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DIABETIC RETINOPATHY A PREDICTOR OF SEVERITY OF CORONARY ARTERY DISEASE

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ABSTRACT

OBJECTIVE: To determine the association between diabetic retinopathy and severity of CAD and whether the stage of diabetic retinopathy predicts the severity of CAD or not.

METHODOLOGY: This cross-sectional study was conducted in Cardiology Unit, LRH Peshawar from January, 2017 to June, 2017. Non-probability consecutive sampling was used to include all patients diagnosed with DM for at least 5 years and underwent Coronary Angiography for Angina CCS III/IV after fulfilling the inclusion and exclusion criteria. All included patients underwent fundoscopy and were categorized into: No DR, Pre-PDR and PDR. Coronary Angiography was performed to assess the severity of CAD and patients were categorized into having none, mild, moderate and severe CAD on the basis of number of vessels involved. The correlation between DR and CAD was determined by using Chi-Square test and PORs were calculated by using logistic regression model.

RESULTS: A total of 166 patients with mean age of 55.5±8.6 years were included in the study, of which 79 were males. 35 had no DR, 110 had Pre-PDR and 21 had PDR while 83 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 other risk factors, PORs for severity of CAD with increasing stage of DR were calculated and they significantly increased from 0.54 times for NDR to 1.9 times for Pre-PDR and 2.27 times for PDR.

CONCLUSION: Diabetic Retinopathy is not only strongly associated with CAD but higher stage of retinopathy predicts a more severe CAD.

KEYWORDS: CAD=Coronary Artery Disease, DR=Diabetic Retinopathy, NDR=No Diabetic Retinopathy, Pre-PDR=Pre-proliferative Diabetic Retinopathy, PDR=Proliferative Diabetic Retinopathy, CCS=Canadian Classification Scale

INTRODUCTION Uncontrolled DM with chronic hyperglycemia leads to micro and macro vascular complications.[1] Studies have shown DM as an independent risk factor for CAD. Diabetic nephropathy and diabetic retinopathy 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 PAD, silent CAD and silent 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 macro vascular manifestations of DM. The interplay between microvascular and macro vascular manifestations needs to be determined and whether DR is associated with CAD also needs to our attention. So far, 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 DR with

CAD,[9,10] probably because of incorporation of specific CVD events like CV deaths, non-fatal MI or CHF.[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 POR for CAD.

MATERIALS AND METHODS: This cross-sectional was conducted in LRH, Cardiology unit from January, 2017 to June, 2017 after approval from the hospital ethical board. Patients with DM for at least 5 years presenting to LRH cardiology with history of angina CCS III/IV for coronary angiography were included in the study. Patients with previous history of ACS, angioplasty or bypass surgery, congenital heart disease, cardiomyopathy, heart failure, CKD, 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. Non-probability consecutive sampling was used. A written informed concent was taken from all included patients. A thorough history taking, physical examination, BIIs, ECG and echocardiography were performed to fulfill the inclusion and exclusion criteria. Written informed consent was taken from all included patients. Fundoscopy was performed with Reister ophthalmoscope for all included patients and were categorized into: No DR, Pre-PDR and PDR. **:** Patients were labelled as having pre proliferative DR if they had micro aneurysm 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 sever DR were in proliferative phase with neo vascularization in retina.

Coronary angiography was performed by senior interventional cardiologists in the cath: lab under Axiom Artis Siemens 2005 machine to assess the severity of CAD. Patients were categorized into having no CAD, mild CAD, moderate CAD and sever CAD based on none VD, SVD, DVD, TVD of more than 70% in vessels of >1.5mm caliber respectively. All data including demographic variables were recorded in a predesigned proforma.

STATISTICAL ANALYSIS: The whole data was analyzed in SPSS Version 20.0. Continuous variables like age, HbA1C levels were recorded in mean ± SD. Categorical variables like sex, DR, CAD were recorded in frequencies and percentages. 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 included patients are given in Table I.

VARIABLES	NO DR (C1)	PRE PDR (C2)	PDR (C3)	X^2 Sig: C1-C2	X^2 Sig: C2-C3
NO: OF PATIENTS	35(100%)	110(100%)	21(100%)	---	---
AGE	54.2±9.2	55.5±8.6	55.5±7.1	0.38	0.41
MALE	19(54.2%)	51(46.3%)	9(42.8%)	0.61	0.69
FEMALE	16(45.7%)	59(53.6%)	12(57.1%)	0.5	0.4
DM DURATION	8.9±1.3	10.1±1.2	11.1±1.1	0.001	0.004
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
HTN DURATION	5.2±1.6	5.1±1.8	6.2±1.1	0.5	0.03
SMOKING	16(45.7%)	46(41.8%)	8(38.0%)	0.6	0.2
FHx CAD	8(22.8%)	45(40.9%)	7(33.3%)	0.05	0.12
FHx DM / HTN	11(31.4%)	83(75.4%)	17(80.9:%)	0.05	0.31
SBP	141.1±1.9	142.2±4.5	143.1±4.6	0.07	0.31
DBP	91.1±1.1	91.6±2.9	90.8±1.1	0.5	0.3
REST ECG CHANGES	13(35%)	52(47%)	13(63%)	0.05	0.04
ETT +VE					
ANT: LEADS	6(15%)	62(57%)	19(90%)	0.03	0.04
INF: LEADS	13(35%)	21(19%)	1(5%)	0.31	0.06
MISCELLANEOUS	16(50%)	27(24%)	1(5%)	0.05	0.05
DIASTOLIC DYSF:	10(27%)	45(41%)	15(70.9%)	<0.05	<0.05
TGs	163.0±47.6	196.7±59.1	174.9±46.2	---	---
LDL	116.4±22.9	124.6±30.9	124.9±34.6	---	---
HDL	41.7±3.5	39.5±5.0	40.8±3.2	---	---
CHOLESTEROL	190.9±30.9	200.2±24.5	199.5±22.1	---	---
HbA1C	6.9±0.7	8.0±1.1	8.8±1.3	0.001	0.001
HbA1C CAT:					
<7 GOOD	27(77%)	25(22.7%)	2(9.5%)	<0.05	<0.05
7-8.5 SATISFACTORY	06(17%)	55(50.01%)	4(19.0%)	<0.05	<0.05
>8.5 POOR	02(5.7%)	30(27.3%)	15(71.4%)	<0.05	<0.05

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

35 patients had no DR, 110 had Pre-PDR, and 21 had PDR. 35 patients had no CAD on coronary angiography while 63 patients had mild CAD, 50 had moderate CAD and 18 had severe CAD. Correlation between DR and CAD had been calculated by using Chi-Square test as shown in Table II.

VARIABLES	CAD					
DR	**NO CAD**	**MILD CAD**	**MOD CAD**	**SEVER CAD**	**X^2-value**	**Sig:**
NDR	**20**	15	0	0	**55.9**	**0.001**
Pre PDR	15	**48**	44	3	**77.1**	**0.001**
PDR	0	0	6	**15**	**86.7**	**0.001**

Table II: CORRELATION OF DIFFERENT STAGES OF DR WITH SEVERITY OF CAD

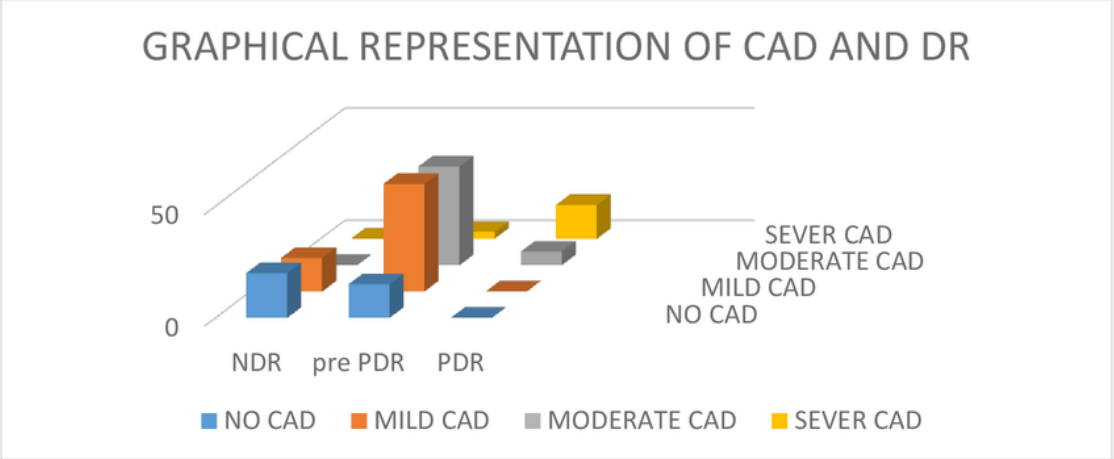

Fig: I GRAPHICAL REPRESENTATION OF CAD AND DR

PORs for CAD with increasing grade of DR were calculated using logistic regression model as shown in Table III. The PORs increased from 0.54 times for NDR to 1.9 times for Pre-PDR and 2.27 times for PDR.

DR	**CAD**				
	POR	**Exp(B)**	**CI for Exp(B)**	**Df**	**Sig:**
NDR	0.54	0.51	0.35-0.71	1	0.01
Pre PDR	1.9	2.25	1.19-4.26	1	0.001
PDR	2.27	2.79	1.46-3.97	1	0.001

Table III:POR FOR INCREASING CAD WITH INCREASE IN STAGE OF DR

PORs for various other comorbid conditions causing CAD were also calculated and are given in Table IV.

VARIABLE	**POR**	**Exp(B)**	**Sig:**	**VARIABE**	**POR**	**Exp(B)**	**Sig:**
AGE	0.32	0.62	0.15	**LDL**	**0.61**	**1.00**	**0.03**
MALE SEX	**1.17**	**1.11**	**0.04**	**TGs**	**1.71**	**0.99**	**0.01**
INSULIN	0.35	0.61	0.32	CHOESTEROL	0.12	0.92	0.32
HYPERTENSION	**0.81**	**1.01**	**0.04**	HDL	0.29	0.71	0.61
SMOKING	**1.78**	**0.99**	**0.003**	**HbA1C**	**0.49**	**1.61**	**0.01**
FAMILY Hx	0.65	0.53	0.22				

Table IV: OTHER CONDITION AFFECTING THE POR OF CAD

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 developed the association between diabetic nephropathy and CAD, [13, 14, 15] which is a late and genetically affected complication of DM.[16] Microalbuminuria presents in 20-40 percent of patients with DM over a span of 10-15 years with progression to overt nephropathy over 15-20 years.[17] 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. At 20 years, almost all patients have developed DR with 50% entering the proliferative phase.[19] Recent research demonstrates that inflammation plays a vital role in both DR and CAD progression.[20]

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 existed between no DR and no CAD with a value of 55.9($p<0.001$), correlation between pre-PDR and mild CAD with x^2 value of 77.1($p<0.001$), strong correlation between PDR and severe CAD with x^2 value of 86.7($p<0.001$). So, 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 from 0.54 times to 2.27 times with NDR to PDR. Another advantage 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 Fawzia et al[21] who reported 80% stenotic disease in patients with PDR and Ohno et al[22] reporting that diabetics with retinopathy had significant CAD and needed CABG but went unrecognized. These results also coincide with Gimeno-Orna et al[23] who elaborated DR as a risk factor for CAD.

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: 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.

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