DIABETIC RETINOPATHY AS A PREDICTOR OF SEVERITY OF CORONARY ARTERY DISEASE

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ABSTRACT

OBJECTIVES: To determine the association between diabetic retinopathy (DR) and severity of coronary artery disease (CAD) and evaluate the relation of stage of DR with severity of CAD.

METHODS: This cross-sectional study was conducted in Cardiology Unit, Lady Reading Hospital, Peshawar from January-June, 2017. Patients with diabetes mellitus for >5years who underwent coronary angiography (CA) were included. All patients underwent fundoscopy and categorized into: *No-DR, pre-proliferative-DR and proliferative-DR*. CA was performed to assess the severity of CAD and patients were categorized into: *none, mild, moderate and severe CAD* on the basis of number of vessels involved or left main stem (LMS) disease. The correlation between DR and CAD was determined by chi-square test and prevalence odd ratios (POR) were calculated by using logistic regression model.

RESULTS: A total of 166 patients with mean age of 55.5±8.8years were included in the study, of which 79 were males, 35 had no-DR, 110 had pre-proliferative-DR and 21 had proliferative-DR while 63 patients had mild CAD, 50 had moderate CAD and 18 had severe CAD. By using Chi square test, association between DR and severity of CAD was calculated to be 86.68 (p-0.000). After adjustments for various risk factors, PORs for severity of CAD with increasing stage of DR were found to be significantly increased from 0.27 times for no-DR to 4.27 times for pre-proliferative-DR and 6.33 times for proliferative-DR.

CONCLUSION: DR is not only strongly associated with CAD but higher stage of retinopathy predicts a more severe CAD increasing the odds of CAD by 2.27 times.

KEYWORDS: Coronary Artery Disease (MeSH); Diabetic Retinopathy (MeSH); Diabetes Mellitus (MeSH).

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INTRODUCTION

Uncontrolled diabetes mellitus (DM) with chronic hyperglycemia leads to micro and macrovascular complications.[1] Studies have shown DM as an independent risk factor for coronary artery disease (CAD). Diabetic nephropathy and diabetic retinopathy (DR) are the usual manifestations of microvascular insult secondary to DM leading to significant morbidity among diabetics. Early detection and intervention is needed to prevent vasculopathy.[2] A number of studies have reported occult atherosclerosis, silent peripheral arterial disease (PAD), silent CAD and silent myocardial infarction (MI) among patients with DM.[3,4] CAD is a major cause of morbidity and mortality among diabetics.[5,6] It's one of the macrovascular manifestations of DM. The interplay between microvascular and macrovascular manifestations needs to be determined whether DR is associated with CAD and also it needs our attention. So far, only studies regarding the correlation of diabetic nephropathy with CAD are available and major research has been done in this regard but no significant insight regarding the correlation of DR with CAD is yet available.[7,8] A few studies have provided us with inconclusive evidence of correlation of DR with CAD,[9,10] probably because of incorporation of specific cardiovascular events like cardiovascular (CV) deaths, non-fatal MI or chronic heart failure (CHF) but these studies have not correlated the stage of DR with severity of CAD.[11,12] In our study, we aim to determine the correlation of DR with severity of CAD and to determine the effects of DR in predicting the prevalence odds ratio (POR) for CAD.

METHODS

This cross-sectional study was conducted in Cardiology Unit, Lady Reading Hospital (LRH), Peshawar from January, 2017 to June, 2017 after approval from the hospital ethical board. Patients with diabetes mellitus for at least 5 years presenting to cardiology unit LRH with a history of angina CCS III/IV (Canadian Cardiovascular Society Angina Grading Scale III/IV)[13] who underwent coronary angiography were included in the study. Patients with previous history of acute coronary syndrome (ACS), angioplasty or bypass surgery, congenital heart disease, cardiomyopathy, heart failure, chronic kidney disease (CKD), chronic liver disease (CLD), anemia, malignancies, hypertensive retinopathy, cataracts or history of cataract surgery, retinal pathologies like pan-retinitis, maculopathies, conjunctivitis and retinal photocoagulation were excluded from the study to limit confounding bias. Non-probability consecutive sampling was used for patient inclusion. A written informed consent was taken from all included patients. A thorough history taking, physical examination, relevant blood investigations, electrocardiography (ECG) and echocardiography were performed to fulfill the inclusion and exclusion criteria. Fundoscopy was performed by two senior residents of cardiology; well-trained in fundus examination, with Reister ophthalmoscope

TABLE I: BASE LINE CHRACTERISTICS OF PATIENTS ENROLLED IN THE STUDY

VARIABLES	NO DR (C1)	PRE PDR (C2)	PDR (C3)	X^2 Sig: C1-C2	X^2 Sig: C2-C3
Number of Patients	35(100%)	110(100%)	21(100%)	---	---
Age (years)	54.2±9.2	55.5±8.6	55.5±7.1	---	---
Males	19(54.2%)	51(46.3%)	9(42.8%)	---	---
Females	16(45.7%)	59(53.6%)	12(57.1%)	---	---
Diabetes Mellitus Duration (years)	8.9±1.3	10.1±1.2	11.1±1.1	---	---
Insulin Use	9(25.7%)	28(25.4%)	8(38.0%)	0.71	0.05
Hypertension	18(51.4%)	66(60%)	12(57.1%)	0.8	0.5
Hypertension Duration (years)	5.2±1.6	5.1±1.8	6.2±1.1	----	-----
Smoking	16(45.7%)	46(41.8%)	8(38.0%)	0.6	0.2
Family History of CAD	8(22.8%)	45(40.9%)	7(33.3%)	0.05	0.12
Family History of DM/HTN	11(31.4%)	83(75.4%)	17(80.9%)	0.05	0.31
Systolic Blood Pressure (mmHg)	141.1±1.9	142.2±4.5	143.1±4.6	---	---
Diastolic Blood Pressure (mmHg)	91.1±1.1	91.6±2.9	90.8±1.1	---	---
Rest ECG Changes	13(35%)	52(47%)	13(63%)	0.05	0.04
ETT +ve					
Anterior Leads	6(15%)	62(57%)	19(90%)	0.03	0.04
Inferior Leads	13(35%)	21(19%)	1(5%)	0.31	0.06
Miscellaneous	16(50%)	27(24%)	1(5%)	0.05	0.05
Diastolic Dysfunction	10(27%)	45(41%)	15(70.9%)	<0.05	<0.05
Triglycerides (mg/dl)	163.0±47.6	196.7±59.1	174.9±46.2	---	---
Low Density Lipoproteins (mg/dl)	116.4±22.9	124.6±30.9	124.9±34.6	---	---
High Density Lipoproteins (mg/dl)	41.7±3.5	39.5±5.0	40.8±3.2	---	---
Cholesterol (mg/dl)	190.9±30.9	200.2±24.5	199.5±22.1	---	---
HbA_{1c} (gm/dl)	6.9±0.7	8.0±1.1	8.8±1.3	---	---
HbA_{1c} Category:					
<7 (Good)	27(77%)	25(22.7%)	2(9.5%)	---	---
7-8.5 (Satisfactory)	06(17%)	55(50.01%)	4(19.0%)	---	---
>8.5 (Poor)	02(5.7%)	30(27.3%)	15(71.4%)	---	---

DR=Diabetic retinopathy; NDR=No diabetic retinopathy; PDR=proliferative diabetic retinopathy; CAD=coronary artery disease; ETT=Exercise tolerance test; DM=diabetes mellitus; HTN=hypertension

for all included patients who were categorized into: No DR, pre-proliferative DR and proliferative DR. Patients were labelled as having pre proliferative DR if they had micro aneurysms in all four quadrants of retina, dot and blot hemorrhages, venous beading in >2 quadrants and cotton wool spots in at least one quadrant on fundoscopy. Patients with severe DR were in proliferative phase with neo vascularization in retina.[14]

Coronary angiography was performed by senior interventional cardiologists in the cardiac catheterization laboratory under Axiom Artis Siemens 2005 machine to assess the severity of CAD. Patients were categorized into having none, mild, moderate and severe CAD based on number of vessels of >1.5mm caliber that are more than 70% stenosed i.e., None, single vessel disease (SVD), double vessel disease (DVD), triple vessel disease (TVD) respectively. In addition, patients with left main stem (LMS) stenosis of 50% or more were also categorized into severe CAD. All data including demographic variables were recorded in a predesigned proforma.

The data was analyzed in SPSS Version 20.0. Continuous variables like age, HbA1C levels were recorded in mean±SD. Categorical variables like sex, diabetic retinopathy, coronary artery disease were recorded in frequency and percentages. Comparison of categorical variables was done by using Chi square test. Correlation between DR and CAD was established with Chi-Square test. PORs were calculated by using logistic regression model.

RESULTS

A total of 166 patients were included in the study with a mean age 55.5±8.8 years, of which 47.5% were males. Baseline characteristics of patients are given in Table I. Out of the included patients, 35 had no DR, 110 had Pre-PDR, and 21 had PDR whereas 35 patients had no CAD on coronary angiography while while 63 patients had mild CAD, 50 had moderate CAD and 18 had severe CAD. By using Chi square test, association between DR and severity of CAD was calculated to be 86.68 (p-0.000) as shown in Table II. Also the chi square results for individual comparison of no DR with no CAD came out to be significant i.e.; 55.9(0.001). For pre PDR and mild CAD association result was 77.1(0.001) and for PDR vs sever CAD association result was 86.7(0.001). PORs for CAD with increasing grade of DR were calculated using logistic regression model as shown in Table III. The PORs increased from 0.27 times for

TABLE II: CORRELATION OF DIFFERENT STAGES OF DIABETIC RETINOPATHY WITH SEVERITY OF CORONARY ARTERY DISEASE

VARIABLES		CORONARY ARTERY DISEASE (CAD)					
		No CAD	Mild CAD	Moderate CAD	Severe CAD	X^2-value	Sig:
DR	NDR	20	15	0	0	86.68	0.000
	Pre PDR	15	48	44	3		
	PDR	0	0	6	15		

NDR=No diabetic retinopathy; PDR=proliferative diabetic retinopathy; pre-PDR=pre proliferative diabetic retinopathy

TABLE III: PREVALENCE ODDS RATIO FOR INCREASING SEVERITY OF CORONARY ARTERY DISEASE WITH INCREASING STAGE OF DIABETIC RETINOPATHY

	CAD		
Diabetic Retinopathy	**POR**	**CI for OR**	**P-value**
NDR	0.27	0.18-0.38	0.01
Pre PDR	4.27	3.61-8.09	0.001
PDR	6.33	3.31-9.01	0.001

NDR=No diabetic retinopathy; PDR=proliferative diabetic retinopathy; CAD=coronary artery disease

NDR to 4.27 times for Pre-PDR and 6.33 times for PDR. PORs for various other comorbid conditions causing CAD were also calculated and are given in Table IV.

DISCUSSION

Diabetic Retinopathy is one of the microvascular complications of DM. It takes 5-10 years for a diabetic to develop DR. So far, studies have shown the association between diabetic nephropathy and CAD,[15-17] which is a late and common complication of DM.[18] Microalbu-minuria presents in 20-40 percent of patients with DM over a span of 10-15 years with progression to overt nephro-pathy over 15-20 years.[19] On the contrary, DR is an early sign of microvascular damage significantly correlated with poor glycemic control and uncontrolled DM. Within 5 years of diagnosis, 58% type I diabetics and 80% of type II diabetics develop DR.[20] At 20 years, almost all patients have developed DR with 50% entering the proliferative phase.[20] Recent research demonstrates that inflammation plays a vital role in both DR and CAD progression.[21]

In our study, we saw the correlation of different stages of DR with severity of CAD. There was no statistically significant difference among different baseline variables of patients in different DR categories. However, based on our analysis, significant correlation was found between no DR and no CAD, pre-PDR and mild CAD and PDR and severe CAD. Severity of CAD increased with increase in the stage of retinopathy. Also, we calculated PORs for CAD with increasing DR stages. PORs for CAD increased with increasing the stages of DR. Another strength of our study was that we studied different comorbid conditions which increase the PORs for CAD. These include male sex, hypertension, smoking, high LDL levels, high TG levels, and high HBA1C levels came out to be significant.

Our results are comparable to the studies performed by El-Demerdash F, et al[22] who reported 80% stenotic disease in patients with PDR and Ohno T, et al[23] reported that diabetics with retinopathy had significant CAD and needed CABG but went unrecognized. These results also coincide with Gimeno-Orna JA, et al[24] who elaborated DR as a risk factor for CAD.

Early management of CAD among diabetics is to increase their life expectancy. Diabetics should undergo frequent fundoscopic exams not only to protect their vision but also to predict CAD severity. Any abnormal fundoscopic findings should prompt the need for CAD screening.

STRENGTHS AND LIMITATIONS

One of the strengths of our study is that we not only found correlation between each stage of DR and severity of CAD but also calculated the PORs for CAD with each stage of DR. Second, the tool we used to assess the severity of CAD i.e. coronary angiography is a gold standard.

The study also had a few limitations, including the fact that ophthalmoscopic and angiographic findings are observer biased. Second, it's a single center study with a moderate sample size.

CONCLUSION

Diabetic Retinopathy is not only strongly associated with coronary artery disease but we also conclude that a higher stage of diabetic retinopathy is associated with a worsening severity of CAD.

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TABLE IV: RISK FACTORS AFFECTING THE PREVALENCE ODDS RATIO OF CORONARY ARTERY DISEASE

	CORONARY ARTERY DISEASE (CAD)	
VARIABLE	**POR**	**Sig:**
Age	0.18	0.15
Male Sex	**1.29**	**0.04**
Insulin	0.21	0.32
Hypertension	**0.81**	**0.04**
Smoking	**1.77**	**0.003**
Family History	0.60	0.22
Low Density Lipoproteins	**0.61**	**0.03**
Triglycerides	**1.69**	**0.01**
Cholesterol	0.11	0.32
High Density Lipoproteins	0.290	0.61
HbA_{1c}	**0.788**	**0.01**

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AUTHORS' CONTRIBUTIONS

Following authors have made substantial contributions to the manuscript as under:

MSJ: Concept & study design, acquisition of data, drafting the manuscript, final approval of the version to be published.

ZUZ: Acquisition of data, final approval of the version to be published.

SAH: Acquisition, analysis & interpretation of data, final approval of the version to be published.

SN: Analysis & interpretation of data, critical review, final approval of the version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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