



Original Article

Study of relationship between diabetic retinopathy and coronary disease among type 2 diabetic patients

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ABSTRACT

Introduction-Diabetes mellitus (DM) is a type of chronic metabolic disease, which is marked by persistent hyperglycemia caused by impaired insulin secretion, insulin action, or both [1]. It has become a significant health issue in the world, developing countries have a significant contribution to disease burden. Recently, the number of diabetics in the world has shot up, with a significant proportion going to the low- and middle-income nations [2]. **Material and Methods**-Study Design-The present study was conducted as a hospital-based cross-sectional observational study to evaluate the relationship between diabetic retinopathy and coronary artery disease among patients with Type 2 Diabetes Mellitus. Study Setting-The study was carried out in the Department of General Medicine, in collaboration with the Departments of Ophthalmology and Cardiology, at Sri Aurobindo Institute of Medical Sciences and Post Graduate Institute (SAIMS), Indore, Madhya Pradesh, which is a tertiary care teaching hospital catering to a large patient population. Study Duration-The study was conducted over a period of 18 months. **Result**-There was also a significant correlation between the severity of diabetic retinopathy and the coronary artery disease ($p=0.009$), and a variety of abnormalities, such as RWMA ($p=0.003$), LV systolic dysfunction ($p=0.011$), LV diastolic dysfunction ($p=0.021$), and several others including MR ($p=0.019$), TR ($p=0.018$), LVH ($p=0.005$), RV dysfunction ($p=0.002$), PAH ($p=0.001$), and pericardial effusion ($p=0.014$). These observations indicate that progressive levels of diabetic retinopathy are strongly related to the rise of burden of coronary artery diseases and heart dysfunction pointing to diabetic retinopathy as a key indicator of systemic cardiovascular pathology in Type 2 Diabetes Mellitus.

Conclusion-Retinopathy in diabetic patients was discovered to have a strong correlation with coronary cardiac disease and various heart related defects. The study participants had a high burden of myocardial dysfunction that was determined through the use of echocardiography. Motion abnormalities of the regional walls, left ventricular systolic dysfunction, ejection fraction reduction, dysfunction of the diastole, the abnormalities of the valves, ventricular hypertrophy, dysfunction of the right ventricle, hypertension of the pulmonary arteries, and effusion of the pericardium were much more prevalent in the patients with advanced diabetic retinopathy. Regular cardiovascular examinations of patients with diabetic retinopathy can help to early diagnose those at risk so that they can be timely addressed and better shield against poor cardiovascular prognosis.

Keywords: Type 2 Diabetes Mellitus, Diabetic Retinopathy, Coronary Artery Disease, Cardiovascular Dysfunction, Echocardiography.

INTRODUCTION

Diabetes mellitus (DM) is a type of chronic metabolic disease, which is marked by persistent hyperglycemia caused by impaired insulin secretion, insulin action, or both [1]. It has become a significant health issue in the world, developing countries have a significant contribution to disease burden. Recently, the number of diabetics in the world has shot up, with a significant proportion going to the low- and middle-income nations [2]. Through genetic vulnerability, swift urbanization, as well as the changes in lifestyle, such as diet and increased inactivity, India and China alone have almost a third of all cases of diabetes worldwide [2,3]. This burden is further compounded by the Asian Indian phenotype typified by insulin resistance, central obesity, and a greater activity in metabolic and cardiovascular complications [4].

Traditional cardiovascular risk prediction tools like the Framingham risk score and the UKPDS risk engine have proven to be less than ideal in patients with diabetes. Because of complicated interactions of metabolic and vascular factors that are specific to diabetes, these models fail to properly predict cardiovascular risk. This means that there is a dire need to have better predictive algorithms that can more effectively stratify cardiovascular risk in diabetic patients [5,6]. Currently used models of predicting CAD among diabetic people are still not accurate and applicable in the clinical practice, which only underscores the importance of other kinds of markers [7].

Diabetic retinopathy pathogenesis is characterized by the damage or damage of the retinal microvasculature under the influence of chronic hyperglycemia to its capillary leakage, the formation of microaneurysms, retinal ischemia, and neovascularization. These transformations are mediated by various biochemical pathways, which comprise formation of advanced glycation end-products, oxidative stress, protein kinase Cs activation, and inflammation of low grades. Notably, these processes are not limited to the retina, but rather are evidence of a generalized microangiopathic process of various vascular beds [8].

Pathophysiology between diabetic retinopathy and coronary artery disease is complicated and multifactorial. There are similar underlying mechanisms that exist in both diseases, such as oxidative stress, endothelial dysfunction, chronic inflammation, and microvascular rarefaction. These common pathways can justify the common soil hypothesis, which views that microvascular and macrovascular complications of diabetes develop because of analogous metabolic disruptions [8]. Therefore, diabetic retinopathy can be a surrogate outcome of a systemic vascular disease, as the overall burden of atherosclerosis.

Thus, the current research was conducted in order to find out the connection between coronary artery disease and diabetic retinopathy among individuals with Type 2 Diabetes Mellitus. This study will examine the relationship between the severity of diabetic retinopathy and the presence of a coronary artery disease and examine clinico-epidemiological profile of patient and determine cardiovascular involvement in diabetic retinopathy. This strategy could help to enhance the process of risk stratification and clinical outcomes of diabetic patients.

Aims and Objective:

Aim:

To study relationship between diabetic retinopathy and coronary artery disease among Type 2 diabetic patients

Objectives:

1. To study clinico-epidemiological profile of patients of diabetic retinopathy.
2. To assess coronary artery disease in all diabetic retinopathy patients.
3. To associate occurrence of coronary artery disease with different stages of diabetic retinopathy among type 2 diabetic patients.

BACKGROUND

Definition and Classification of Diabetes Mellitus: Diabetes mellitus (DM) is a collection of metabolic diseases, which includes a chronic state of hyperglycemia caused by insulin secretion and/or interaction problems. Chronic high weretes of blood glucose cause changes in carbohydrate, lipid and protein metabolism and ultimately causes structural and functional impairment of various organ systems especially of the retina, renal, peripheral neural, cardiac, and vascular systems. With the alarming rate of socioeconomic changes, westernized lifestyles in India has led to the increasing prevalence of diabetes in this country. As epidemiological studies have indicated, there are higher prevalence rates in urban population although rural areas are experiencing a gradual increase in disease occurrence as well.[|human|>The prevalence rates have been found to be more in the urban population, but in rural areas, an increase in disease prevalence has also gradually been noted.

Indian studies have shown that diabetes is more prone to occur in a young age and a low body mass index of South Asians than the Western population. This puts the patients at risk of a long-term duration of the disease and severe development of vascular complications early on[9].

DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is a progressive microvascular complication of diabetes mellitus due to damage to blood vessels of the retina resulting from chronic hyperglycemia. It is described as high vascular permeability, measureable capillary obstruction, neovascularization of the retina, and retinal ischemia. DR still continues to cause one of the highest rates of preventable blindness in working-age adults on a global basis[10]. DR is essentially divided into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is the initial phase and is marked by microaneurysms, retinal hemorrhages, hard exudates, as well as cotton wool spots. PDR is an advanced form of the disease and is defined by neovascularization which is brought about by retinal ischemia, and elevated production of vascular endothelial growth factor (VEGF) [11].

Pathogenesis of Diabetic Retinopathy-The DR pathogenesis is a combination of several biochemical and hemodynamic dysfunctions predetermined by the chronic hyperglycemia. Chronic hyperglycemia leads to the impairment of endothelial function, basement membrane hypertroph, pericyte destruction, superoxide anaerobic stress, and retinal ischemia.[12].

Clinical Features and Diagnosis-Cases of early DR can take years before the appearance of symptoms. In serious cases, the visual symptoms tend to arise because of the edema of the macula, bleeding of the vitreous, retinal detachment or ischemia [13].

Diagnosis continues to be based on fundoscopy. Retinal changes involve microaneurysms, dot and blot bleeds, cotton wool spots, venous beading, intraretinal microvascular defects and neovascularization.[14].

Importance of Combined Screening in Type 2 Diabetes Mellitus

DR plus CAD screening is clinically significant since the two complications often go hand in hand in patients with diabetes. Timely trained retinal screening can improve the detection of those that are at increased risk of cardiovascular disease which can be followed up by timely intervention to avert cardiovascular disease.

Material and Methods

Study Design

The present study was conducted as a **hospital-based cross-sectional observational study** to evaluate the relationship between diabetic retinopathy and coronary artery disease among patients with Type 2 Diabetes Mellitus.

Study Setting-The study was carried out in the **Department of General Medicine**, in collaboration with the **Departments of Ophthalmology and Cardiology**, at **Sri Aurobindo Institute of Medical Sciences and Post Graduate Institute (SAIMS), Indore, Madhya Pradesh**, which is a tertiary care teaching hospital catering to a large patient population.

Study Duration-The study was conducted over a period of **18 months**

Study Population-The study population comprised patients diagnosed with **Type 2 Diabetes Mellitus with diabetic retinopathy**, attending the **Outpatient Department (OPD) and Inpatient Department (IPD)** of the Department of General Medicine at SAIMS during the study period. Eligible patients fulfilling the inclusion and exclusion criteria were enrolled in the study.

Sample Size-The sample size for the present study was determined based on previously published literature evaluating the association between diabetic retinopathy and coronary artery disease among patients with Type 2 Diabetes Mellitus. The calculation was performed using standard statistical methods for estimating sample size in observational studies involving proportions and odds ratios.

Thus, a total of **150 patients with Type 2 Diabetes Mellitus and diabetic retinopathy** were included in the study to achieve sufficient statistical power and to allow meaningful analysis of the association between diabetic retinopathy and coronary artery disease.

Selection Criteria

Inclusion Criteria

- Patients aged **more than 18 years**
- Diagnosed cases of **Type 2 Diabetes Mellitus**
- Presence of **diabetic retinopathy confirmed on fundus examination**

- Patients who provided **written informed consent**

Exclusion Criteria

- Duration of diabetes mellitus less than **1 year**
- **Uncontrolled hypertension** (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg despite optimal therapy)
- Patients with **known non-diabetic retinal diseases**
- Patients who did not provide consent for participation

RESULTS

The current cross-sectional observational study in the hospital was undertaken at the Outpatient Department (OPD) and Inpatient Department (IPD) of the Department of General Medicine of Sri Aurobindo Institute of Medical Sciences and Post Graduate Institute (SAIMS), Indore among 115 patients who reported with Type 2 Diabetes Mellitus and diabetic retinopathy. Every patient that meets the inclusion and exclusion criteria were clinically, biochemically, ophthalmologically, electrocardiographically, and echocardiographically assessed to determine if there exists a correlation between diabetic retinopathy and coronary artery disease.

Table 1: Distribution of Duration of Diabetes Mellitus (n = 115)

Duration of Diabetes Mellitus	Number of Patients	Percentage (%)
<1 year	21	18.3
1–5 years	56	48.7
6–10 years	25	21.7
>10 years	13	11.3
Total	115	100

Mean duration of diabetes mellitus: 6.8 ± 5.9 years

Most of the patients had diabetes of between 1-5 years (48.7%), and 6-10 years (21.7%). The study population was 18.3% diabetic patients with a duration of less than 1 year and 11.3% with diabetes duration of more than 10 years. Poor diabetic retinopathy and coronary artery disease were linked with increasing period of diabetes.

Table 2: Hypertension Distribution of Study Population (n = 115)

Hypertension	Number	Percentage (%)
Present	58	50.4
Absent	57	49.6
Total	115	100

One of the key comorbidities that were found during the research was hypertension. Among 115 patients, 58 patients (50.4%) were hypertensive, 57 patients (49.6%) were normotensive. Hypertension also plays an important role in terms of cardiovascular risk in patients with diabetic retinopathy and could lead to microvascular and macrovascular complications developmental progression.

Table 3: Distribution of HbA1c Levels (n = 115)

HbA1c Level (%)	Number of Patients	Percentage (%)
<7%	24	20.9
7–10%	56	48.7
>10%	35	30.4
Total	115	100

Almost fifty percent of the patients (48.7%) had an HbA1c of 7.1 percent and 30.4 percent had an HbA1c of above 10 percent demonstrating chronic, uncontrolled diabetes mellitus.

Table 4: Distribution of Total Cholesterol Levels (n = 115)

Total Cholesterol (mg/dL)	Number of Patients	Percentage (%)
<200	83	72.2
≥200	32	27.8
Total	115	100

Majority of patients (72.2%) had a total cholesterol level lower than 200 mg/dl and 27.8% patients had hypercholesterolemia.

Table 5: Distribution of Diabetic Retinopathy

DR Stage	Number	Percentage (%)
R0 – No Retinopathy	84	73.0
R1 – Background DR	8	7.0
R2 – Pre-proliferative DR	23	20.0
Total	115	100

Most of the patients were under the classification of the R0 -No Retinopathy (73.0%). Pre-proliferative diabetic retinopathy (R2) was detected in 20.0% of the patients, and background diabetic retinopathy in 7. 0% patients (R1). The implications of such findings are that the proportion of diabetic patients with retinal microvascular changes was recurrent, indicating that with disease burden there progression of diabetic retinal involvement.

Table 6: Prevalence of Coronary Artery Disease Among Study Participants (n = 115)

Coronary Artery Disease	Number of Patients	Percentage (%)
Present	75	65.2
Absent	40	34.8
Total	115	100

Sixty-eight percent (65.2) of 115 patients were found to have coronary artery disease and 40 patients (34.8) had no CAD. The prevalence of coronary artery disease as shown in the present study reflects a high degree of association amid diabetic retinopathy and cardiovascular involvement. The findings substantiate the idea that diabetic retinopathy can be a helpful clinical predictor of systemic vascular disease, and underlying coronary atherosclerosis in Type 2 Diabetes Mellitus patients.

Table 7: Distribution of ECG Findings Among Study Participants (n = 115)

ECG Findings	Number of Patients	Percentage (%)
ACS-Anterior Wall Myocardial Infarction (AWMI)	39	33.9
ACS-Inferior Wall Myocardial Infarction (IWMI)	17	14.8
ACS-Non-ST Elevation Myocardial Infarction (NSTEMI)	13	11.3
Unstable Angina (UA)	6	5.2
Extensive / Evolving AWMI	5	4.3
IWMI with RVMI	4	3.5
IWMI with PWMI / IPWMI	3	2.6
AWMI with PWMI / IWMI	2	1.7
Posterior Wall MI (PWMI)	1	0.9
Right Ventricular MI (RVMI)	1	0.9
Lateral / Anterolateral Wall MI	2	1.7
Old CAD / Old MI Changes	4	3.5
LMCA Pattern	1	0.9
Conduction Abnormalities (LBBB/RBBB/Mobitz Block)	3	2.6
NSR with CAD	1	0.9
Total	115	100

The electrocardiographic abnormalities that were suggestive of ischemic heart disease were detected in most of the participants of the study. The most prevalent ECG abnormality was anterior wall myocardial infarction (AWMI) which was found in 39 patients (33.9%), then inferior wall myocardial infarction (14.8%), and NSTEMI (11.3%). Some of the patients too exhibited a concomitant infarction pattern, conduction and myocardial infarction changes, and remnant ischemia. These results suggest that the disease patients with diabetic retinopathy have a strong load of coronary artery disease and further confirm the relationship between diabetic microvascular disease and cardiovascular involvement.

There was also a significant correlation between the severity of diabetic retinopathy and the coronary artery disease ($p=0.009$), and a variety of abnormalities, such as RWMA ($p=0.003$), LV systolic dysfunction ($p=0.011$), LV diastolic dysfunction ($p=0.021$), and several others including MR ($p=0.019$), TR ($p=0.018$), LVH ($p=0.005$), RV dysfunction ($p=0.002$), PAH ($p=0.001$), and pericardial effusion ($p=0.014$). These observations indicate that progressive levels of diabetic retinopathy are strongly related to the rise of burden of coronary artery diseases and heart dysfunction pointing to diabetic retinopathy as a key indicator of systemic cardiovascular pathology in Type 2 Diabetes Mellitus.

DISCUSSION

The diabetes mellitus is one of the most common chronic metabolism disorders in the world and is known to be linked with a large set of microvascular and macrovascular complications. Diabetic retinopathy (DR), which is a typical microvascular complication of diabetes, has long been considered as a visual symptom of chronic hyperglycemia. But, there is mounting evidence to believe that diabetic retinopathy is a manifestation of systemic vascular impairment and could be of significant value in cardiovascular disease. The coronary artery disease (CAD), the greatest macrovascular complication of diabetes mellitus, is the most frequent source of morbidity and mortality in the diabetic population. As diabetic retinopathy and coronary artery disease both use endothelial dysfunction, chronic inflammation, oxidative stress, and accelerated atherosclerosis as common pathogenic processes, diabetic retinopathy presence and severity can potentially be useful predictors of underlying cardiovascular risk.

The average type of diabetes mellitus in the study was 6.8 ± 5.9 years. Almost fifty percent of the patients (48.7) had 1-5 years of diabetes and 21.7 years were with the 6-10 years range level of diabetes disease. Those patients taking more than 10 years of diabetes made 11.3 percent of the sample of the study.

One of the most critical factors of diabetic microvascular and macrovascular complications is the duration of diabetes. Persistent exposure to hyperglycemia causes accumulating endothelial dysfunction, accretion of advanced glycation end products, oxidative stress, inflammation, and vascular remodeling, which eventually cause retinal and cardiovascular damages.

The results of the current paper coincide with the findings described in the works by Cheung et al. [15], Pradeepa et al. [16] and Hsu et al. [17], who have shown that the risk of diabetic retinopathy and cardiovascular problems have a significant connection with the period of diabetes. Eid et al. [18] and Attia et al. [19] also suggested comparable observations and found a disease duration as a separate predictor of severe retinal involvement.

Duration of diabetes showed a very significant relation with the severity of diabetic retinopathy in the current research ($p=0.002$). Higher rate of diabetic retinopathy was noted in 61.5% of diabetic patients with over 10 years of diabetes against 9.5% in patients with less than one year of disease. These results are a clear indication of the additive damaging effects of long-term hyperglycemia on the retinal vasculature and are adding to prior data that long-term diabetes aggravates the course of microvascular diseases.

However, 58 patients (50.4) had hypertension and 57 patients (49.6) had no hypertension. In this way, about 50% of the study population had co-existing hypertension.

Hypertension has been proven to be a predisposing factor to diabetic retinopathy and coronary artery disease. High blood pressure also helps to cause endothelial damage, vascular permeability, capillary plugging, accelerated atherosclerosis and poor blood flow autoregulation of the retina. Therefore, severe retinal and cardiovascular complications are likely to occur in hypertensive diabetic patients.

The hypertension prevalence is similar to those observed in the current study and those documented by Demerdash et al. [20], Jibrán et al. [21] and Gupta et al. [22] who found high prevalence of hypertension among diabetic patients with retinopathy and cardiovascular disease.

There was significant correlation between diabetic retinopathy and hypertension severity ($p=0.004$). In hypertensive patients, 29.3% were in diabetic retinopathy stage of complete loss of vision as opposed to 10.5% of normotensive. The results are in line with those of the UKPDS and other ground-breaking studies that showed that the maintenance of blood pressure is a valuable approach in slowing diabetic retinopathy and cardiovascular complications.

The prevalence of the study participants whose HbA1c had below 7, between 7 and 10, and above 10 was 20.9, 48.7 and 30.4 respectively.

The statistically significant correlation was between HbA1c and the severity of diabetic retinopathy ($p=0.007$). Only 5.6% of patients with HbA1c level not less than 7, but more than 8.5 exhibited advanced retinopathy, and on the other hand, 28.1% of patients with HbA1c level not less than 8.5 were found to have advanced retinopathy.

This result reinforces the lines of evidence demonstrating a strong correlation between chronic hyperglycemia and retinal microvascular damage. The same has been observed in other studies by DCCT, UKPDS, Guo et al. [23] and Attia et al. [19] who established that continued deterioration of glycemic control is associated with a significant risk of diabetic retinopathy evolution.

In the current trial, 84 patients (73.0%) were in the R0 group, and 8 (7.0%), and 23 (20.0) patients were in the R1 and R2 groups, respectively. To analyze patients, patients they were further classified into early diabetic retinopathy (R0 + R1), representing 80.0% of patient cases and advanced diabetic retinopathy (R2), representing 20.0% of a patient.

The high prevalence of early diabetic retinopathy in the current study can be explained by the higher awareness, better testing of ophthalmological screening and earlier detection of the retinal disease associated with diabetes. Nevertheless, the result, that is, one-fifth of patients developed advanced diabetic retinopathy is still clinically significant as the presence of advanced retinal illness is linked to a higher likelihood of visual loss and systemic vascular issues.

Our results are similar to those of Pradeepa et al. [16], Gupta et al. [22], and Hsu et al. [17] who concluded that diabetic retinopathy severity is correlated with both the aggravation of metabolic control and the duration of diabetes and the escalating burden of cardiovascular risks.

Electrocardiographic analysis of the participants showed a significant morbidity of ischemic heart diseases among participants of the study. Anterior wall myocardial infarction (AWMI) was the most frequent ECG abnormality with 39 patients (33.9%). Among the patients, 17 patients (14.8%), and 13 patients (11.3%), respectively, were diagnosed with a case of inferior wall myocardial infarction and a case of NSTEMI.

The other ECG anomalies were unstable angina, changing patterns of myocardial infarction, straight anterior wall arterolateral myocardial infarction, right ventricular arterolateral myocardial infarction, involvement of the left main coronary artery, conduction anomalies, and pre-existing ischemic changes.

The prevalence of AWMI in the current report could indicate a high rate of engagement of the left anterior descending coronary artery, which brings to the left ventricles and extensively covers the myocardium; it is usually involved in the atherosclerotic disease among diabetic patients.

High incidences of ischemic ECG abnormalities in diabetic retinopathy patients corroborate earlier findings that have indicated high cardiovascular morbidity in diabetic patients with retinal microvascular disease. Gupta et al. [22], Attia et al. [19], and Jibrán et al. [21] authored similar reports that reported an increased prevalence of myocardial ischemia and infarction in diabetic patients with advanced retinopathy.

CONCLUSION

Retinopathy in diabetic patients was discovered to have a strong correlation with coronary cardiac disease and various heart related defects. A large percentage of the patients proved to have signs of coronary artery illness, electrocardiographic anomalies and severe structural and functional changes in the heart on the two-dimensional echocardiography.

Coronary artery disease among patients with diabetic retinopathy was prominent in percentage, which showed that damage of retinal microvascular is often accompanied by presence of atherosclerosis in the coronary arteries. Significantly higher rates of coronary artery disease were observed in relation to advanced diabetic retinopathy indicating that the presence of retinal disease progression equals that of the systemic vascular process.

The study participants had a high burden of myocardial dysfunction that was determined through the use of echocardiography. Motion abnormalities of the regional walls, left ventricular systolic dysfunction, ejection fraction reduction, dysfunction of the diastole, the abnormalities of the valves, ventricular hypertrophy, dysfunction of the right ventricle, hypertension of the pulmonary arteries, and effusion of the pericardium were much more prevalent in the patients with advanced diabetic retinopathy. These results suggest that a progressing retinal disease is correlated with a progressive cardiac involvement.

Regular cardiovascular examinations of patients with diabetic retinopathy can help to early diagnose those at risk so that they can be timely addressed and better shield against poor cardiovascular prognosis. Diagnosis and appropriate management of hyperglycemia, hypertension, obesity and dyslipidemia at an early stage are still critical measures that help minimize the retinal and cardiovascular complications in Type 2 Diabetes Mellitus patients.

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