN patient even with proper vision(22-24). We used easily arranged and inexpensive clinical tests to measure the balance, and found that the DPN group performed significantly worse compared to the non-DPN group, on all four parts of the balance test. The results remained statistically significant after controlling for age, protective sensation and other potential confounding factors (Table 3). Our findings is in agreement with others showing that DPN patients perform worse on a one-leg static balance test, compared to controls(4;5;25). We found that the difference between the groups for the one-leg standing test was most statistically significant for the right compared to the left one-leg standing test. We did not ask the patients to identify their dominant and non-dominant leg. It is highly unlikely that this may have influenced the results, but may have induced an analytic bias. However, the finding is interesting seen together with Cimbiz et al., who reported the right leg to be the dominant in the majority of his subjects, and further that the maximal balance reduction in the DPN group was found on the dominant leg(5).

We did not assess the plantar foot pressure, but studies using plantar pressure analysers have reported that DPN patients have elevated foot pressure in addition to reduced ankle and 1st MTP joint ROM(3;26). The determination of the 1st MTP joint ROM has been identified as a fairly exact test to identify a foot with elevated plantar pressure, and hence being a foot at risk for developing foot ulcers(3). Like Zimney et al. we found a statistically significant difference in the 1st MTP joint ROM between the groups, but this difference was lost when we

controlled for age, strength, balance and sensibility. Like others we can not report any statistical significant difference between the groups for the ankle plantar and dorsal flexion ROM measured with a goniometry(27).

The ability to stand on heels and toes are effortless tests that do not require any technical equipment, which makes them suitable for population based surveys(28). We found that the inability to stand on heels, as a measure of the Tibialis anterior strength, was statistically significant worse in the DPN-group compared to the non-DPN-group. This is in agreement with previous reports suggesting that more severe impairment is found in the ankle extensors (Tibiales anterior) compared to the flexors (Gastrocnemius)(29). However, the findings in the literature are conflicting. Andersen et al. found similar degrees of weakness and atrophy of the ankle extensors and flexors, and has suggested that the functional differences between the ankle extensors and flexors is not caused by selective weakness or atrophy of the ankle extensors, but is a consequence of the biomechanical properties of the ankle joint in combination with a higher capacity of the ankle flexors(30).

Atrophy of the foot muscles has been said to be closely related to the severity of neuropathy(29), and occur prior to the clinically detectable initiation of DPN(31). We found that the DPN-group was statistically significant weaker in the Flexor Hallucis muscle (innervated by the Tibial nerve), but not in the Extensor Hallucis muscle (innervated by the deep Peroneal nerve) compared to the non-DPN-group. This finding remained after controlling for confounding factors, and is in agreement with van Schie et al., who reported that the Tibial innervated muscles were weaker compared to the Peroneal innervated muscles in DPN subjects(32).

In summary, the DPN subjects preformed poorer on all the tests, especially for the protective sensation and the balance test. The DPN patients may therefore be at an increased risk of falling and more likely to develop secondary disabilities such as fractures, ulcers and amputations. The inexpensive and feasible tests presented here may be applied in health care services in developing countries to identify diabetic patients at high risk for developing foot-complications. These patients should be identified in time and receive education and improved care in order to diminish the risk of impairments and disabilities, and thereby reduce the burden and cost for both to the individual family as well as to the society at large.

Acknowledgements

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Duality of interest The authors declare that there is no duality of interest for this study.

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9. APPENDICES

9.1. Appendix 1 – Questionnaire and Evaluation form

ID number: .....
Registration no: …….
Name of the patient: .....
Phone number: .....
Date of interview: .....
Interview taken by: .....

Medical record book:
Weigh .....kg Date: .....
Fasting glucose
Previous level: ..... Date: …….
Current level: ……..... Date: ……
Blood Lipid profile Date: .....
S.Cholesterol: .....
S.TG: .....
S.HDL: .....
S.LDL: .....
Urine test Date: .....
Albumin level: .....
Acetone level: .....
Urine sugar: .....

Demographic characteristics:
Age .....years
Gender:
- o Female
- o Male

Education .....years
What is your occupation?
1. Student
2. House wife
3. Manual work
4. Office work
5. Business
6. Unemployed
7. Retired

What is the household's monthly income? .....Tk.
What is your monthly income? .....Tk.

How is your living situation?

- Alone
- With family
    - Number of family members ……

How is your housing condition?
- Pipe water
- Electricity

Patient history:
For how long have you had diabetes? .....years

What kind of diabetes treatment do you use?
- Diet
- Insulin
- Tablets
- Non

Do you have other family members with known diabetes?
- Father
- Mother
- Brother
- Sister
- Wife/Husband
- Other
- Non

Do you have impaired renal function?
- Yes
- No
- Don't know

Do you have impaired vision?
- Yes
    - Wear glasses
    - No glasses
- No
- Don't know

Have you had any previous foot ulcer?
- Yes
    - Left
    - Right
    - Don't remember
- No
- Don't know

Have you got any lower limb amputation?
- Yes
    - Left

    - Right
- No

Life style and food consumption:

What is you smoking history?

- Never smoked
- Ex-smoker
- Current smoker
    - Occasionally
    - Daily <10
    - Daily 10-20
    - Daily >20

How much vegetable do you eat?

- <3 per day
- 3-7 per day
- >7 per day

How much wheat /rice/ maize (bread, cereal, chapatti) do you eat?

- <3 unit per day
- 3-7 unit per day
- >7 unit per day

How much fish do you eat?

- None or once a week
- <3 times per week
- >3 times per week

How much chicken do you eat?

- None or once a week
- <3 times per week
- >3 times per week

How much beef do you eat?

- None or once a week
- <3 times per week
- >3 times per week

How physical active (walk/ run/ bike/ play cricket/work out) are you?

- <30 minutes per day
- 30-60 minutes per day
- 1-2 hours per day
- 2-4 hours per day
- > 4 hours per day
- Never

Have you difficulty in walking long distances (more than one kilometre)?

- no
- moderate

- cannot do

Have you difficulty in standing for long periods (thirty minutes)?
- no
- moderate
- cannot do

Foot care awareness

How often you wash you feet?
- Every week
- Every day
- Several times a day

Have you got a washing assistance?
- Yes
- No

How often you inspect you feet?
- Every day
- Every week
- Every month

What kind of shoe do you wear most?
- Trainers, "Slip-ons", casual shoes
- Slippers, open toe shoes
- No shoes (barefoot)

Neuropathy symptom score

Do you experience any pain/discomfort in you lower extremity? What kind? (Tick one)

2	Yes, a burning/numbness/tingling feeling	
1	Yes, a fatigue/ cramping /aching feeling	
0	No	

Where are the feelings present? (Tick one)

2	In your feet?	
1	In your calves?	
0	Elsewhere?	

Do you experience any exacerbation of the feelings at night?

2	Yes, symptoms exacerbate at night	
1	No, Symptoms present day and night	
0	No, Symptoms present at daytime only	

Do the feelings wake you up from sleep?

1	Yes	
0	No	

Does any manoeuvre reduce the feelings? (Tick one)

2	Yes, walking	

1	Yes, standing	
0	Yes, sitting/lying	
0	Non	

Total score _____

_____*Symptoms*

Maximum abnormal score is 9
Mild symptoms 3-4, moderate symptoms 5-6, severe symptoms 7-9

Biochemical Examination:

HbA_{1c} .....
Random Glucose level .....
Lipid profile .....
S.Cholesterol .....
S.TG .....
S.HDL .....
S.LDL .....

Albumin creatinine ratio .....
Acetone level .....
Urine sugar .....

Clinical examination:

BP ……

Anthropometrics parameters:

Weight .....
Height ……
BMI ……
West heap ratio ……

Deformity assessment

Each deformity score 1 when present and 0 when absent, on either foot.

Deformity	Left	Right
Hammer or claw toes (PIP in flexion, DIP and MTP in extension)		
Hallux valgus (Prominence 1st metatarsal head, first toe is inclined latteraly)		
Charcot arthropathy (Increased ROM, new bone formation, increased fluid)		
Pes cavus (high arch, the heel is in varus position. Often there is claw toes.)		
Pes plantus (collapsed arch, medial boarder almost touches the ground)		

Total score (max score is 10 points) _____

Muscle strength evaluation

Gastrocnemius (plantar flexion with the knee extended)

Grade	Performance	Left	Right
0	Supine, No contraction is palpable		
1	Supine, Contraction is palpable, no joint motion		
2	Side lying (gravity minimized), moves through a small plantar flexion motion		
3	Prone (against gravity), moves into plantar flexion and holds the test position		
4	Stand on one leg with the knee extended, plantar flexion ending on tiptoe (light resistance)		
5	Stand on one leg with the knee extended, plantar flexion ending on tiptoe, 5 repetitions (maximal resistance)		

Total score (max score is 10 points) _____

*Tibialis anterior (*dorsal flexion and inversion of the foot)

Grade	Performance	Left	Right
0	Prone, No contraction is palpable		
1	Prone, Contraction is palpable, no joint motion		
2	Side lying, moves through a small dorsal flexion and inversion motion with gravity minimized		
3	Sitting, moves into dorsal flexion and inversion, and holds the test position against gravity		
4	Stands on heels, holds dorsal flexion and inversion position (light resistance)		
5	Stands on heels, holds dorsal flexion and inversion position while taking 5 steps (maximal resistance)		

Total score (max score is 10 points) _____

Flexor hallucis brevis and longus (Plantar flexion of the 1st MTP and IP joints, additional to plantar flexion and inversion of the foot.)

Grade	Performance	Left	Right
0	Sitting, no contraction is palpable		
1	Sitting, contraction is palpable, no joint motion		
2	Sitting, moves through a small plantar flexion motion of the 1st toe with gravity minimized		
3	Supine, moves into plantar flexion of the 1st toe and holds the test position against gravity		
4	Supine, moves into plantar flexion of the 1st toe and holds the test		

	position against light resistance. Resistance is applied beneath the proximal and distal phalanx of the great toe.		
5	Supine, holds the 1st toe in resting position against maximal resistance, tested statically. Resistance is applied beneath the proximal and distal phalanx of the great toe.		

Total score (max score is 10 points) _____

Extensor hallucis brevis and longus (Extension (dorsal flexion) of the 1st MTP and IP joints, additional to dorsal flexion of the foot)

Grade	Performance	Left	Right
0	No contraction is palpable		
1	Contraction is palpable, no joint motion		
2	Supine, moves through a small extension motion of the 1st toe with gravity minimized		
3	Sitting, moves into extension of the 1st toe and holds a test position against gravity		
4	Sitting/supine, moves into extension of the 1st toe and holds test position against light resistance. Resistance is applied to the dorsum of the proximal and distal phalanx of the great toe		
5	Sitting/supine holds the 1st toe in resting position against maximal resistance, tested statically. Resistance is applied to the dorsum of the proximal and distal phalanx of the great toe		

Total score (max score is 10 points) _____

Reflex evaluation

Patellar tendon reflex

		Left	Right
Absent	2		
Present with reinforcement	1		
Normal: jerk into the knee extension	0		

Total score (max score is 4 points) _____

Neuropathy disability score

Ankle reflex (tendon hammer)

Grade	Performance	Left score	Right score
2	Absent		
1	Present with reinforcement		
0	Normal		

Vibration (128 HZ turning fork at hallux)

	Right foot: Wrong (W) or Correct (C)	Left foot: Wrong (W) or Correct (C)
1st		
2nd		
3rd		

Grade	Performance	Left score	Right score
1	Reduced/absent: 1 of 3 correct answers		
0	Present: 2 of 3 correct answers		

Pin prick (pencil and cotton wool, dorsum of foot)

Grade	Performance	Left score	Right score
1	Reduced/absent: incorrect answers		
0	Present: correct answers		

Temperature (warm/cold sponge, plantar side)

Grade	Performance	Left score	Right score
1	Reduced/absent: incorrect answers		
0	Present: correct answers		

Total score _____

_____*Sign*

Points per side, thus the maximum abnormal score is 10
Mild sign 3-4, moderate sign 5-6, severe sign 7-9

Monofilament test *(Cutanus pressure perception/Sensitivity)*
Repeat the application twice at the same site with at least one "false" application, in which no filament is applied. Protective sensation is present if the patient has 2 of 3 correct answers per site. Protective sensation scores 0, absent protective sensation scores 1.

Left foot – plantar site, Wrong (W) or Correct (C)

Application	Heel :	1^{st} metatarsal head	5^{th} metatarsal head
1^{st}			
2nd			
3rd			
Total correct answers			
Protective sensation	YES=0 NO=1	YES=0 NO=1	YES=0 NO=1

Right foot – plantar site, Wrong (W) or Correct (C)

Application	Heel :	1^{st} metatarsal head	5^{th} metatarsal head
1^{st}			
2nd			
3rd			
Total correct answers			
Protective sensation	YES=0 NO=1	YES=0 NO=1	YES=0 NO=1

Refill time
Capillary nail refill time of great toe

Point	Refill time	Left	Right
2	>5 seconds		
1	2-5 seconds		
0	< 2 seconds		

Total score (max score is 4 points) _____

Pedal Pulse
Each pulse score 0 when present and 1 when absent, on either foot.

	Left	Right
Posterior tibial		
Dorsalis pedis		

Total score (max score is 4 points) _____

Ulcer assessment
Modified Meggit-Wagner Ulcer Classification

Points	ulcer	Left	Right
0	No		
1	superficial ulcer		
2	full-thickness ulcer		

Total score (max score is 4) _____

Range of motion evaluation
Ankle joint: Dorsal flexion (dorsal surface moves in cranial direction)

Points	Range of motion	Left	Right
2	Absent: +10-0 degrees		
1	Reduced: 0-10 degrees		
0	Normal: 10-20 degrees		

Total Score (max score is 4 points) _____

Ankle joint: Plantar flexion plantar surface moves in caudal direction (0-45)

Points		Left	Right
2	Absent: +10-0 degrees		
1	Reduced: 0-20 degrees		
0	Normal: 20-45 degrees		

Total Score (max score is 4 points) _____

1st toe MTP Extension (dorsal flexion)

Points	Range of motion	Left	Right
2	Absent +10-0		
1	Reduced 0-20		
0	Normal 20-45		

Total Score (max score is 4 points) _____

1st toe: MTP Flexion (plantar flexion)

Points	Range of motion	Left	Right
2	Absent: +10-0 degrees		
1	Reduced: 0-20 degrees		
0	Normal: 20-45 degrees		

Total Score (max score is 4 points) _____

Modified Index of Muscle Function - IMF *Balance and coordination*
IMF is a function test for the lower extremity. There are 13 parts, if the patient can not perform the two first once, the test will be stopped. The test is preformed without shoes, if not it must be stated.

	Points	Left w/comments	Right w/comments
Balance and coordination			

One leg standing with eyes open for 30 seconds	0 = ≥ 30 sec 1 = 15 – 29 sec 2 = 0 – 14 sec		
Narrow two leg standing with the eyes closed for 30 seconds	0 = 0 = ≥ 30 sec 1 = 15 – 29 sec 2 = 0 – 14 sec		
Walk forward on a 2 meter line with eyes open	0 = no problems 1 = with problems 2 = do not manage		
(0-8p) Sum			

9.2. Appendix 2 – Informed Consent Statement

The researcher is Kjersti Mørkrid from the University of Oslo. The title of the study is: *"The prevalence of and risk factors for diabetic peripheral neuropathy, additional to the level of functioning among Bangladeshi diabetic out patient diagnosed five to ten years ago"*

You may refuse to say yes and not participate in this study. You should be aware that even if you agree to participate, you are free to withdraw at any time. If you do withdraw from this study, it will not affect your relationship with this unit or the services it may provide to you in the future.

The purpose of this study is to describe the extent of and risk factors for developing foot problems related to diabetes, and to describing the level of functioning relating to everyday life activities such as walking and bending.

You will be asked to make you medical record available for the researcher. An interpreter will ask you questions regarding your demographics, medical history and lifestyle. Your feet will examined by the researcher, and you will be asked to do activities related to every day life. The examination will take approximately one hour. A few patients might feel some discomfort during the examination, but there is no anticipated risk in participating in the research. The benefit is that you will get a thorough examination of you feet. The research findings might be used in order to prevent diabetic foot complications. You will not be paid, but refreshments are available during the examination.

The researcher will use a study number, so your name will not be associated in any way with the information collected about you or with the research findings from this study. The researcher will not share information about you unless required by law or you give written permission. By saying yes to participate in the research you give permission for the use and disclosure of your information for purposes of this study. You may withdraw your consent to participate in this study at any time. You have the right to cancel your permission at any time, by sending your written request to: Kjersti Mørkrid, Gjøvikgt 1b, 0470 OSLO, NORWAY.

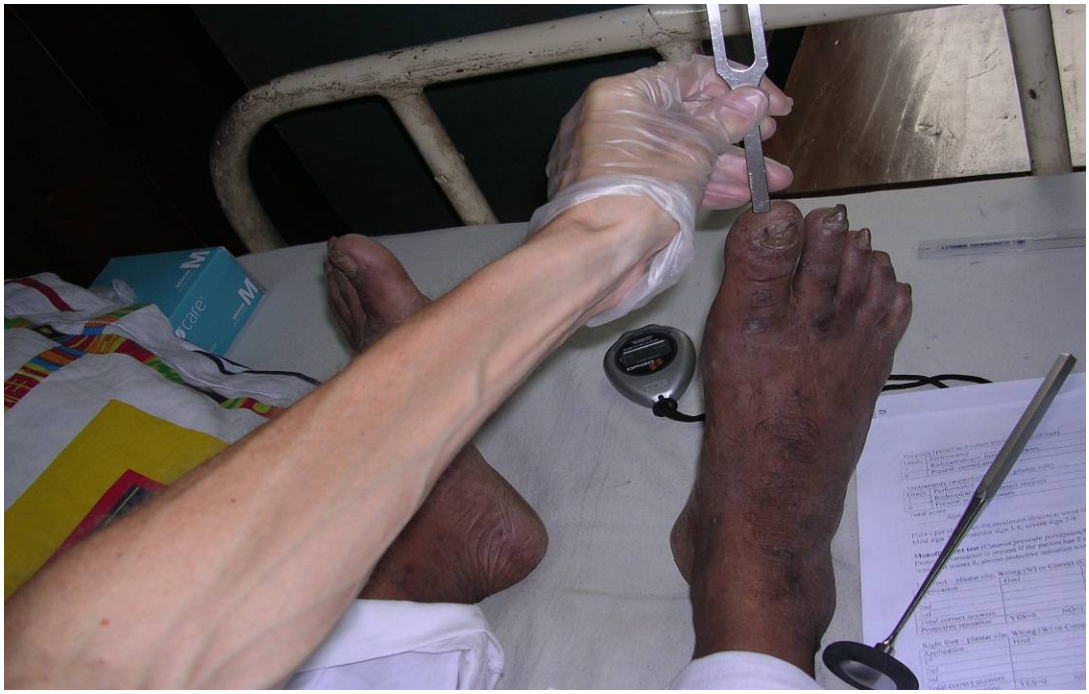
I have had the opportunity to ask, and I have received answers to, any questions I had regarding the research. If I have any additional questions about my rights as a research participant, I may cal (?) or write an e-mail (kjersti.morkrid@studmed.uio.no) to the researcher. By saying yes I affirm to participate in the research.

9.3. Appendix 3 – Pictures from the fieldwork

Picture one: The examination room

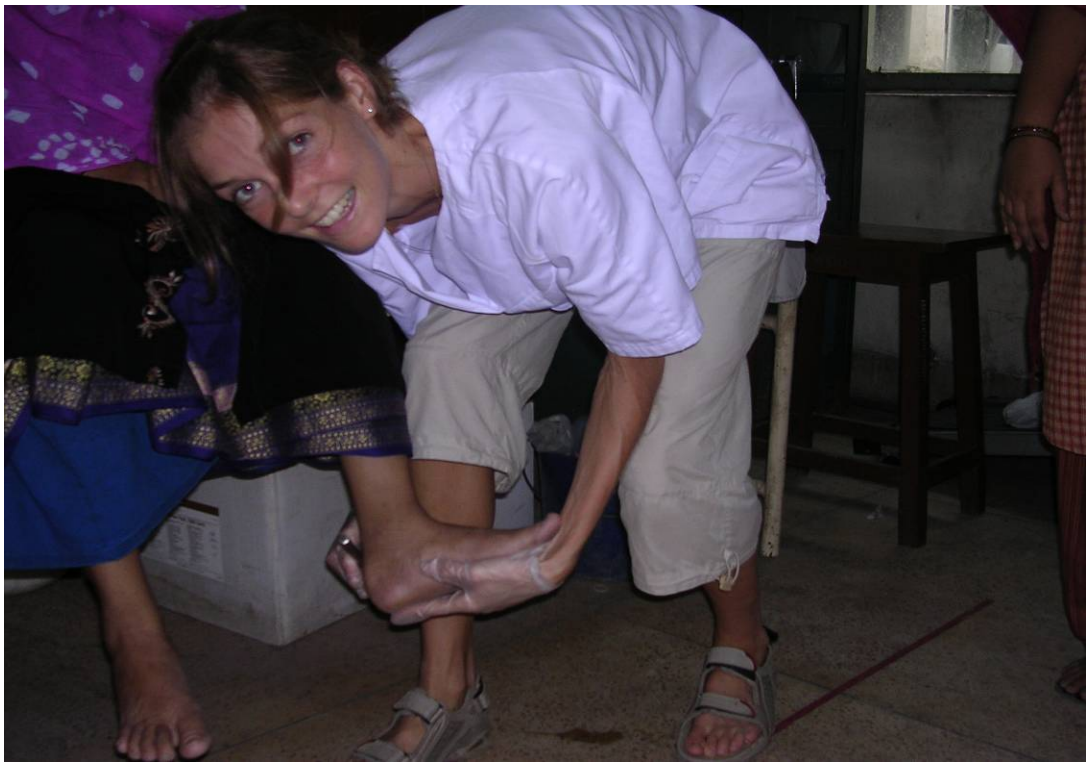
Picture two: Shuana Sultana interviewing the patient

Picture three: Ferdous Ara (Urme) explaining the tests to the patient



Picture four: The vibration perception test (tuning fork)

Picture five: The cutaneous pressure perception test (10.0g monofilament)


Picture six: The Achilles tendon reflex (Babinski hammer)

Picture seven: The one-leg standing test

Picture eight: Ferdous Ara (Urme) marking the Eppendorf tubes