CARDIOVASCULAR RISK FACTORS AND DIABETIC FOOT SYNDROME IN SOUTH INDIAN DIABETIC POPULATION

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The diabetic foot syndrome is one of the most frequent reasons for hospitalization among the diabetic population and also one of the most common cause for lower-limb amputation. Apart from the obvious associated morbidity, patients with diabetic foot have an increased risk of death from cardiovascular diseases. Correction of glycaemia, serum lipids and blood pressure lead to a regress in progression of diabetes complications. In this article, the influence of cardiovascular risk factors on occurrence and progression of the diabetic foot syndrome in the Indian diabetic population during a 1-year follow up was analyzed.

Key words: diabetic foot, cardiovascular risk, peripheral neuropathy, retinopathy, age, smoking.

The number of people with diabetes worldwide was estimated at 131 million in 2000; it is projected to increase to 66 million by 2030 [1]. Previous studies have indicated that diabetic patients have up to a 25% lifetime risk of developing a foot ulcer [2]. The annual incidence of diabetic foot ulcers is ~3%, and the reported incidence in U.S. and U.K. studies ranges as high as 10% [3]. Once an ulcer has developed, there is an increased risk of wound progression that may ultimately lead to amputation; diabetic ulceration has been shown to precede amputation in up to 85% of cases [3]. Peripheral neuropathy and peripheral vascular disease are main underlying conditions in the development of diabetic foot syndrome. Apart from tight glycemic control, no other evidence-based treatment is known to ameliorate and prevent diabetic foot. So, identifying potentially modifiable risk factors for diabetic foot syndrome is crucial. Cardiovascular risk reduction has over the last 10 years become major part of type 2 diabetes care. The purpose of this paper is to determine the role of cardiovascular risk factors in diabetic foot ulcers development.

Materials and Methods

The study was conducted in Dialife Diabetic Centre, Manjeri, Kerala, South India in 2007—2009. All type 2 diabetic patients who came to the centre in study period were enrolled. The baseline examination included 1893 patients (1139 men and 754 women; mean [±SD] age 51 ± 10 years; mean duration of diabetes 9.9 ± 5.9 years). Written informed consent was obtained from all patients. Information about sociodemographic background variables, course of diabetes, its treatment and complications, neuropathic symptoms, foot problems, claudication, cardiovascular diseases and diet modification was collected from patients by means of a structured interview. Pin-prick testing at the hallux, Semmes-Weinstein monofilament testing at the plantar surface of the foot, 128 Hz tuning fork and Achilles tendon reflex testing were assessed to diagnose diabetic neuropathy [4]. Assessment of the ankle-brachial pressure index (ABI) by Doppler ultrasonography was used for presence or absence of ischemia. A foot ulcer was defined as a full-thickness skin break at least to Wagner stage 1, occurring distal to the malleoli.

Baseline measurements included fasting and 2-hour postprandial blood glucose, HbA1c, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Levels of low-density lipoprotein (LDL) cholesterol were calculated as well as glomerular filtration rate (by Cockroft-Gault and MDRD formulas). The urinary albumin excretion rate was measured from a single 24-hour urine collection. A urinary albumin excretion rate of 20 to 200 μg per minute was defined as microalbuminuria; a rate greater than 200 μg per minute was defined as macroalbuminuria. The presence and severity of diabetic retinopathy were assessed from retinal photographs (two fields per eye) obtained with a wide-angle camera and scored centrally by one expert in reading changes of retinopathy.

Cardiovascular disease was defined as either a history of physician-diagnosed cardiovascular disease (e.g., previous myocardial infarction, angina, coronary-artery bypass grafting, or stroke) or ischemic changes detected on a 12-lead electrocardiogram. Systolic and diastolic blood pressure, body mass index, waist circumference were evaluated. Physical activity classified as low if it takes less than 1 hour per week.

After 1-year of follow up all patients were interrogated about progression or new onset of diabetic foot ulcers by phone.

The statistical analysis was performed with Statistica (version 8.0). The characteristics of patients were compared with the use of Student's t-test or the Mann—Whitney U test where appropriate. The possibility of a threshold effect in the relation between glycosylated hemoglobin values and the risk of diabetic foot ulcers was evaluated by comparing the linear and exponential trend lines according to quintiles of glycosylated hemoglobin. The relation between risk factors and the incidence of foot ulcers was analyzed with the use of logistic-regression models. All logistic-regression models were adjusted for the duration of diabetes and glycosylated hemoglobin values. Statistically significant level was determined at $p < 0,05$.

Results

Baseline data of the 1893 diabetic patients compares in Table 1. Diabetic foot ulcers were diagnosed in 14.8% cases. Those in whom foot ulcers were revealed were older with longer diabetes history, had higher baseline postprandial glucose and glycosylated hemoglobin level, more often were smokers, had higher prevalence of cardiovascular disease and diabetes complications.

After 1-year follow up 120 patients (7.4%) were missing to re-evaluation, 37 patients (2.2%) were died. New onset of diabetic foot ulcer had 41 patients, 55 patients had progression to the higher grade of the diabetic foot by Wagner classification. All patients were divided into two groups according to whether diabetic foot did or did not progress during 1 year follow up. Patients with new onset and progression of diabetic foot ulcers were combined into the same group. Baseline characteristics of this groups presented in Table 2. Patients in whom ulcers advanced were on average 4.1 years older, had diabetes for 3.1 years longer, and had poorer blood glucose control (a glycosylated hemoglobin value 0.5 percent higher) at baseline than those in whom ulcers did not progressed.

Table 1

Baseline characteristics of the study population according to presence of diabetic foot ulcers at the study start

Parameters	With diabetic foot ulcers (n = 281)	Without diabetic foot ulcers (n = 1612)	p value
Age, years	56.1 ± 10.2	50.4 ± 10.4	< 0.001
Male, %	33.2	32.7	ns
BMI, kg/m^2	23.9 ± 3.6	29.3 ± 1.1	ns
Waist circumference, cm	91.7 ± 9.1	90.6 ± 10.1	ns
History of smoking, %	45.2	23.1	0.004
Duration of type 2 diabetes, years	11.1 ± 7.0	6.9 ± 5.7	< 0.001
Fasting blood glucose, mg/dl	155 ± 48	152 ± 48	ns
2 hour postprandial blood glucose, mg/dl	243 ± 67	232 ± 71	0.018
HbA1c, %	7.9 ± 1.7	7.0 ± 1.5	< 0.001
History of cardiovascular disease, %	45.9	27.3	< 0.01
Systolic blood pressure, mm Hg	137.1 ± 22.1	132.6 ± 19.1	< 0.01
Diastolic blood pressure, mm Hg	81.2 ± 11.8	81.9 ± 9.9	ns
Arterial hypertension, %	86.8	74.7	< 0.01
Total cholesterol, mg/dl	198 ± 37	195 ± 37	ns
Low density lipoprotein cholesterol, mg/dl	123 ± 32	122 ± 59	ns
High density lipoprotein cholesterol, mg/dl	44 ± 10	44 ± 9	ns
Triglycerides, mg/dl	158 ± 56	150 ± 51	0.049
Glomerular filtration rate by MDRD, ml/min/1,73m^2	76.2 ± 19.9	82.5 ± 21.2	< 0.001
Albumin excretion rate, μg/min	9.9 (4.3; 353.1)	9.4 (4.3; 146.1)	ns
Microalbuminuria or macroalbuminuria, %	59.5	35.7	< 0.001
Ankles-brachial index	1.0 ± 0.19	0.99 ± 0.08	ns
Any retinopathy, %	49.2	31.8	< 0.001

Table 2

Baseline characteristics of the study population according to incidence of diabetic foot ulcers after 1 year follow up

Parameters	No diabetic foot progression (n = 1640)	Diabetic foot progression (n = 96)	p value
Age, years	50.3 ± 10.9	54.4 ± 12.1	0.02
Male, %	51.2	59.5	ns
BMI, kg/m^2	23.9 ± 3.8	23.0 ± 3.7	ns
Waist circumference, cm	90.7 ± 10.2	88.6 ± 9.4	ns
History of smoking, %	17.9	58.5	< 0.001
Duration of type 2 diabetes, years	6.9 ± 5.7	10.0 ± 5.5	< 0.01
Fasting blood glucose, mg/dl	152 ± 48	149 ± 56	ns
2 hour postprandial blood glucose, mg/dl	232 ± 71	225 ± 70	ns
HbA1c,%	7.0 ± 1.5	7.5 ± 1.3	< 0.001
History of cardiovascular disease, %	33.9	59.4	< 0.001
Systolic blood pressure, mm Hg	132.6 ± 19.2	135.5 ± 19.7	ns
Diastolic blood pressure, mm Hg	81.9 ± 9.9	85.6 ± 10.8	0.018
Arterial hypertension, %	78.2	96.5	< 0.001
Total cholesterol, mg/dl	195 ± 37	203 ± 42	ns
Low density lipoprotein cholesterol, mg/dl	122 ± 59	138 ± 33	< 0.01
High density lipoprotein cholesterol, mg/dl	44 ± 9	42 ± 7	ns
Triglycerides, mg/dl	150 ± 51	148 ± 28	ns
Glomerular filtration rate by MDRD, ml/min/1,73 m^2	82.6 ± 21.3	82.2 ± 19.9	ns
Albumin excretion rate, μg/min	9.3 (6.1; 347.2)	10.0 (5.2; 354.4)	0.03
Microalbuminuria or macroalbuminuria, %	41.2	65.5	< 0.001
Ankles-brachial index	0.97 ± 0.09	0.91 ± 0.26	0.004
Any retinopathy, %	48.5	51.4	ns

In unadjusted comparisons, patients in whom foot ulcers advanced also had higher baseline level of low density lipoprotein (LDL) cholesterol and albumin excretion rate and a lower ABI. More patients in whom ulcers progressed had baseline hypertension, microalbuminuria or macroalbuminuria, a history of cardiovascular disease, and a history of smoking.

Adjustment for possible confounding by the two major known determinants of diabetic foot — duration of diabetes and glycosylated hemoglobin value — attenuated or abolished some associations with diabetic foot progression (Table 3). The risk factors that remained significantly associated with the development of foot ulcers were baseline cardiovascular risk factors (ABI, levels of LDL cholesterol and triglycerides). The urinary albumin excretion rate at baseline was also elevated in patients in whom ulcers progressed.

Table 3

Risk factors for diabetic foot progression after adjustment for glycosylated hemoglobin value and duration of diabetes

Variable	Odds Ratio (95% CI)	*p* value
Waist circumference, cm	1.35 (1.16—1.62)	0.04
History of smoking, %	1.56 (1.18—2.05)	< 0.001
History of cardiovascular disease, %	2.75 (1.71—4.52)	< 0.001
Arterial hypertension, %	1.98 (1.20—2.73)	< 0.001
Low density lipoprotein cholesterol, mg/dl	1.23 (1.04—1.52)	0.01
Triglycerides, mg/dl	1.38 (1.17—1.59)	0.01
Albumin excretion rate, μg/min	1.37 (1.11—1.54)	0.001
Microalbuminuria or macroalbuminuria, %	1.46 (1.08—2.10)	0.02
Ankles-brachial index	1.49 (1.22—1.61)	< 0.001
Any retinopathy, %	1.8 (1.23—2.31)	0.001

After adjustment for glycosylated hemoglobin value and duration of diabetes, we found that the presence of hypertension, albuminuria (either microalbuminuria or macroalbuminuria), any retinopathy, history of cardiovascular disease, and history of smoking at baseline were significantly associated with newly diagnosed and progressed diabetic foot ulcers. Both former and current smoking at baseline were significantly related to foot ulcers when included separately, with adjustment for glycosylated hemoglobin values and duration of diabetes. Since both smoking groups had similar risk, they are presented jointly.

Discussion

In the South Indian type 2 diabetic patients cohort 14.8% had a foot ulcer. Compared with other studies based on known diabetes, the proportion with history of foot ulcer in our study is high [4, 5]. The lower rates of foot ulcer history identified in previous population-based studies may be due to the fact that these studies were conducted in different healthcare settings and may not have been representative of the general diabetic patient population.

In this population-based study during a period of one year, the incidence of new onset of diabetic foot ulcers was 2.5%, whereas progression of existing ulcers were observed in 19,6%, confirming strong contributions of glycemic control and duration of diabetes to the risk of diabetic foot ulcers [6]. We observed that cardiovascular risk factors, such as hypertension, smoking, abdominal obesity, and elevated triglyceride levels, and

the presence of cardiovascular disease at baseline appear to be related to newly diagnosed or progression of diabetic foot ulcers. Association between the risk factors and increased diabetes-related morbidity and mortality were reported early [7]. Patients who died during follow-up had more retinopathy (42 vs 16%, $p = 0.002$), neuropathy (57 vs 23%, $p < 0.001$), microalbuminuria (45 vs 6%, $p < 0.0001$), coronary heart disease (50 vs 13%, $p < 0.0001$), and peripheral vascular disease (27 vs 9%, $p = 0.005$) at baseline than patients who survived. In a multiple logistic regression analysis macroangiopathy ($p = 0.004$), neuropathy ($p = 0.007$), HbA1c ($p = 0.018$) and albumin excretion rate ($p = 0.016$) were independent risk factors for death. Mortality in patients with neuropathy is high, and the cause of death is often coronary heart disease [7]. Previous cross-sectional studies have reported associations between diabetic neuropathy and height [8], cigarette smoking [9], low levels of HDL cholesterol [10], and hypertension [10], in addition to established risk factors, level of glycemia, and duration of diabetes. A follow-up of subjects with either type 1 or type 2 diabetes suggested that both type 1 and type 2 diabetes and markers of microvascular disease were associated with the severity of neuropathy [11].

The baseline cross-sectional data in the present study are evidence of a strong association between foot ulcer progression and other microvascular complications, suggesting a common pathogenic mechanism. We found that macrovascular complications of diabetes relate significantly to a history of foot ulcer. This is strongly supported by the recent American Diabetes Association statement on preventive foot care in diabetes [12]. Macrovascular complications probably reflect disease severity. In busy clinical practices, with limited time available during practitioner-patient encounters, macrovascular complications probably receive primary focus, and the state of the feet may easily be overlooked. However, the presence of macrovascular complications should indicate careful foot inspection.

Apart from the use of medication to induce glucose values approaching normoglycemia, no other treatments currently exist to reduce the progression to neuropathy. Aggressive treatment of hypertension is now standard clinical practice in the management of nephropathy and retinopathy [13], and the results of the present study make a case for clinical trials to confirm the efficacy of antihypertensive agents and possibly other strategies for cardiovascular risk reduction in slowing the progression of diabetic foot.

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СЕРДЕЧНО-СОСУДИСТЫЕ ФАКТОРЫ РИСКА И СИНДРОМ ДИАБЕТИЧЕСКОЙ СТОПЫ У ЖИТЕЛЕЙ ЮЖНОЙ ИНДИИ, СТРАДАЮЩИХ САХАРНЫМ ДИАБЕТОМ

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Синдром диабетической стопы — одна из наиболее частых причин госпитализации и ампутации нижних конечностей у больных, страдающих сахарным диабетом. Пациенты с синдромом диабетической стопы, кроме наличия у них сопутствующей патологии, относятся к группе высокого риска смерти от сердечно-сосудистых заболеваний. Коррекция уровня глюкозы, липидов в крови и артериального давления приводит к снижению частоты диабетических осложнений. В статье проанализировано влияние сердечно-сосудистых факторов риска на возникновение и развитие синдрома диабетической стопы у индийского населения в течение одного года наблюдения.

Ключевые слова: диабетическая стопа, сердечно-сосудистый риск, периферическая полинейропатия, ретинопатия, возраст, курение.