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A study of diabetic retinopathy in diabetic foot syndrome in Western Regional Institute of India

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ABSTRACT

Background: Diabetes is a rapidly growing health challenge and potential epidemic across low-and-middle-income countries like India. Diabetic retinopathy (DR) is a consequence of diabetic microangiopathy, which may cause visual deterioration due to macular edema in any stage and vitreous hemorrhage or tractional retinal detachment in the advanced proliferative retinopathy stages. **Aims and Objectives:** The aim was to study the retinopathy status in diabetic patients with a risk of diabetic foot syndrome (DFS) visiting a western regional hospital in India. **Materials and Methods:** In this cross-sectional study, all patients with diabetes mellitus (DM) with a risk of DFS, visiting a tertiary care hospital during the study period, underwent an ophthalmological evaluation for documentation of their retinopathy status. **Results:** One hundred and fourteen patients diagnosed to have a risk profile for DFS were included in the study. Their mean age was 61.22 years and 81.6% were males. The mean duration of DM was 12.24 years, respectively. Of the 114 patients, 72 had DR. An increased presence of retinopathy in patients with an increased risk grade of diabetic foot (DF) was found significant by the Chi-square test. ($P<0.001$). **Conclusion:** Our study found an increased presence of DR in Western Indian cohort with DFS. The severity of retinopathy was greater in patients with higher grades of risk for DF, therefore establishment of an association between DR and DFS will help in developing an integrated management strategy for these two grave consequences of diabetes.

Key words: Diabetic foot syndrome; Diabetes; Diabetic retinopathy; Retinopathy; Western India

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INTRODUCTION

Diabetes is a rapidly growing health challenge and potential epidemic across low-and-middle-income countries like India.[1] It is projected that by 2025, the number of cases of diabetes in India would be 69.9 million with a vast majority still undiagnosed.[1,2] The diabetic population is growing rapidly and with the advances in the medical field life expectancy has increased, but the disability-free life has decreased.[3] The increase in the duration of the disease is associated with conditions resulting from changes in the microvasculature of the body including nephropathy, neuropathy, and retinopathy.

Diabetic retinopathy (DR) is a consequence of diabetic microangiopathy, which may cause visual deterioration due to macular edema (ME) in any stage and vitreous hemorrhage or tractional retinal detachment in the advanced proliferative retinopathy stages.

Diabetic foot syndrome (DFS) is another important consequence of long-term uncontrolled diabetes, which occurs due to a combination of peripheral neuropathy and micro vasculopathy in the lower limb extremities. A combination of diabetic foot (DF) and retinopathy would affect the population in the working age group the most. This can be avoided by improving methods for early detection and treatment of these complications.

Diabetes can be classified into two broad etiopathogenetic categories. First category, Type 1 diabetes, the cause is an absolute deficiency of insulin secretion such individuals

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at risk can be often identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. The second category Type 2 diabetes which is much more prevalent, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.

The development and progression of DR is primarily caused by the tissue-damaging effects of chronic hyperglycemia that results in a complex interplay of multiple mechanism, which cause two basic changes within the retinal vessels, namely: Abnormal permeability and occlusion with ischemia and subsequent neovascularization.

DR has two main stages, non-proliferative and proliferative. These two stages can be further broken down into four distinct stages: Mild non-proliferative, moderate non-proliferative, severe non-proliferative, and proliferative retinopathy. The longer you have diabetes and the less control you have on your blood sugar put you at a higher risk of developing DR.

Mild non-proliferative retinopathy, The first stage, is the hardest to recognize. Symptoms are mild but may include an increase in blurred vision caused by small bulges in the blood vessels of the retina known as microaneurysms resulting in leakage of the blood vessels. Proper management of blood sugar can delay the development of complications.

Moderate non-proliferative retinopathy – In this stage, blurriness becomes more apparent, and your visual acuity may begin to decline. The blood vessels within the retina begin to swell causing changes to the retina. These physical changes to the retina may lead to diabetic macular edema (DME). DME is when fluid begins to build up in the central-most region of the retina – the macula, affecting your vision.

Severe non-proliferative retinopathy – The third stage of DR is also known as pre-proliferative retinopathy. In this stage, the blood vessels in the retina are blocked, significantly reducing the amount of blood going to the retina. This prevents the retina from functioning properly and triggers a protein called vascular endothelial growth factor (VEGF) to create new blood vessels. Therefore, vision may decline, and you may lose the ability to properly see at night. There is an increase in floaters or dark spots in your field of vision. Treatment will be necessary to slow the progression of further vision loss.

Proliferative DR (PDR) – The final and most advanced stage of DR is very serious. Large areas of the blood vessels in the retina are obstructed preventing the retina from receiving proper nutrients to function. Patients may notice a reduction in their peripheral vision at this stage. In this stage, the retina grows new blood vessels to compensate for the lack of blood flow. This is known as neovascularization. These weak vessels may bleed into the vitreous, known as vitreous hemorrhage causing an increase in dark floaters or complete blockage of vision. In addition, these blood vessels may form scar tissue on the retina leading to a retinal detachment. Vitreous hemorrhage and retinal detachments cause significant loss of vision.

The two most commonly used classification systems for DR are a simplified early treatment DR study (ETDRS) scale and the International Clinical DR Disease Severity Scale.[4]

DME is the accumulation of excess fluid in the extracellular space within the retina in the macular area, typically in the inner nuclear, outer plexiform, Henle's fiber layer, and subretinal space. DME can develop at any stage, but is more frequent as the severity of DR increases. DME threatening or at the fovea is more likely to result in blurred vision and metamorphopsia. DME classifications were based on the ETDRS definitions of clinically significant ME.

Most patients with developed DR have no symptoms until ME or PDR presents. Although panretinal laser photocoagulation and intraocular VEGF inhibitor injection are effective for ME or PDR related visual impairment, they benefit more in preventing visual loss than in reversing deteriorated visual acuity.

DFS is a major complication of diabetes mellitus (DM). The management of DF ulcerations requires interdisciplinary cooperation of diverse medical fields and active exchange between medical and care/assistant professions. For DFS prevalence rates between 4% and 15% have been recorded. Among all possible complications of DM Type 2, DFS is the leading reason for hospitalization. Among all diabetics, the lifetime risk for developing a DF ulceration is 25% of which the majority will need amputation within 4 years of initial diagnosis.[5-8]

Known risk factors for DF ulceration are: Patient age; previous ulceration(s); and sensorimotor diabetic polyneuropathy(s). According to epidemiological data, solely neuropathy is accountable for about 50% of the cases of DFS. Peripheral arterial occlusive disease on its own is accountable for just 15% of the cases, whereas, in 35%, foot ulcerations develop as a combination of both neuropathy and angiopathy.[9-13] The Wagner ulcer classification system by orthopedic staff (P.M.S.) is used to classify DF lesions.[14]

As the diabetic population is rapidly increasing in India, it makes them prone to developing DF ulcers (DFUs) due

to the delayed wound healing and neuropathy caused by DM. DF is most serious and disabling complication of DM resulting in increased morbidity and mortality. DFU is the most common cause of non-traumatic foot amputation worldwide. As the pathogenic mechanism of DR and DFU is the same, it has been studied that most of the people having DFU also have DR.

Hence, all people having DF should undergo a complete ophthalmic evaluation to rule out DR in such patients and if DR is found, the patients should be provided with proper treatment to save them from visual handicap occurring for the same. The current study aims at studying co-existence of DR and DF U and their association between various grades of DFU and DR.

Aims and objectives

The aim was to study the retinopathy status in diabetic patients with a risk of diabetic foot (DF) syndrome visiting a western regional hospital in India.

MATERIALS AND METHODS

This prospective observational study was conducted over the duration of August 2020–August 2022 at the western regional institute of ophthalmology in India. It aimed to investigate the relationship between DFS and its ocular manifestations. The study utilized medical devices including an indirect ophthalmoscope, 20D lens, and dilatation drops. Patient selection criteria were meticulous, with inclusion criteria comprising indoor or outdoor diabetes patients presenting with DF and the presence of other medical comorbidities such as hypertension or renal diseases. The study followed a cross-sectional observational design and enrolled all patients diagnosed with both DM and DFS during the study period. Before enrolment, patients were comprehensively informed about the study and provided written consent. A detailed medical history was taken for each participant. DF grading was conducted using the Michigan neuropathy scoring instrument and methodology aligned with the risk classification of the international working group on the DF (IWGDF).[15] The grading scale was:

- Grade 0: Sensations intact
- Grade 1: Diminution of sensation or loss of protective sensation without deformities and intact blood supply
- Grade 2: Diminished sensation, foot deformities such as hammer toes, claw toes, and/or peripheral arterial disease
- Grade 3: Previous/present ulcer or amputation.

A thorough ophthalmological evaluations were done, encompassing visual acuity assessment using Snellen's chart, anterior segment examination through slit lamp, and dilatation and fundus examination with an indirect ophthalmoscope. Patients with conditions hindering fundus examination, such as corneal opacity or mature cataract, were excluded from the study. The grading of retinopathy was according to the ETDRS classification. In cases of unequal retinopathy, the retinopathy of greater severity was considered for evaluation. Overall, this study's meticulous methodology and comprehensive approach aimed to contribute valuable insights into the management and understanding of diabetic patients, particularly concerning DFS and its ocular manifestations.

RESULTS

In our study, a cohort of 114 patients diagnosed with DF across various grades was examined, with grading conducted following the classification system of the IWGDF. The patient demographic revealed a predominance of males, accounting for 81.6%, while females comprised 18.4%. The mean age of the participants was 61.22 (±6.56) years, with an average diabetes duration of 12.24 (±4.71) years. (Tables 1 and 2) Analysis indicated a correlation between prolonged diabetes duration and increased prevalence of DF severity and retinopathy. Among the participants, 72 individuals exhibited DR.

A significant association was found between the severity of DF and DR (P=0.0163). This shows an increased presence of DR in higher grade of DF (Table 3).

Within the subset of patients with grade 3 DF (57 patients), varying degrees of non-proliferative DR (NPDR) and PDR were observed, with nine displaying mild NPDR, 18 moderate NPDR, eight severe NPDR, and eight exhibiting PDR changes. Notably, the chief complaint among 96% of patients was diminished vision. While 59.65% had no history of ocular surgery, 13.16% underwent bilateral cataract surgery, and 24.16% had unilateral cataract extraction surgery. In addition, three patients underwent pterygium excision surgery. The mean average HbA1c level was measured at 8.92 (±1.28), indicative of long term uncontrolled diabetes. Hypertension was prevalent in 76 out of 114 patients, with 52 of these individuals also presenting with DR. However, no significant association was established between DF and hypertension (P=0.1180). These findings underscore the multifaceted nature of diabetic complications, emphasizing the importance of comprehensive management strategies to mitigate associated risks effectively.

DISCUSSION

The prevalence of DM is rising in India, estimating 80 million and is expected to increase to 135 million by

2045. DM not only reduces quality of life (QOL) and life expectancy but is also a major cause of several microvascular complications and macrovascular complications that lead to blindness, renal failure, myocardial infarction, stroke, and the necessity to amputate limbs. The burden of DM -associated complications worldwide is therefore a major health-care problem that we urgently need to find solutions to. DR usually affects both eyes. The longer a person has diabetes, the more likely they will develop DR. If left untreated, DR can cause blindness. DFU is one of the most serious and disabling complications of DM, resulting in significantly elevated morbidity and mortality. Vascular insufficiency and associated neuropathy are important predisposing factors for DFU, and DFU is the most common cause of non-traumatic foot amputation worldwide.

The fact that the majority (63.16%) of patients with a DFU had DR raises concerns about the impact of this combined disability on patient's QOL. Specifically, increased rates of depression because of a DFU and fear of amputation, lead to a lower QOL. Moreover, psychiatric problems and changes in lifestyle resulting from disability may place unexpected burdens on patients and their families. Moreover, DR has also been reported to decrease QOL the progression of DR into PDR usually causes significant and disabling vision loss, which leads to an even more significant decrease in QOL. Therefore, from a QOL perspective, patients with both a DFU and DR, and particularly those with PDR, are in a very serious condition. We believe that it is essential to refer patients to ophthalmologists when they are diagnosed with a DFU. To prevent any further decrease in QOL, the timely diagnosis and treatment of DR are crucial. These consequences can be avoided by early detection and early treatment of these complications when it is still under control. An association between DFS and DR must be found so that better screening and referral protocols could be initiated which would further help in early detection and treatment of both diseases.

This study consists of 114 patients presenting with DF at western regional institute of India. The mean age was 61.22 years and 82% were male showing an increased prevalence of DFU in males. This is supported by Vishwanath et al.,[18] in South Indian population. The prolonged duration of DM is associated with increased complications. In our study, the mean duration of DM was 12.24 years and 63.16% suffered from DR. The IWGDF guidelines have been used in our study to grade the DF to include pre-ulcerative stages of DF also. In our study 63.16% of patients with DF had DR 20.18% had mild 24.56% had moderate NPDR, 9.65% had severe NPDR and 8.77% had PDR. These contrasts with Hwang et al.,

Table 1: Diabetic duration based on DR

Fundus	n	Minimum	Maximum	Mean	SD
No DR	42	5	25	13.74	5.81
Mild NPDR	23	7	20	10.31	2.68
Moderate NPDR	28	7	16	10.72	2.41
Severe NPDR	11	6	20	11.19	3.98
PDR	10	6	25	15.80	5.54

DR: Diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy: PDR: Proliferative diabetic retinopathy SD: Standard deviation

Table 2: Diabetic duration based on DF

DF	n	Minimum	Maximum	Mean	SD
1	35	5	25	10.74	4.361
2	22	7	17	11.09	2.810
3	57	6	25	13.60	5.151

DF: Diabetic foot, SD: Standard deviation

Table 3: Grading of DR in diabetic foot patients

Fundus	Diabetic foot grade			Total
	1.0	2.0	3.0	
No DR	21	7	14	42
Mild NPDR	7	7	9	23
Moderate NPDR	5	5	18	28
Severe NPDR	1	2	8	11
PDR	1	1	8	10
Total	35	22	57	114

Chi-square: 18.739; P=0.0163, DR: Diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy SD: Standard deviation

who found most of their DF patients to have retinopathy (90%), nearly one-half of which was proliferative (55%). This difference may be on account of a difference in the classification of DF between our studies and the patient selection. In a study done in South India, by Karam et al., DR was seen in 67.58% of patients and 17.88% had PDR changes.[20] In 86 patients of with Grade 3 DF in their study, retinopathy was present in 77.9% out of which 36.04% had site-threatening stages of severe NPDR and PDR.[18]

A few studies have investigated the prevalence of DR in patients with DFU. Shahbazian et al.,[19] showed that 33.3% of patients with a DFU of Grade 1 or higher had DR. We speculate that the reason for the markedly lower prevalence of DR in their study than in ours was due to the younger age (61.22 vs. 56.4 years) and shorter durations of diabetes (12.24 vs. 9.83 years) in their cohort. In our study, 57 patients had grade 3 DF, among which 43 patients had DR with eight patients having PDR and eight patients having severe NPDR, 18 having moderate DR and nine having mild DR. Twenty-two patients had Grade 2 DF. One patient had PDR while 14 had mild to severe NPDR. Thirty-five patients had Grade 1 DF with 21 patients not having DR and 14 having DR. Differences in the ethnicity of the study population may contribute to the disparity

of the result. In our study, a significant association was found between DF and DR with (P=0.0163). Seventy-six patients out of 114 patients had hypertension with 52 patients having DR. Forty-one patients with Grade 3 DF had hypertension but no significant association was found between DFU and hypertension (P>0.05).

Retinopathy is considered to be a risk factor for worsening of DF.[19] Conversely, the presence of DF is a predictor for progress to the proliferative stages of DR.[20] A statistically significant association between the presence of retinopathy in advanced grades of DF was noted in the present study. The severity of the retinopathy was also found to be greater in patients with higher grades of DF. Hwang et al., too noted a similar association of proliferative retinopathy and DF. They speculate it to be a result of increased oxidative stress and endothelial damage.

Our study also stresses the importance of multidisciplinary approach in the management of diabetes and its complications. Patients with DFU should be evaluated for DR and ophthalmologists should be referring patients with DR, especially severe NPDR and PDR to a podiatrist for DFU evaluation, which will prevent complications of DR and DFU.

Limitations of the study

Limitations of our study lies in small sample size and hospital-based set-up. Further population-based studies with large sample sizes can reaffirm our findings.

CONCLUSION

With rising diabetic population, dreaded complications like DFS and DR are also on rise. The data showing the relationship between these two complications are still inadequate among the Indian population. India is headed to become the diabetic capital of the world in future. With the increased prevalence rate and an increase in rate of various complications, the QOL is severely affected. With recent medical advances, the life span has increased considerably with an impact on QOL. Hence this study is based on trying to find association between DF and DR to help detect them and treat them at early stage and decrease morbidity. As both these complications, it can produce visual and/or physical handicap.

A determined and well-planned strategy would be needed to be incorporated as an integrated approach to prevent complications due to diabetes. The result of our study supports the need of a system where an ophthalmologist and surgeon/physician specialist in DF would work as a unit. This would support an ophthalmology referral in DF patients and a DF specialist referral when DR is diagnosed.

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SSE- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **VKP**- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **NJP**- Design of study, statistical analysis and interpretation; **KYT**- Coordination and manuscript revision, review manuscript; **NPS**- Review manuscript; **SSE**- Literature survey and preparation of figures; **SHR**- Coordination and manuscript revision**; PYN**- Review manuscript; **NDL**- Review manuscript.

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