



## Evaluation of different dermatological lesions in diabetic patients suffered from diabetic retinopathy

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### Abstract

Metabolic abnormalities of insulin and elevated blood glucose level leads to multiple vascular, neurological and immunological abnormalities mainly affecting cardiovascular, renal and nervous systems, eyes and the skin. Although the mechanism for many diabetes associated skin problems remains unknown, the pathogenesis is multifactorial, possibly linked to abnormal carbohydrate metabolism, altered metabolic pathways resulting in atherosclerosis, microangiopathy, neuron degeneration along with impaired host mechanisms [3]. The skin is a temporary reservoir for excess blood glucose which accounts for tendency to develop pruritus and both bacterial and fungal infections. The association of certain skin diseases with diabetes mellitus has been fairly well recognized. Hence based on above finding present study was planned for Evaluation of Different Dermatological Lesions in Diabetic Patients Suffered from Diabetic Retinopathy.

The present study was planned in Department of Ophthalmology Patna Medical College & Hospital, Patna, Bihar, India. The study was conducted from October 2018 to December 2018. In the present study 25 cases of the diabetic retinopathy suffered from the dermatological lesions were enrolled in the present study. The dermatological examination was done by a dermatologist under proper day light and if needed, using handheld magnifying lens. Examination of the retina was done by an Ophthalmologist using indirect ophthalmoscopy of dilated fundus, fundus photo, fundus fluorescein angiography and optical coherence tomography of the macula. Relevant microbiological and histopathological investigations were carried out to confirm the clinical diagnosis of cutaneous manifestation.

The data generated from the present study concludes that Increasing prevalence of diabetes mellitus, is associated with increased frequency of cutaneous infections as well as diabetes-related dermatoses in general population. Dermatologic manifestation is a highly prevalent complication of diabetes mellitus, severity is directly proportionate with duration, compliance to treatment and glycaemic control of diabetes mellitus.

**Keywords:** dermatological lesions, diabetic, diabetic retinopathy, etc

### Introduction

Diabetic retinopathy is a major cause of blindness, particularly among working-age adults. The degree of retinopathy is highly correlated with Duration of diabetes, Blood glucose levels & BP levels. Nonproliferative retinopathy (also called background retinopathy) develops first and causes increased capillary permeability, microaneurysms, hemorrhages, exudates, macular ischemia, and macular edema (thickening of the retina caused by fluid leakage from capillaries).

Proliferative retinopathy develops after nonproliferative retinopathy and is more severe; it may lead to vitreous hemorrhage and traction retinal detachment. Proliferative retinopathy is characterized by abnormal new vessel formation (neovascularization), which occurs on the inner (vitreous) surface of the retina and may extend into the vitreous cavity and cause vitreous hemorrhage. Neovascularization is often accompanied by preretinal fibrous tissue, which, along with the vitreous, can contract, resulting in traction retinal detachment. Neovascularization may also occur in the anterior segment of the eye on the iris; neovascular membrane growth in the anterior chamber angle of the eye at the peripheral margin of the iris can occur, and this growth leads to neovascular glaucoma. Vision loss with

proliferative retinopathy may be severe.

Diabetes mellitus (DM) is a major medical problem throughout the world. Diabetes causes an array of long-term systemic complications that have considerable impact on the patient as well as society, as the disease typically affects individuals in their most productive years. An increasing prevalence of diabetes is occurring throughout the world. In addition, this increase appears to be greater in developing countries. The etiology of this increase involves changes in diet, with higher fat intake, sedentary lifestyle changes, and decreased physical activity [1].

Diabetic retinopathy often has no early warning signs. Even macular edema, which can cause rapid vision loss, may not have any warning signs for some time. In general, however, a person with macular edema is likely to have blurred vision, making it hard to do things like read or drive. In some cases, the vision will get better or worse during the day.

The first stage, called non-proliferative diabetic retinopathy (NPDR), has no symptoms. Patients may not notice the signs and have 20/20 vision. The only way to detect NPDR is by fundus photography, in which microaneurysms (microscopic blood-filled bulges in the artery walls) can be seen. If there is reduced vision, fluorescein angiography can

show narrowing or blocked retinal blood vessels clearly (lack of blood flow or retinal ischemia).

Macular edema, in which blood vessels leak their contents into the macular region, can occur at any stage of NPDR. Its symptoms are blurred vision and darkened or distorted images that are not the same in both eyes. Ten percent (10%) of diabetic patients will have vision loss related to macular edema. Optical Coherence Tomography can show areas of retinal thickening due to fluid accumulation from macular edema.

In the second stage, abnormal new blood vessels (neovascularisation) form at the back of the eye as part of proliferative diabetic retinopathy (PDR); these can burst and bleed (vitreous hemorrhage) and blur the vision, because these new blood vessels are fragile. The first time this bleeding occurs, it may not be very severe. In most cases, it will leave just a few specks of blood, or spots floating in a person's visual field, though the spots often go away after a few hours.

These spots are often followed within a few days or weeks by a much greater leakage of blood, which blurs the vision. In extreme cases, a person may only be able to tell light from dark in that eye. It may take the blood anywhere from a few days to months or even years to clear from the inside of the eye, and in some cases the blood will not clear. These types of large hemorrhages tend to happen more than once, often during sleep. On fundoscopic exam, a doctor will see cotton wool spots, flame hemorrhages (similar lesions are also caused by the alpha-toxin of *Clostridium novyi*), and dot-blot hemorrhages.

Patients with diabetes often develop ophthalmic complications, such as corneal abnormalities, glaucoma, iris neovascularization, cataracts, and neuropathies. The most common and potentially most blinding of these complications, however, is diabetic retinopathy, which is, in fact, the leading cause of new blindness in persons aged 25-74 years in the United States. Approximately 700,000 persons in the United States have proliferative diabetic retinopathy, with an annual incidence of 65,000. An estimate of the prevalence of diabetic retinopathy in the United States showed a high prevalence of 28.5% among those with diabetes aged 40 years or older<sup>[2]</sup>.

The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease<sup>[3]</sup>.

In the initial stages of diabetic retinopathy, patients are generally asymptomatic, but in more advanced stages of the disease patients may experience symptoms that include floaters, distortion, and/or blurred vision. Microaneurysms are the earliest clinical sign of diabetic retinopathy. Renal disease, as evidenced by proteinuria and elevated blood urea nitrogen (BUN)/creatinine levels, is an excellent predictor of retinopathy; both conditions are caused by DM-related microangiopathies, and the presence and severity of one reflects that of the other. Aggressive treatment of the nephropathy may slow progression of diabetic retinopathy and neovascular glaucoma.

A study by Ito et al. indicated that in patients with type 2 diabetes, the presence of reduced peripheral nerve conduction velocity is associated with the existence of early diabetic retinopathy. The report included 42 patients with type 2 diabetes (42 eyes), who had either no diabetic retinopathy or mild nonproliferative diabetic retinopathy. The investigators found that the latter group had

significantly lower sural sensory conduction velocity and tibial motor conduction velocity than did patients with no diabetic retinopathy, with logistic regression analysis showing these velocities to be independent risk factors for the mild nonproliferative eye disease. The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease<sup>[4]</sup>.

Growth hormone appears to play a causative role in the development and progression of diabetic retinopathy. Diabetic retinopathy has been shown to be reversible in women who had postpartum hemorrhagic necrosis of the pituitary gland (Sheehan syndrome). This led to the controversial practice of pituitary ablation to treat or prevent diabetic retinopathy in the 1950s. This technique has since been abandoned because of numerous systemic complications and the discovery of the effectiveness of laser treatment. It should be noted that diabetic retinopathy has been reported in patients with hypopituitarism as well.

The variety of hematologic abnormalities seen in diabetes, such as increased erythrocyte aggregation, decreased red blood cell deformability, increased platelet aggregation, and adhesion, predispose the patient to sluggish circulation, endothelial damage, and focal capillary occlusion. This leads to retinal ischemia, which, in turn, contributes to the development of diabetic retinopathy.

Fundamentally, diabetes mellitus (DM) causes abnormal glucose metabolism as a result of decreased levels or activity of insulin. Increased levels of blood glucose are thought to have a structural and physiologic effect on retinal capillaries causing them to be both functionally and anatomically incompetent.

A persistent increase in blood glucose levels shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (eg, glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of their primary function (ie, autoregulation of retinal capillaries). This results in weakness and eventual saccular outpouching of capillary walls. These microaneurysms are the earliest detectable signs of DM retinopathy.

In patients with proliferative diabetic retinopathy (PDR), nocturnal intermittent hypoxia/reoxygenation that results from sleep-disordered breathing may be a risk factor for iris and/or angle neovascularization<sup>[5]</sup>.

Neovascularization is most commonly observed at the borders of perfused and nonperfused retina and most commonly occurs along the vascular arcades and at the optic nerve head. The new vessels break through and grow along the surface of the retina and into the scaffold of the posterior hyaloid face. By themselves, these vessels rarely cause visual compromise, but they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.

These new blood vessels initially are associated with a small amount of fibroglial tissue formation. However, as the density of the neovascular frond increases, so does the degree of fibrous tissue formation.

In later stages, the vessels may regress, leaving only networks of avascular fibrous tissue adherent to both the retina and the posterior hyaloid face. As the vitreous contracts, it may exert tractional forces on the retina via

these fibroglial connections. Traction may cause retinal edema, retinal heterotropia, and both tractional retinal detachments and retinal tear formation with subsequent detachment.

In patients with type I diabetes, no clinically significant retinopathy can be seen in the first 5 years after the initial diagnosis of diabetes is made. After 10-15 years, 25-50% of patients show some signs of retinopathy. This prevalence increases to 75-95% after 15 years and approaches 100% after 30 years of diabetes. Proliferative diabetic retinopathy (PDR) is rare within the first decade of type I diabetes diagnosis but increases to 14-17% by 15 years, rising steadily thereafter.

In patients with type II diabetes, the incidence of diabetic retinopathy increases with the disease duration. Of patients with type II diabetes, 23% have nonproliferative diabetic retinopathy (NPDR) after 11-13 years, 41% have NPDR after 14-16 years, and 60% have NPDR after 16 years.

Systemic hypertension, in the setting of diabetic nephropathy, correlates well with the presence of retinopathy. Independently, hypertension also may complicate diabetes in that it may result in hypertensive retinal vascular changes superimposed on the preexisting diabetic retinopathy, further compromising retinal blood flow.

Proper management of hyperlipidemia (elevated serum lipids) may result in less retinal vessel leakage and hard exudate formation, but the reason behind this is unclear.

Pregnant women with proliferative diabetic retinopathy do poorly without treatment, but those who have had prior panretinal photocoagulation remain stable throughout pregnancy. Pregnant women without diabetic retinopathy run a 10% risk of developing NPDR during their pregnancy: of those with preexisting NPDR, 4% progress to the proliferative type [6].

A study by Toda et al. found that among pregnant women with diabetic retinopathy, those who showed progression of the eye disorder tended to have a longer duration of diabetes, to have had diabetic retinopathy prior to pregnancy, and to have higher blood pressure in the second trimester [7].

Of the approximately 16 million Americans with diabetes, 50% are unaware that they have it. Of those who know they have diabetes, only half receive appropriate eye care. Thus, it is not surprising that diabetic retinopathy is the leading cause of new blindness in persons aged 25-74 years in the United States. Approximately 700,000 Americans have proliferative diabetic retinopathy, with an annual incidence of 65,000. Approximately 500,000 persons have clinically significant macular edema, with an annual incidence of 75,000.

Diabetes is responsible for approximately 8000 eyes becoming blinded each year, meaning that diabetes is responsible for 12% of blindness [8]. The rate is even higher among certain ethnic groups. An increased risk of diabetic retinopathy appears to exist in patients of Native American, Hispanic, and African American heritage. With increasing duration of diabetes or with increasing age since its onset, there is a higher risk of developing diabetic retinopathy and its complications, including diabetic macular edema or proliferative diabetic retinopathy. Nonetheless, a literature review by Sabanayagam et al. indicated that although the prevalence of diabetes has increased worldwide, the incidence of diabetic retinopathy-related blindness has

fallen, especially in developed nations [9].

Metabolic abnormalities of insulin and elevated blood glucose level leads to multiple vascular, neurological and immunological abnormalities mainly affecting cardiovascular, renal and nervous systems, eyes and the skin. Although the mechanism for many diabetes associated skin problems remains unknown, the pathogenesis is multifactorial, possibly linked to abnormal carbohydrate metabolism, altered metabolic pathways resulting in atherosclerosis, microangiopathy, neuron degeneration along with impaired host mechanisms 3. The skin is a temporary reservoir for excess blood glucose which accounts for tendency to develop pruritus and both bacterial and fungal infections. The association of certain skin diseases with diabetes mellitus has been fairly well recognized. Hence based on above finding present study was planned for Evaluation of Different Dermatological Lesions in Diabetic Patients Suffered from Diabetic Retinopathy.

### Methodology

The present study was planned in Department of Ophthalmology Patna Medical College & Hospital, Patna, Bihar, India. The study was conducted from October 2018 to December 2018. In the present study 25 cases of the diabetic retinopathy suffered from the dermatological lesions were enrolled in the present study. The dermatological examination was done by a dermatologist under proper day light and if needed, using handheld magnifying lens. Examination of the retina was done by an Ophthalmologist using indirect ophthalmoscopy of dilated fundus, fundus photo, fundus fluorescein angiography and optical coherence tomography of the macula. Relevant microbiological and histopathological investigations were carried out to confirm the clinical diagnosis of cutaneous manifestation.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

**Inclusion Criteria:** Patients having diabetic retinopathy having diabetes mellitus.

**Exclusion Criteria:** Patients suffering from ophthalmological conditions like hypertensive retinopathy, vascular occlusion and advanced cataract that may affect the findings were excluded from the study.

### Results & Discussion

Diabetes mellitus (DM) is the most common endocrine disorder characterized by hyperglycemia. Global estimate of type 2 diabetics in the year 2030 is likely to be 552 million. The International Diabetes Federation (IDF) documents the total number of diabetic subjects to be around 61.3 million in India and this is further set to raise to 101.2 million by the year 2030. While all other complications of diabetes have been extensively studied, the aspect of dermatological complications is relatively unexplored.

Dermatologic manifestation is commonly seen in diabetes mellitus which affects quality of life. The manifestations are varied from simple lesions, infections to life threatening conditions as diabetic foot, etc. Whenever patients present with multiple skin manifestations, their diabetic status

should be checked because many a times these manifestations can serve as diagnostic marker for underlying diabetes. As the duration of diabetes increased, the likelihood of developing skin manifestations also increases. Early diagnosis and appropriate management can prevent disability caused by these complications.

Cutaneous signs of diabetes mellitus generally appear after the primary disease has developed but may appear coincidentally with its onset, or even precede diabetes by many years. Although the mechanism for many diabetes-associated skin conditions remains unknown, the pathogenesis of others is linked to abnormal carbohydrate metabolism, other altered metabolic pathways, atherosclerosis, microangiopathy, neuron degeneration, and impaired host mechanisms [10]. Association of at least 30% of patients with diabetes mellitus with some type of cutaneous involvement was observed during the course of their chronic disease [11].

**Table 1:** Demographic Details

Parameters	No. of Cases
Age	
21 – 30 years	1
31 – 40 years	4
41 – 50 years	11
51 – 60 years	6
61 & above years	3
Sex	
Males	13
Females	12
Total	25

**Table 2**

Parameters	Observed in No. of Cases
Very mild NPDR	1
Mild NPDR	3
Moderate NPDR	8
Severe NPDR	2
PDR	4
CSME	7

**Table 3:** Most prevalent Dermatological lesions

Parameters	Observed in No. of Cases
Diabetic dermopathy (shin spots)	10
Xerosis	8
IGH	7
Ichthyosis	6
Intertrigo	2
Tinea Versicolor	1
Chronic Paronychia	1
Tinea Unguium	1

**Table 4:** Less prevalent Dermatological lesions

Parameters	Observed in No. of Cases
Eczema	2
Melasma	1
Lichen Amyloidosis	1
Varicose veins	1
Fissure feet	1
Sclerodactyly	1
Plain warts	1

Xerosis can ranged from mild skin dryness with minimal scales to severe dry skin with profuse scaling, asteatotic

dermatitis. Advanced glycation products of proteins in the stratum corneum, as well as autonomic neuropathy, have been attributed to the pathogenesis of xerosis can be linked to advanced glycation products of proteins in the stratum corneum, autonomic neuropathy which are commonly seen in diabetes [12]. Loss of hair over shin was due to vascular changes in uncontrolled, long standing diabetes such as macroangiopathy and peripheral vascular disease Diabetic dermopathy is the common manifestation presenting as single or multiple well-demarcated brown atrophic macules, predominantly on the shins.

Pathophysiology of skin disorders in diabetes is poorly understood [13]. Skin disorders in diabetes is caused by either diabetes induced metabolic changes in skin or by associated complications like vasculopathy and neuropathy. Diabetic complications are caused by direct damage caused by hyperglycemia and also by hyperglycemia induced non-enzymatic glycosylation of structural and regulatory proteins, lipids and nucleic acids. This causes accumulation of advanced glycosylation products (AGE) [14].

Specific receptors are present in many cell surfaces for the AGE. This initiates the different intracellular signaling cascade that can cause the diabetic complications. This AGE causes inhibition of keratinocyte proliferation and migration, protein biosynthesis, inducing endothelial cell apoptosis, decreasing nitric oxide synthesis and impairing phagocytosis and chemotaxis from several cells [15]. Also AGE act in several ways, causing reactive oxygen species (ROS) formation, impairing ROS clearance, as well as intra and extracellular proteins dysfunction thus inducing pro inflammatory cytokines through nuclear factor  $\kappa\beta$  (NF- $\kappa\beta$ ) pathway [16]. They alters collagen properties by decreasing flexibility and solubility and increasing its rigidity [17].

Also, AGEs plays a major role in the development of fibrosis in DM [17], in skin aging [15], and in diabetes-related immunosuppression [18]. This Diabetes-related immunosuppression affects skin wound healing by leukocyte impaired function and malfunction of growth factors [19]. Bertheim et al. showed that diabetic patients with severe joint mobility on the hands had an increased epidermal thickness, with abnormal hyaluronic acid distribution on skin layers [20]. Due to altered action of insulin on keratinocyte proliferation, differentiation and migration it causes impaired epidermal barrier function and delayed wound healing [21, 23]. Also skin surface pH in intertriginous regions of diabetics is significantly elevated compared to non-diabetic patients [24]. In additional normal stratum corneum hydration, reduced sebaceous gland activity and altered skin elasticity is noted [25].

Opinion is divided regarding this issue. According to an Indian study in 2008 [26], no correlation was demonstrated between glucose control and dermatologic manifestations. But an Iranian study [27] as well as a study by Rayfield [28] showed definite relationship between foot ulcers and fungal infections with HbA1C levels.

Other skin manifestations were also noted in small amount. There is a definite association between diabetes mellitus and dermatological diseases. A good glycemic control reduces the incidence and severity of cutaneous disorders with or without known pathogenesis. Diabetes mellitus has a detrimental effect on microcirculation and dermal collagen which plays major role in skin disorders in diabetic patients. Dermatological morbidity can be reduced by early diagnosis and treatment which will eventually improve quality of life,

in diabetic patients.

Diabetes Mellitus involves the skin quite often and whenever patients present with multiple skin manifestations; their diabetic status should be checked. Many of these manifestations, especially the more common ones, might be explained on the basis of the attachment of glucose to proteins, and the subsequent metabolism of this combination, which results in changes in structure, function and colour.

### Conclusion

The data generated from the present study concludes that Increasing prevalence of diabetes mellitus, is associated with increased frequency of cutaneous infections as well as diabetes-related dermatomes in general population. Dermatologic manifestation is a highly prevalent complication of diabetes mellitus, severity is directly proportionate with duration, compliance to treatment and glycaemic control of diabetes mellitus.

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