Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1287–1292

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Association of diabetic foot ulcers with chronic vascular diabetic complications in patients with type 2 diabetes

Magdy H. Megallaa, Azza A. Ismail, Mohammed H. Zeitoun, Mai S. Khalifa*

Unit of Diabetes and Metabolism, Department of Internal Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt

ARTICLE INFO

Article history:
Received 13 January 2019
Accepted 23 January 2019

Keywords:
Type 2 diabetes
Diabetic foot ulcer
Vascular complications.

ABSTRACT

Context: Diabetes mellitus is a common disease which is prevalent globally, presenting with chronic complications and constitutes a major risk to the patient. Diabetic foot ulcers are the single biggest risk factor for non-traumatic lower limb amputations in persons with diabetes. We aimed to screen for the chronic vascular diabetic complications in patients with diabetic foot ulcers (DFUs) and to assess the association of diabetic foot ulcers with these complications in the study group.

Subjects and methods: This cross-sectional study included 180 type 2 diabetic patients (aged 30–70 years) with diabetic foot ulcers who attended the Outpatient Clinic of Diabetes in Alexandria Main University Hospital. Full diabetic foot examination was done to all study subjects. DFUs were assessed using University of Texas Diabetic Wound Classification System. HbA1c, LDL-C, serum creatinine, and urinary albumin creatinine ratio (ACR) were measured for all study subjects. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation. Fundus examination was done for all study subjects.

Results: The prevalence of diabetic kidney disease (DKD) and diabetic retinopathy (DR) was 86.1% and 90% respectively among the study group. 86.7% of patients had neuropathic DFUs, 11.1% of them had ischemic DFUs and 2.2% had neuro-ischemic DFUs. Regarding diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) as risk factors for developing DFU, the prevalence of both of them respectively was 82% and 20% among the study group. There was statistically significant association between both DKD, DR and peripheral neuropathy. There was also statistically significant association between both DKD, DR and peripheral arterial disease (PAD).

Conclusion: Chronic vascular diabetic complications are common among type 2 diabetic patients with diabetic foot ulcers. There is statistically significant association between these complications and diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD).

1. Introduction

The onset of type 2 diabetes mellitus (T2DM) is often insidious and silent. The asymptomatic phase of hyperglycemia accounts for the relatively high prevalence of complications at initial presentation [1]. The chronic hyperglycemia in diabetes mellitus (DM) is associated with long-term damage, dysfunction and failure of various organs including the eyes, kidneys, nerves, heart, and blood vessels [2].

A large part of the burden of disease, as well as health care costs, are related to the development of chronic complications of diabetes [3]. The resulting complications are grouped under microvascular disease and macrovascular disease. Microvascular complications include retinopathy, nephropathy and neuropathy [4]. The major macrovascular complications include accelerated cardiovascular disease resulting in myocardial infarction, cerebrovascular disease manifesting as strokes and peripheral arterial disease [4].

Diabetic foot is one of the most serious, costly, and devastating complications of diabetes, defined as a foot affected by ulceration, associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes [5,6]. Diabetic foot complications are the leading cause of hospital admissions, lower limb amputation and mortality in patients with diabetes worldwide [7].

Early recognition of patients with feet at risk for ulcers and amputation and the appropriate management, offered by a

* Corresponding author. Unit of Diabetes & Metabolism, Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt.
E-mail address: Mai_saeed3@yahoo.com (M.S. Khalifa).

https://doi.org/10.1016/j.dsx.2019.01.048
1871-4021/

multidisciplinary team, can reduce the rates of these outcomes [8].

Diabetic patients with diabetic foot syndrome have a mortality rate greater than twofold when compared with non-ulcerated diabetics. In addition, the 5-year mortality rate following amputation is estimated at 39–68%, a life expectancy comparable to aggressive types of cancer or advanced congestive heart failure [9].

The factors that lead to lower limb amputation are diabetic neuropathy, peripheral vascular disease, foot bone deformities, and external trauma. The sensory dysfunction associated to foot deformities increases the risk of foot ulceration which may be complicated by peripheral arterial disease (PAD), preventing the proper healing process [10].

2. Subjects And Methods

This cross-sectional study included 180 type 2 diabetic patients (aged 30–70 years) with diabetic foot ulcers who attended the Outpatient Clinic of Diabetes in Alexandria Main University Hospital in the period between July 2017 and December 2017.

After giving their consent, all study participants were subjected to a full demographic and medical history assessment including age, duration of diabetes, type of treatment, smoking, hypertension. All patients underwent a complete physical examination including measurement of height, weight, and calculation of body mass index (BMI).

Full diabetic foot examination was done to all study subjects including inspection, testing for sensory neuropathy using 10 g monofilament, assessment of vibration perception threshold (VPT) [11], deep tendon reflexes, assessment of diabetic foot ischemia (dorsalis pedis pulsation by palpation and hand-held doppler).

Calculation of ankle brachial index (ABI) was done. We used University of Texas Diabetic Wound Classification System [12] for assessment of the DFUs.

First-morning spot urine sample was obtained to assess urinary ACR where albuminuria was defined by ACR $\geq$30 mg/g Cr. HbA1c, HDL-C, LDL-C and serum creatinine were measured for all study subjects. The eGFR was calculated using CKD-EPI equation [13,14]. Fundus examination was done by an Ophthalmologist.

2.1. Statistical analysis of the data

Descriptive statistics (mean $\pm$ SD, as well as frequencies and percentages) which were computed for all clinical and demographic variables, Student t-test and Mann Whitney test were done. Spearman coefficient was used to find out correlation with the studied parameters. *P* value $\leq$ 0.05 was considered statistically significant.

3. Results

Regarding demographic data, 53.3% of the study group were in the age group from 50 to 60 years 75.6% were males, and 64.4% had longer duration of diabetes for more than 10 years. In our study population, 55.6% were smokers, 62.2% of them were hypertensive, and 64.4% were on insulin therapy. The mean BMI of the study group was 29.08 $\pm$ 4.49 kg/m^2, with 37.8% of them were overweight and 31.1% were obese.

The mean LDL-Cholesterol was 105.5 $\pm$ 27.11 mg/dl and 62.2% of the study group had abnormally high levels $\geq$100 mg/dl, while the mean HDL-cholesterol level was 40.02 $\pm$ 5.85 mg/dl and 55.6% had abnormally low levels (<40 mg/dl for males and <50 mg/dl for females). The mean HbA1C level was 10.10 $\pm$ 2.18% and 95.6% had abnormally high level (HbA1C>7%).

Regarding the types of DFUs, 86.7% had neuropathic DFUs, 11.1% had ischemic DFUs and 2.2% had neuro-ischemic type. Using University of Texas Grading System, 44.4% of the study group had grade I stage A ulcer, 17.8% had grade I stage B ulcer and 13.3% had grade II stage A ulcer. Fig.1:

About 64% of the study group had loss of protective sensation tested by 10 g monofilament and 82.2% had abnormal vibration perception threshold (VPT). About 20% of patients had abnormal ABI. The prevalence of diabetic retinopathy in the study group was more than 90%. Regarding DKD, 86.1% had albuminuria and the mean eGFR was 86.0 $\pm$ 25.84. There was statistically significant association between albuminuria and VPT (p=0.001) and ABI (p=0.031). There was no statistically significant association between albuminuria and severity of DFUs. VPT had significant negative correlation with eGFR. Fig.2:

However, there was no statistically significant correlation between eGFR and ABI (See Table 1).

There was statistically significant association between diabetic retinopathy and VPT (P = 0.008). Also there was statistically significant association between diabetic retinopathy and ABI (P = 0.001).

Regarding the association between DR and severity of DFUs, 93.1% of the study group who had grade I ulcer had non-proliferative diabetic retinopathy (NPDR), while two thirds of those who had grade II and III ulcers had NPDR (61.5 and 66.7% respectively) with statistically significant association between diabetic retinopathy and the grade of diabetic foot ulcers (p < 0.001). Fig. 3:

Ninety two percent of the study group who had stage A ulcer had NPDR, 78.6% of those who had stage B ulcer had NPDR, all cases with stage C ulcer (100.0%) had NPDR, while 66.7% of those who had stage D ulcer had NPDR with statistically significant association between diabetic retinopathy and the stage of diabetic foot ulcers (p=<0.001). Fig. 3:

4. Discussion

In the present study, the results showed that diabetic foot ulcers were common in males, older age, longer duration of diabetes. Most of the patients were smokers, hypertensive and on insulin therapy. 68.9% of the studied patients were either overweight (37.8%) or obese (31.1%).

In agreement with the results of our study, systematic review and meta-analysis through searching PubMed, EMBASE, ISI Web of science, and Cochrane database was performed to study the global epidemiology of diabetic foot ulceration and it was found that diabetic foot ulcer was more prevalent in males than in females. The patients with diabetic foot ulcers were older, had a lower body mass index, longer diabetic duration, and had more hypertension and smoking history [15].

Data suggested that diabetic foot was more common in male diabetic patients than female patients. One explanation of this gender difference might be the involvement in increased physical work in males [15] added to that associated neuropathy making them more prone to injury. Also it may be attributed to smoking habits that are more predominant in males.

The contribution of obesity to the risk of diabetic foot ulceration is inconclusive. Previous studies have revealed that obesity might be associated with diabetic foot ulcers [16,17]. However, there are also prospective studies showing that BMI has no significant correlation with diabetic foot ulceration [18,19]. One study demonstrated that the association between BMI and diabetic foot ulcers was J-shaped, and patients with BMI <25 kg/m2 and BMI > 45 kg/m2 were correlated with higher risk of developing diabetic foot ulceration [20].

Leila Yazdanpanah et al. [21] found in a Population-Based Diabetic Foot Cohort (ADFC Study) Two Year Follow Up Study that patients treated with insulin were more likely to develop foot

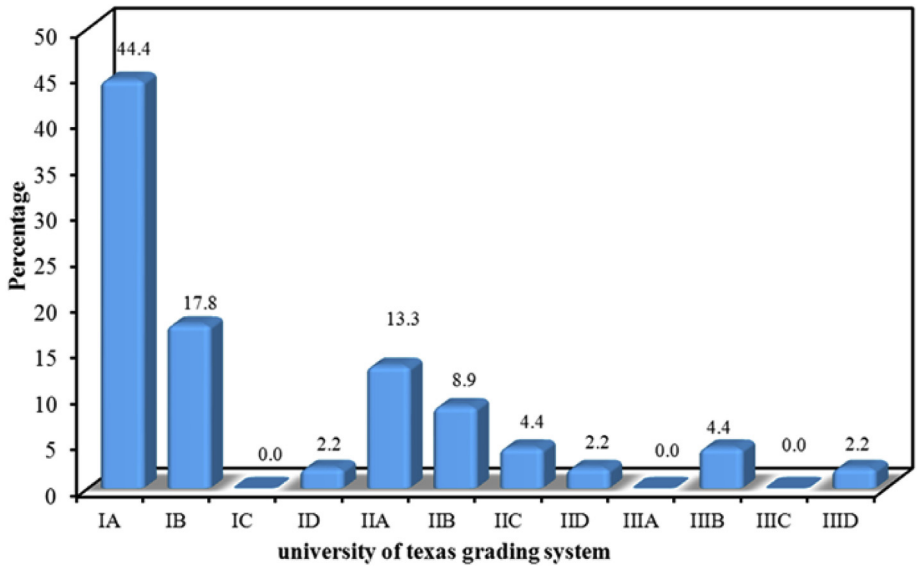

Fig. 1. Distribution of the study group according to University of Texas Ulcer Grading System.

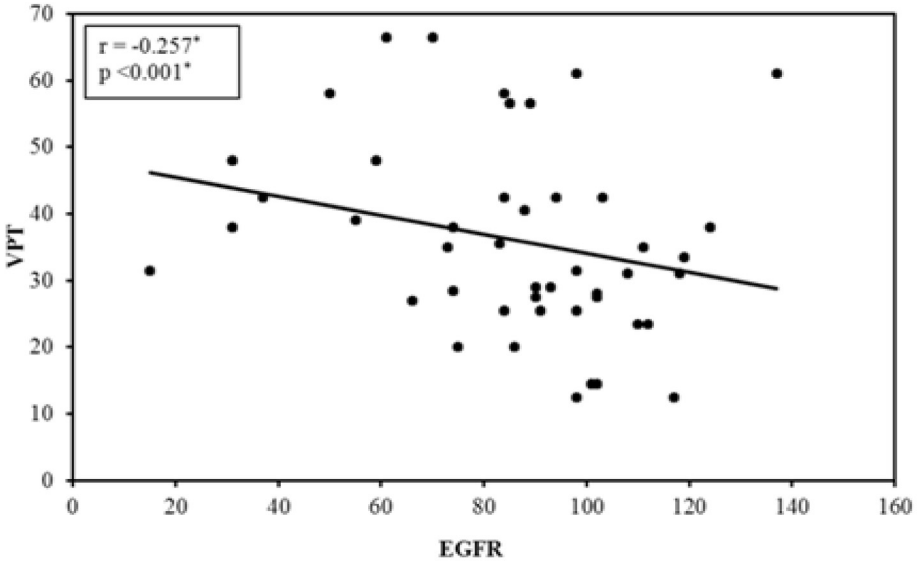

Fig. 2. Correlation between eGFR and VPT.

Table 1
Correlation of eGFR with VPT and ABI.

	EGFR	
	R	p
VPT	−0.257[a]	<0.001[a]
ABI	0.120	0.108

r: Pearson coefficient.
[a] Statistically significant at $p \leq 0.05$.

ulcers than were patients whose diabetes is managed with oral antidiabetic agents or lifestyle modification alone.

Vibha et al. [22] , in agreement with the results of our study, in a community-based study to assess the prevalence of diabetic foot syndrome (DFS) and associated risk factors among people with diabetes mellitus, found that the subjects with DFS were 4.5 times more likely to be using insulin compared to oral hypoglycemic agents (OHAs). This could be attributed to the fact that initiation of insulin therapy implies later stages in the natural history of DM. This also may correlate with association of DFS with longer duration of DM.

In the current study, it was found that poor glycemic control was a significant risk factor for DFUs. These findings were confirmed by other studies [23–25] that showed that poor glycemic control was the main factor causing diabetic foot problems. Previous studies have also shown that HbA1c was a contributory factor for DFU [26,27] This may be because of hyperglycemia, which has been considered a risk factor for the development of DFUs because of its contribution toward the development of peripheral neuropathy and microvascular complications [28].

Our study revealed that 86.7% of the studied patients had neuropathic diabetic foot ulcers, 11.1% of them had ischemic diabetic foot ulcers while 2.2% had neuro-ischemic type. S. Bajaj et al. [29] , during their study which has been conducted in the North of

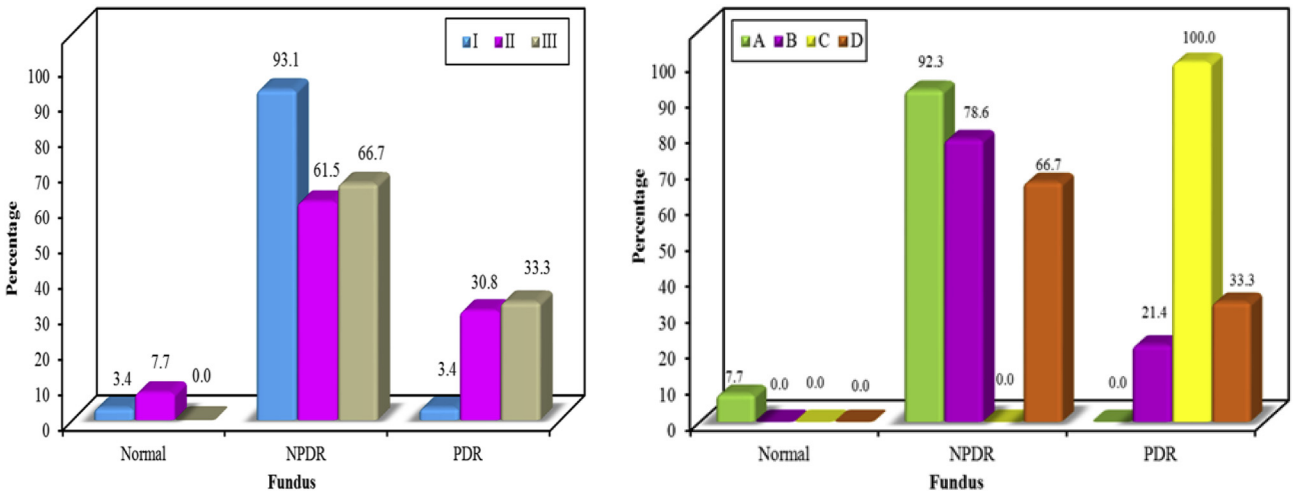

Fig. 3. Relation between DR and severity (grading/staging) of DFUs.

India, found that 30% of patients with diabetes with new ulcers were having neuro-ischemic ulcers (NIUs) whereas 70% were having neuropathic ulcers (NPUs). NIUs are on a rise as other authors in more recent studies have also found NIUs ranging from 23.3% to 30.5% [24,30]. However, Chalya et al. reported neuro-ischemic ulcers to be only 4.4% [31].

In the present study, the results showed that 64.4% of patients had loss of protective sensations tested by 10 g monofilament and 82.2% of them had abnormal VPT. Regarding PAD, our study revealed that only 20% of patients had abnormal ABI. Almobarak et al. [32] agreed with the results of our study finding that the prevalence of neuropathy in association with diabetic foot was 82.1%. Sharma et al. [33] and Vibha et al. [22] found that the prevalence was 95.85% and 51.8% respectively. Other results were observed in Indian studies done by George H et al. [34] in Tamil Nadu and Mackson Nongmaithem et al. [35] in Maharashtra, where prevalence of peripheral neuropathy was found to be 47%.

In Tanzania, it was noted that 100% of patients who presented with foot ulcers to a large Diabetes Outpatient Clinic, had varying degrees of severity of peripheral neuropathy [36]. S. Vijayasarathy et al. found during their study to assess prevalence and risk factors of peripheral arterial disease in diabetic foot ulcers that the prevalence of PAD in DFUs was found to be 36% [37]. Muthiah A et al. agreed with the results of the previous study in their study on diabetic foot and its association with peripheral artery disease demonstrating a prevalence of 38%, 57 patients out of 150 patients had PAD associated with diabetic foot ulceration [38].

In the present study, the results showed that 86.1% of the patients had albuminuria with the majority of them (84.4%) had mild CKD (stage I and II). The prevalence of diabetic retinopathy in the patients was more than 90%.

There was statistically significant association between albuminuria and VPT and ABI. VPT had significant negative correlation with eGFR. However, there was no statistically significant correlation between eGFR and ABI.

Bhavya et al. [39] found in a study of association between microalbuminuria and microvascular complications in type 2 diabetes mellitus that the incidence of microalbuminuria is significantly associated with the prescence of retinopathy and peripheral neuropathy. Hurley et al. [40], in a prospective study of risk factors for foot ulceration that has been conducted in the west of Ireland, found a statistically significant association between declining levels of eGFR and the probability of having abnormal sensory or vascular function on foot screening.

Chronic DFUs and DR are severe complications of Type 2 diabetes. Their pathogenesis has been debated, but DR is generally considered to be of microvascular origin, whereas DFUs are more likely caused by mixed micro- and macrovascular disease. The importance of DR as a risk factor for developing DFUs has been reported by a large number of investigators since 1975, when Walsh et al. [41] presumed a possible association between these complications. Likewise, in a recently published meta-analysis, DR was present in 33% of people without and in 64% with DFUs [15].

Sellman et al. [42] found in people with DFU, DR was present in 94% and proliferative DPR in 31%. Hwang et al. [43] similarly reported 90% DR in a Korean population with DFUs, with 55% presenting with proliferative DR.

The results of the present study showed that there was statistically significant association between diabetic retinopathy and peripheral neuropathy. Also there was statistically significant association between diabetic retinopathy and peripheral arterial disease (PAD).

In agreement with the results of our study, Kumar et al. and Won et al. concluded that neuropathy was seen more in patients with coexisting retinopathy [44,45]. Furthermore Katulanda et al reported retinopathy as one of the most important risk factors for DPN [46]. Ji et al. [47] proved that retinopathy was an independent risk factor for diabetic neuropathy. An explanation of this relationship may be that both diabetic retinopathy and peripheral neuropathy have similar pathogenetic mechanisms.

Yi-Wen Chen et al. [48], in a study of prevalence of lower extremity peripheral artery disease in type 2 diabetes patients with proliferative diabetic retinopathy, found that patients with PDR were more likely than patients with NDR to have PAD. Furthermore, a higher proportion of PDR patients had either low or high ABI compared with NDR patients. He also found that PDR was an independent correlation factor of abnormal ABI ($\leq$0.9).

Mei-Yueh Lee et al. [49] evaluated the association between ABI and the development of DR in patients with type 2 DM. The study showed that an abnormally low or high ABI was associated with proliferative DR in patients with type 2 DM [50].

The mechanisms underlying the association between atherosclerosis and DR are unclear. It has been hypothesized that atherosclerosis and DR share common risk factors with regards to the causal pathway [51,52]. This is supported by an apparent common mechanism underlying the development of macro and

micro angiopathies in patients with type 2 DM such as obesity, insulin resistance and hypertension. In addition, neovascularization (retinal angiogenesis) is a hallmark of proliferative DR, and angiogenesis has frequently been reported in advanced atherosclerotic lesions [53,54].

Our study showed that most of the studied diabetic patients (93.1%) who had grade I ulcers had NPDR, while two thirds of those who had grade II and III ulcers had NPDR (61.5, 66.7% respectively) with statistically significant association between diabetic retinopathy and the grade of diabetic ulcer ($p < 0.001$).

Thoiba Karam et al. [55] agreed with our results noting a statistically significant association between the prescence of retinopathy in advanced grades of DFUs. The severity of the retinopathy was also found to be greater in patients with higher grades of DFUs. Hwang et al. [43] also noted a similar association of proliferative retinopathy and diabetic foot ulceration. They speculate it to be a result of increased oxidative stress and endothelial damage occurring in vascular disease in the later stages of diabetes.

5. Conclusion

Diabetic foot ulcers are common in type 2 diabetic patients with longer duration of the disease, male gender, poor glycemic control, peripheral neuropathy. Albuminuria, diabetic retinopathy and peripheral neuropathy are very common among those patients and strongly associated with risk factors of diabetic foot ulceration.

Conflicts of interest

None.

Acknowledgement and Funding

This research was funded by the Unit of Diabetes and Metabolismm, Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt.

References

[1] Gilman AF, Goodman LS, Rall TW, Murad F. Pharmacological basic of therapeutic. seventh ed. New York: MacMillan Publishing Company; 1985. p. 1504–7.
[2] International Diabetes Federation (IDF). Diabetes atlas. seventh ed. Belgium: IDF; 2015.
[3] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. J Am Med Assoc 2005;293(2):217–28.
[4] Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013;93:137–88.
[5] Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet 2005;366(9498):1725–35.
[6] Alexiadou K, Doupis J. Management of diabetic foot ulcers. Diabetes Ther 2012;3(1):4.
[7] Nouvong A, Armstrong DG. Diabetic foot ulcers. In: Cronenwett JL, Johnston KW, editors. Rutherford's vascular surgery. eighth ed. Philadelphia: Elsevier Saunders; 2014. p. 1816–36.
[8] Hinchliffe RJ, Brownrigg JR, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. Diabetes Metab Res Rev 2016;32(Suppl 1):37–44.
[9] Mazlina M, Shamsul A, Jeffery FS. Health-related quality of life in patients with diabetic foot problems in Malaysia. Med J Malaysia 2011;66(3):234–8.
[10] Gerrits EG, Landman GW, Nijenhuis-Rosien L, Bilo HJ. Limited joint mobility syndrome in diabetes mellitus: a minireview. World J Diabetes 2015;6(9):1108–12.
[11] Garrow A, Boulton A. Vibration perception threshold; a valuable assessment of neural dysfunction in people with diabetes. Diabetes Metals Res Rev 2006;22:411–9.
[12] Lavery LA, Armstrong DG, Harkless LB. Clasification of diabetic foot wounds. J Foot Ankle Surg 1996;35:528–31.
[13] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feidman HI, et al. Anew equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12.
[14] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Chronic Kidney Disease Epidemiology Collaboration using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247–54.
[15] Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis dagger. Ann Med 2017;49:106–16.
[16] Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information the Seattle Diabetic Foot Study. Diabetes Care 2006;29:1202–7.
[17] Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care 2000;23:606–11.
[18] Merza Z, Tesfaye S. The risk factors for diabetic foot ulceration. Foot 2003;13:125–9.
[19] Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care 1999;22:1036–42.
[20] Sohn MW, Budiman-Mak E, Lee TA, Oh E, Stuck RM. Significant J-shaped association between body mass index (BMI) and diabetic foot ulcers. Diabetes Metab Res Rev 2011;27:402–9.
[21] Yazdanpanah L, Shahbazian H, Nazari I, Hesam S, Ahmadi F, Cheraghian B, et al. Risk factors associated with diabetic foot ulcer-free survival in patients with diabetes. Diabetes Metab Syndr 2018;12(6):1039–43.
[22] Vibha SP, Kulkarni MM, Ballala ABK, Kamath A, Maiya GA. Community based study to assess the prevalence of diabetic foot syndrome and associated risk factors among people with diabetes mellitus. BMC Endocr Disord 2018;18:43.
[23] Ali SM, Basit A, Sheikh T, Mumtaz S, Hydrie MZ. Diabetic foot ulcer — aprospective study. J Pakistan Med Assoc 2001;51:78–81.
[24] Nyamu PN, Otieno CF, Amayo EO, McLigeyo SO. Risk factors and prevalence of diabetic foot ulcers at Kenyatta National Hospital, Nairobi. East Afr Med J 2003;80:36–43.
[25] Dubský M, Jirkovská A, Bem R, Fejfarová V, Skibová J, Schaper NC, et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis of a Eurodiale subgroup. Int Wound J 2012;10(5):555–61.
[26] Shahi SK, Kumar A, Kumar S, Singh SK, Gupta SK, Singh TB. Prevalence of diabetic foot ulcer and associated risk factors in diabetic patients from north India. J Diabet Foot Complications 2012;4:83–91.
[27] Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. Diabetes Care 2006;29:1288–93.
[28] Martín Borge V, Herranz de la Morena L, Castro Dufourny I, Fernández Martínez A, Pallardo Sánchez LE. Diabetic foot and risk factors. Med Int 2007;24(6):263–6.
[29] Bajaj S, Mahajan A, Grover S, Mahajan V, Goyal P, Gupta VK. Peripheral vascular disease in patients with diabetic foot ulcers - an emerging trend: a prospective study from north India. J Assoc Phys India 2017;65(5):14–7.
[30] Mohan V, Premlatha G, Shastry NG. Peripheral vascular disease in non-insulin dependent diabetes mellitus in South India. Diabetes Res Clin Pract 1995;27:235–40.
[31] Chalya PL, Mabula JB, Dass RM, Kabangila R, Jaka H, Mchembe MD, et al. Surgical management of Diabetic foot ulcers: a Tanzanian university teaching hospital experience. BMC Res Notes 2011;4:365.
[32] Almobarak AO, Awadalla H, Osman M, Ahmed MH. Prevalence of diabetic foot ulceration and associated risk factors: an old and still major public health problem in Khartoum, Sudan? Ann Transl Med 2017;5(17):340.
[33] Sharma R, Kapila R, Sharma AK, Mann J. Diabetic foot disease- incidence and risk factors: a clinical study. J Foot Ankle Surg 2016;3(1):41–6.
[34] George H, Rakesh PS, Krishna M, Alex R, Abraham VJ, George K, et al. Foot care knowledge and practices and the prevalence of peripheral neuropathy among people with diabetes attending a secondary care rural hospital in southern India. J Fam Med Prim Care 2013;2:27–32.
[35] Nongmaithem M, Bawa APS, Pithwa AK, Bhatia SK, Singh G, Gooptu S. A study of risk factors and foot care behavior among diabetics. J Fam Med Prim Care 2016;5:399–403.
[36] Gulam-Abbas Z, Lutale JK, Morbach S, Archibald LK. Clinical outcome of diabetes patients hospitalized with foot ulcers, Dar es Salaam, Tanzania. Diabet Med 2002;19:575–9.
[37] Thulasikumar G, Vijayasarathy S. Assessment of prevalence and risk factors of peripheral arterial disease in diabetic foot ulcer. Int J Surg Med 2017;3(3):156–66.
[38] Muthiah A, Kandasamy R, Nagulan S, Madasamy A. A study on diabetic foot and its association with peripheral artery disease. Int Surg J 2017;4:1217–21.
[39] Bhavya N, Kumar VA. A study of association between microalbuminuria and microvascular complications in type2 diabetes patients. J Med Sci 2017;3(1):6–10.
[40] Hurley L, Kelly L, Garrow AP, Glynn LG, McIntosh C, Alvarez-Iglesias A, et al. A prospective study of risk factors for foot ulceration: the West of Ireland Diabetes Foot Study. QJM 2013;106(12):1103–10.
[41] Walsh CH, Soler NG, Fitzgerald MG, Malins JM. Association of foot lesions with retinopathy in patients with newly diagnosed diabetes. Lancet 1975;1:878–80.
[42] A. Sellman, P. Katzman, S. Andreasson, et al.Clinical sciences in lund, Lund University, Department of Endocrinology, Skane University Hospital, and 3Department of Ophthalmology, Skane University Hospital, Lund, Sweden.

[43] Hwang DJ, Lee KM, Park MS, Choi SH, Park JI, Cho JH, et al. Association between diabetic foot ulcer and diabetic retinopathy. PLoS One 2017;12. e 0175270.
[44] Kumar HK, Kota S, Basile A, Modi K. Profile of microvascular disease in type 2 diabetes in a tertiary health care hospital in India. Ann Med Health Sci Res 2012;2:103–8.
[45] Won JC, Kwon HS, Kim CH, Lee JH, Park TS, Ko KS, et al. Prevalence and clinical characteristics of diabetic peripheral neuropathy in hospital patients with Type 2 diabetes in Korea. Diabet Med 2012;29:e290–6.
[46] Katulanda P, Ranasinghe P, Jayawardena R, Constantine GR, Sheriff MH, Matthews DR. The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. Diabetol Metab Syndrome 2012;4:21.
[47] Ji N, Zhang N, Ren ZJ, Jia KB, Wang L, Ni JX, et al. Risk factors and pain status due to diabetic neuropathy in chronic long-term diabetic patients in a Chinese urban population. Chin Med J 2012;125:4190–6.
[48] Chen YW, Wang YY, Zhao D, Yu CG, Xin Z, Cao X, et al. High prevalence of lower extremity peripheral artery disease in type 2 diabetes patients with proliferative diabetic retinopathy. PLoS One 2015;10(3). e0122022.
[49] Kawasaki R, Cheung N, Islam FM, Klein R, Klein BE, Cotch MF, et al. Is diabetic retinopathy related to subclinical cardiovascular disease? Ophthalmology 2011;118:860–5.
[50] Lee MY, Hsiao PJ, Huang JC, Hsu WH, Chen SC, Chang JM, et al. Abnormally low or high ankle - brachial index is associated with the development of diabetic retinopathy in type 2 diabetes mellitus. Sci Rep 2018;8:441.
[51] de Kreutzenberg SV, Coracina A, Volpi A, Fadini GP, Frigo AC, Guarneri G, et al. Microangiopathy is independently associated with presence, severity and composition of carotid atherosclerosis in type 2 diabetes. Nutr Metabol Cardiovasc Dis 2011;21:286–93.
[52] Klein R, Marino EK, Kuller LH, Polak JF, Tracy RP, Gottdiener JS, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the cardiovascular health study. Br J Ophthalmol 2002;86: 84–90.
[53] Stern MP. Diabetes and cardiovascular disease. The “common soil” hypothesis. Diabetes 1995;44:369–74.
[54] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615–25.
[55] Karam T, Kamath YS, Rao LG, Rao KA, Shenoy SB, Bhandary SV. Diabetic retinopathy in patients with diabetic foot syndrome in South India. Indian J Ophthalmol 2018;66(4):547–50.