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Chapter

Prevalence and Association of Diabetic Retinopathy with Diabetic Foot Ulcer: A Cross-Sectional Observational Study

Shaista Zafar, Kashif Rahim, Inayat Ullah Khan, Muhammad Yasin, Muhammad Dawood and Shamim Saleha

Abstract

We aimed to elucidate prevalence and association of diabetic retinopathy (DR) in patients with diabetic foot ulcer (DFU) from Pakistan. In this cross-sectional study, about 225 DFU patients who underwent ophthalmic examinations within 6 months of diagnosis of foot ulceration were included. The medical records of 305 diabetic patients without DFU were included as controls. The association of DR with DFU was assessed by comparing DFU patients with proliferative DR (PDR) and DFU patients without PDR. Out of 225 DFU patients, 215 patients (95.6%) had DR and 169 patients (75.1%) had PDR. The prevalence of DFU was significantly greater (P = 0.0527) among the male diabetic patients, whereas advanced age of these patients (≥41 years) had a significant effect (P = 0.0286) on development and progression of PDR. A longer duration of diabetes (≥10 years) was identified as a significant contributing factor for the development of both DFU (P = 0.0029) and PDR (P = 0.0299). Moreover, the risk of PDR increased in diabetic patients with higher DFU grades (grade 3 and grade 4). In conclusion, retinopathy was prevalent in DFU patients. Therefore, DFU patients with advancing age and longer duration of diabetes should undergo retinal examinations for timely diagnosis and management of DR.

Keywords: diabetic foot ulcer, diabetic retinopathy, risk factors, Pakistan

1. Introduction

Diabetes mellitus (DM) is a metabolic disease, caused by chronic hyperglycemia as a result of defects in secretion of insulin, resistance to insulin action, or a combination of the two. Type 1 and type 2 are two main types of diabetes. Type 1 diabetes mellitus (T1DM) results from absolute deficiency of insulin secretion, and type 2 diabetes mellitus (T2DM) results from combined defects in both relative deficiency of insulin secretion and insulin resistance [1]. T2DM is the dominant form of diabetes which account to approximately >85% of all diabetes cases [2]. Diabetic foot ulcer (DFU) is the most devastating complication of diabetes, with a global prevalence of 6.3%, and is more common in patients with type 2 diabetes [3].

The lifetime risk of foot ulceration in patients with diabetes lies somewhere in the range of 15 and 25% [4, 5], with a yearly rate of around 2–3% [6].

Diabetic is associated with microvascular complications, including retinopathy, neuropathy, and nephropathy, and macrovascular complications, including ischemic coronary illness, stroke, and peripheral vascular disease [7]. Diabetic retinopathy (DR) is a common complication of diabetes that affects vision. DR damages the blood vessels of the light-sensitive tissue at the back of the eye (retina) that results in blindness if left undiagnosed and untreated. It is estimated that 20 years after diagnosis, those with type 1 diabetes and 60% of those with type 2 diabetes will have some level of retinopathy [8]. Approximately 4 million individuals around the globe are estimated to losing their sight from diabetic retinopathy, the main source of visual impairment in patients aged 20–74 years [9]. The risk of development and progression of DR is closely associated with the type 1 diabetes [8], longer duration of diabetes [10], advancing age [11], poor glycemic control [12], high blood pressure [13] and elevated serum lipids [14].

The descriptive analytical studies have demonstrated that diabetic retinopathy (DR) is among one of the major contributing factors in the development of foot ulceration and subsequent lower limb amputation in diabetic patients [11, 15–17]. Importantly, DFU patients with PAD are less likely to heal and more likely to require amputation compared to patients without PAD. Moreover, retinal screening in people with diabetic foot ulceration, followed by treatment of sight-threatening retinopathy, may prevent severe vision loss or blindness [18]. It is therefore essential that DR is diagnosed in all diabetic patients with a foot ulcer. There is a significant rise in the prevalence of diabetes and its complications in Pakistan, causing a major social and economic burden [19, 20]. Therefore, this study was conducted with an aim to investigate the prevalence of DR in patients with a DFU in Pakistan and to elucidate the potential association between DR and DFU.

2. Materials and methods

This was a cross-sectional observational study conducted in the diabetology clinic at Pakistan Institute of Medical Sciences (PIMS), located in federal capital of Pakistan, which is the largest tertiary care referral hospital. This study was conducted between March 2017 and February 2018 as per the guidelines of the Declaration of Helsinki, and the Institutional Ethical Committee approval was obtained before initiation. The study was explained, and written informed consent of the patients was obtained before their recruitment. Inclusion criteria were as follows: (1) all type 2 diabetic patients and only those type 1 diabetes patients with diabetes duration of more than 5 years, diagnosed with foot ulcers based on the Wagner ulcer classification, were included in this study. (2) Patients were included in the study only if they underwent ophthalmic examinations particularly funduscopy of the retina within 6 months after DFU diagnosis.

Participated DFU patients were classified into Wagner's grades [21] as follows: grade 1 (superficial ulcer), grade 2 (deep ulcer), grade 3 (ulcer with osteomyelitis), grade 4 (forefoot gangrene), and grade 5 (mid foot or hind foot gangrene). Moreover, the presence and severity of DR among DFU patients were assessed based on the grading of the Global Diabetic Retinopathy Project Group [22]. A five-stage disease severity classification for DR includes no apparent retinopathy (no DR), proliferative DR (PDR), and mild, moderate, or severe non-proliferative DR (NPDR). Clinical information and demographic details were obtained from medical records of participating patients. The medical records of diabetic patients without a DFU who also visited the diabetology clinic at PIMS for a health checkup were included as control.

Analysis of recruitment data was performed by using SPSS-PC version 16.0, and then tables and graphs were constructed to display characteristics of studied patients. The association between DR and DF was determined by using the Chi-square test. P-values <0.05 were considered significant.

3. Results

Data of patients recruited in the study was analyzed and summarized in **Table 1**. Among 225 patients with foot ulceration, majority of them were male (62.7%) and had type 2 (60%) diabetes. Most DFU patients were aged 41 years old and over (88.4%) and had diabetes since ≥10 years (65.8%), high HbA1c ≥ 7% (77.3%), and higher level of systolic blood pressure (72.4%). Statistically, significant differences were observed among diabetic patients with a foot ulcer or without a foot ulcer in relation to gender (P = 0.0527) and diabetes duration (P = 0.0029) only.

Additionally, DFU patients with PDR were compared with DFU patients without PDR as shown in **Table 1**. The PDR was less prevalent in diabetic males with foot ulcers (53.8%) in comparison to those without foot ulcers (66.1%). The DFU patients with PDR had type 2 diabetes (66.9%), advanced age (82.8%), longer

Characteristics of patients	**Diabetes (N = 530)**		**P value**	**DFU (N = 225)**		**P value**
	Diabetes with DFU (N = 225)	**Diabetes without DFU (N = 305)**		**DFU with PDR (N = 169)**	**DFU without PDR (N = 56)**	
Gender						
Male	141 (62.7)	215 (70.5)	0.0527*	91 (53.8)	37 (66.1)	0.1024
Female	84 (37.3)	90 (29.5)		78 (46.2)	19 (33.9)	
Age (years)						
≤41	26 (11.6)	37 (12.1)	0.7084	29 (17.2)	19 (33.9)	0.0286*
≥41	199 (88.4)	268 (87.9)		140 (82.8)	37 (66.1)	
Duration of diabetes (years)						
≤10	77 (34.2)	135 (44.3)	0.0029*	24 (14.2)	17 (30.4)	0.0299*
≥10	148 (65.8)	170 (55.7)		145 (85.8)	39 (69.6)	
Type of diabetes						
Type 1	90 (40)	111 (36.4)	0.3352	56 (33.1)	22 (39.3)	0.4170
Type 2	135 (60)	194 (63.6)		113 (66.9)	34 (60.7)	
HbA1c level						
≤ 7%	51 (22.7)	95 (31.1)	0.1638	30 (17.8)	11 (19.6)	0.7577
≥ 7%	174 (77.3)	210 (68.9)		139 (82.2)	45 (80.4)	
Blood pressure (mmHg)						
Systolic	163 (72.4)	229 (75.1)	0.4882	122 (72.2)	41 (73.2)	0.8807
Diastolic	62 (27.6)	76 (24.9)		47 (27.8)	15 (26.8)	

**Statistically significant*

Table 1.
Basic characteristics of diabetic patients with or without diabetic foot ulcer (DFU).

Types of DR	Diabetics with a DFU, N = 225(%)	Diabetics without a DFU, N = 305 (%)
No DR	10 (4.4)	255 (83.6)
Mild NPDR	11 (4.9)	10 (3.2)
Moderate NPDR	26 (11.6)	16 (5.2)
Severe NPDR	9 (4.0)	7 (2.3)
PDR	169 (75.1)	17 (5.6)

Table 2.
Prevalence of DR in patients with a DFU and in diabetic patients without a DFU .

duration of diabetes (85.8), high HbA1c ≥ 7% (82.2%), and elevated systolic blood pressure (72.2%) than DFU patients without PDR. The significant contributing factors of PDR among DFU patients were advanced age (p = 0.0286) and longer duration of diabetes (0.0299).

In terms of DR among diabetic patients with foot ulceration, 215 patients (95.6%) had DR and 169 patients (75.1%) had PDR. 11 patients (4.9%) had mild NPDR, 26 patients had moderate NPDR (11.6%), and 9 patients had severe NPDR (4.0%), as shown in **Table 2** and **Figure 1**. Moreover, the common ulcer grades were 3 (41.8%) and 4 (31.6%), among DFU patients with DR (**Table 3**).

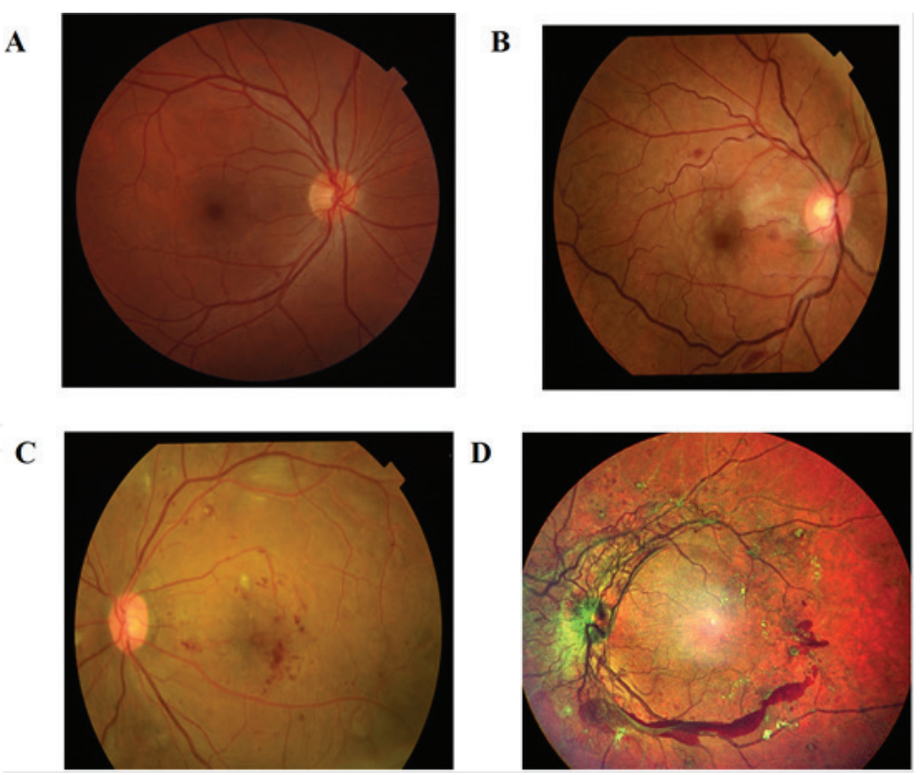

Figure 1.
Fundus photographs of some studied patients show clinical grades of DR. (A) Mild NPDR phenotypes based on the presence of only two microaneurysms and the absence of macular edema. (B) Moderate NPDR phenotypes based on the presence of scattered microaneurysms, dot-blot hemorrhages, hard exudates, and diffuse macular edema. (C) Severe NPDR phenotypes based on the presence of scattered microaneurysms, dot-blot hemorrhages, hard exudates, cotton wool spots, and clinically significant macular edema. (D) PDR phenotypes based on the presence of new vessels on the disc (NVD), new vessels elsewhere (NVE), preretinal hemorrhage, retinal hemorrhages, tractional bands, and laser marks of the previous pan retinal photocoagulation (PRP).

Wagner's grades	No DR, N = 10	Mild NPDR, N = 11	Moderate NPDR N = 26	Severe NPDR N = 9	PDR, N = 169	Total N (%)
Grade 1	2	1	3	0	17	23 (10.2)
Grade 2	1	3	3	2	28	37 (16.4)
Grade 3	4	5	11	2	72	94 (41.8)
Grade 4	3	2	9	5	52	71 (31.6)
Grade 5	0	0	0	0	0	0 (0)

Table 3.
Distribution of diabetic patients with DR according to ulcer grades.

4. Discussion

Diabetes is a common disease, associated with microvascular and macrovascular diseases that contribute to an increased risk of foot ulcers and subsequent lower extremity amputations in diabetic patients [7]. Population-based studies identified that DR is among one of the contributing diseases that significantly increased risk for foot ulceration in diabetic populations of Saudi Arabia [23], Korea [11], Spain [15], Iran [16] and India [17]. However, data is limited about contribution of DR in development of foot ulceration in diabetic population of Pakistan.

The present study revealed that the majority (95.7%) of DFU patients had DR, with 71.9% demonstrated PDR. A similar study reported that DR was prevalent (90%) in the US diabetic patients with foot ulcers, and about more than half of these patients had PDR [11]. Pemayun et al. in a hospital-based case-control study found PAD to be a major predictive factor for poor outcome among hospitalized DFU patients [24]. Previously, Nwanyanwu et al. in a retrospective cohort study assessed that chronic foot ulcers might contribute to retinopathy progression due to the reason that a significant proportion of diabetic chronic ulcer patients with NPDR who progressed to PDR in their analysis [25]. Among DFU patients with PDR, 73.4% had advanced Wagner's grades (grades 3 and 4) of foot ulceration in the present study. Hwang et al. found association of PDR with DFU and speculated that elevated oxidative stress and endothelial dysfunction can cause PDR in the advanced stages of diabetes [11].

The cross-sectional diabetes studies reported that prevalence of foot complications increases among diabetic males with advanced age and longer duration of diabetes [10, 11, 19, 23]. In the current study, diabetic patients with foot ulcers were compared with those without foot ulcers to find significant determinants for foot ulcer in diabetic patients, and it was found that a significant number of diabetic males were at a greater risk for the development of foot ulcers. Higher average height, higher plantar pressure, inadequate self-care practices, inappropriate shoes, and frequent exposure to traumatic events and frequently found peripheral insensate neuropathy have been identified as risk factors contributing to foot ulceration in diabetic males [26, 27]. Additionally, DFU patients were classified into the PDR or NPDR group; our results showed that diabetic males with foot ulcers had a higher prevalence of PDR comparatively to females, but this difference was not significant. Similarly, a diabetes study from the United Kingdom reported that PDR was more prevalent in males than in females [28]. In contrast, a community-based study in China showed that diabetic females were associated with increased risk of PDR [29]. This gender difference observed in present and previous studies could not identify it as a risk factor contributing to PDR in diabetic patients with foot ulceration.

Importantly, advancing age has been observed as a contributing factor to foot ulceration in diabetic patients in many studies [11, 23]. Although prevalence of foot ulcers was determined high among advanced age diabetic patients in current study, a statistically significant difference was not observed in terms of increasing age (≥41 years) of diabetic patients with and without foot ulceration. On the other hand, our study demonstrated statistically significant correlation between PDR and advanced age of DFU patients. In contrast to this observation, Hwang et al. [11] in a recent study failed to show a correlation between PDR and advanced age of DFU patients. Similarly, Li and Wang reported lower prevalence of DR in elderly diabetic patients and suggested that favorable control of blood glucose, blood pressure, and blood lipids effectively prevented the occurrence of DR in diabetic patients [30]. Therefore, it seems that high blood glucose levels and elevated systolic blood pressure have contributed to the developing of PDR in elderly DFU patients in current study.

Comparatively high prevalence of foot ulcers was observed among diabetic patients with diabetes duration more than 10 years in the current study, and this observation was significant. A previous study from Sudan supported our observation [10]. In two different previously conducted diabetic foot studies, the average duration of diabetes in DFU patients was 13.2 [31] and 8.2 years [32]. Based on current and previous observations, we hypothesize that the lengthy duration of diabetes is a significant risk factor for the development of diabetic foot ulceration. In addition, Chawla et al. in a study reported that chronic hyperglycemia and diabetes duration are among the main contributing factors to development and progression of DR in diabetic patients with foot ulcer [33]. The results of the present study also showed that lengthy duration of diabetes was a significant risk factor in progression of PDR among patients with DFU. In agreement with our results, Hwang et al. also reported that the foot ulcer patients with PDR had a longer duration of diabetes compared to those with NPDR [11].

5. Conclusion

In summary, the present study showed that a large proportion of advanced age patients with longer duration of diabetes had retinopathy and were at substantial risk of developing foot ulceration. Therefore, in advanced age DFU patients, and particularly those with longer duration of diabetes, early detection of DR and timely treatment may decrease the risk of severe vision loss or blindness.

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Conflict of interest

The author(s) declare that they have no competing interests.

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References

[1] Karalliedde J, Gnudi L. Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. Nephrology, Dialysis, Transplantation. 2016;**31**(2):206-213. DOI: 10.1093/ndt/gfu405

[2] Forouhi NG, Wareham NJ. Epidemiology of diabetes. Medicine (Abingdon). 2014;**42**(12):698-702. DOI: 10.1016/j.mpmed.2014.09.007

[3] Zhang et al. Global epidemiology of diabetic foot ulceration: A systematic review and meta-analysis. Annals of Medicine. 2017, 2017;**49**(2):106-116. DOI: 10.1080/07853890.2016.1231932

[4] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. Journal of the American Medical Association. 2005;**293**(2):217-228

[5] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;**27**(5):1047-1053. DOI: 10.2337/diacare.27.5.1047

[6] Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, et al. The North-West Diabetes Foot Care Study: Incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabetic Medicine. 2002;**19**(5):377-384. DOI: 10.1046/j.1464-5491.2002.00698

[7] Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. Journal of the American College of Cardiology. 2009;**53**(5 Suppl):S35-S42. DOI: 10.1016/j.jacc.2008.09.055

[8] Watkins PJ. Retinopathy. BMJ. 2003;**326**(7395):924-926. DOI: 10.1136/bmj.326.7395.924

[9] Cheung N et al. Diabetic retinopathy. Lancet. 2010;**376**(9735):124-136. DOI: 10.1016/S0140-6736(09)62124-3

[10] 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? Annals of Translational Medicine. 2017;**5**(17):340. DOI: 10.21037/atm.2017.07.01

[11] 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**(4):e0175270. DOI: 10.1371/journal.pone.0175270

[12] Fenwick EK, Xie J, Man REK, Sabanayagam C, Lim L, Rees G, et al. Combined poor diabetes control indicators are associated with higher risks of diabetic retinopathy and macular edema than poor glycemic control alone. PLoS One. 2017;**12**(6):e0180252. DOI: 10.1371/journal.pone.0180252

[13] Cardoso CRL, Leite NC, Dib E, Salles GF. Predictors of development and progression of retinopathy in patients with type 2 diabetes: Importance of blood pressure parameters. Scientific Reports. 2017;**7**(1):4867. DOI: 10.1038/s41598-017-05159-6

[14] Agroiya P, Philip R, Saran S, Gutch M, Tyagi R, Gupta KK. Association of serum lipids with diabetic retinopathy in type 2 diabetes. Indian Journal of Endocrinology and Metabolism. 2013;**17**(Suppl 1):S335-S337. DOI: 10.4103/2230-8210.119637

[15] Dòria M, Rosado V, Pacheco LR, Hernández M, Betriu À, Valls J, et al. Prevalence of diabetic foot disease in patients with diabetes

under renal replacement tin Lleida, Spain. BioMed Research International. 2016;**2016**:7217586. DOI: 10.1155/2016/7217586

[16] Maroufizadeh S, Almasi-Hashiani A, Hosseini M, Sepidarkish M, Omani Samani R. Prevalence of diabetic retinopathy in Iran: A systematic review and meta-analysis. International Journal of Ophthalmology. 2017;**10**(5):782-789. DOI: 10.18240/ijo.2017.05.21

[17] Karam T, Kamath YS, Rao LG, Rao KA, Shenoy SB, Bhandary SV. Diabetic retinopathy in patients with diabetic foot syndrome in South India. Indian Journal of Ophthalmology. 2018;**66**(4):547-550. DOI: 10.4103/ijo.IJO_1000_17

[18] Brownrigg JR, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence-based management of PAD & the diabetic foot. European Journal of Vascular and Endovascular Surgery. 2013;**45**(6):673-681. DOI: 10.1016/j.ejvs.2013.02.014

[19] Shera AS, Jawad F, Maqsood A. Prevalence of diabetes in Pakistan. Diabetes Research and Clinical Practice. 2007;**76**(2):219-222. DOI: 10.1016/j.diabres.2006.08.011

[20] Basit A, Fawwad A, Qureshi H, Shera AS, NDSP Members. Prevalence of diabetes, pre-diabetes and associated risk factors: Second National Diabetes Survey of Pakistan (NDSP), 2016-2017. BMJ Open. 2018 5;**8**(8):e020961. DOI: 10.1136/bmjopen-2017-020961

[21] Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Plastic and Reconstructive Surgery. 2006;**117**(7 supplement):212S-238S. DOI: 10.1097/01.prs.0000222737.09322.77

[22] Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;**110**(9):1677-1682. DOI: 10.1016/S0161-6420(03)00475-5

[23] Al-Rubeaan K, Al Derwish M, Ouizi S, Youssef AM, Subhani SN, Ibrahim HM, et al. Diabetic foot complications and their risk factors from a large retrospective cohort study. PLoS One. 2015;**10**(5):e0124446. DOI: 10.1371/journal.pone.0124446

[24] Pemayun TGD, Naibaho RM, Novitasari D, et al. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: A hospital-based case-control study. Diabetic Foot Ankle. 2015;**6**:29629. DOI: 10.3402/dfa.v6.29629

[25] Harris Nwanyanwu K, Talwar N, Gardner TW, Wrobel JS, Herman WH, Stein JD. Predicting development of proliferative diabetic retinopathy. Diabetes Care. 2013;**36**(6):1562-1568. DOI: 10.2337/dc12-0790

[26] Al-Mahroos F, Al-Roomi K. Diabetic neuropathy, foot ulceration, peripheral vascular disease and potential risk factors among patients with diabetes in Bahrain: A nationwide primary care diabetes clinic-based study. Annals of Saudi Medicine. 2007;**27**(1):25-31. DOI: 10.4103/0256-4947.51536

[27] Peek ME. Gender differences in diabetes-related lower extremity amputations. Clinical Orthopaedics and Related Research. 2011;**469**(7):1951-1955. DOI: 10.1007/s11999-010-1735-4

[28] Kohner EM, Aldington SJ, Stratton IM, Manley SE, Holman RR, Matthews DR, et al. United Kingdom Prospective Diabetes Study, 30: Diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. Archives of Ophthalmology. 1998;**116**(3):297-303. DOI: 10.1001/archopht.116.3.297

[29] Wang J, Zhang RY, Chen RP, Sun J, Yang R, Ke XY, et al. Prevalence and risk factors for diabetic retinopathy in a high-risk Chinese population. BMC Public Health. 2013;**13**:633. DOI: 10.1186/1471-2458-13-633

[30] Li X, Wang Z. Prevalence and incidence of retinopathy in elderly diabetic patients receiving early diagnosis and treatment. Experimental and Therapeutic Medicine. 2013;**5**(5):1393-1396. DOI: 10.3892/etm.2013.1021

[31] 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**:1036-1042. DOI: 10.2337/diacare.22.7.1036

[32] 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 Research Notes. 2011;**4**:365. DOI: 10.1186/1756-0500-4-365

[33] Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian Journal of Endocrinology and Metabolism. 2016;**20**(4):546-551. DOI: 10.4103/2230-8210.183480