Original Article

Association of Diabetic Retinopathy with Angiographic Severity of Coronary Artery Disease in Patients with Non-ST Elevation Myocardial Infarction

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Abstract:

Key Words :
Coronary artery disease, Diabetic retinopathy, Left ventricular ejection fraction, Gensini score

Background: Bed side ophthalmoscopic examination is a simple measure of diagnosis of diabetic retinopathy and has been shown to be a predictor of poor outcome in various cardiovascular conditions including coronary artery disease. The present study was intended to find the relationship between diabetic retinopathy with the severity of coronary artery disease in patients with non ST elevation myocardial infarction (NSTEMI).

Methods: This cross-sectional observational study was conducted with a total of 120 NSTEMI patients with diabetes undergoing coronary angiogram and also fundoscopic examination with fundal photography during the index hospitalization. Study subjects were divided into two groups on the basis of diabetic retinopathy (Group-I: NSTEMI with diabetic retinopathy; Group- II: NSTEMI without diabetic retinopathy). Severity of coronary artery disease was determined by Gensini score and correlation between diabetic retinopathy and Gensini score was assessed.

Results: Gensini score was significantly higher in patients with diabetic retinopathy than that in patients without diabetic retinopathy (62.2±27.7 vs. 43.3±25.3, p<0.001).Gensini score increased with increasing severity of diabetic retinopathy (p <0.001).The risk of having severe CAD in patient with diabetic retinopathy was 13.03 (95% CI =2.410-70.419) (P<0.003). A significant correlation between diabetic retinopathy and Gensini score was noted (p value <0.001)

Conclusion: It may be concluded that presence and severity of diabetic retinopathy is associated with angiographic severe coronary artery disease in patient with NSTEMI and it may be considered as an independent predictor of severity of CAD. As is a bed side assessment, so before performing coronary angiography, it appears to be additive for risk stratification.

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Introduction:

Cardiovascular diseases (CVD) are the most common cause of premature death in the world. CVD account for 50% of all non-communicable disease (NCD) deaths in the world each year and represent a significant threat to human welfare and sustainable development.[1] The exact prevalence of CAD in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available. More recent data indicates that CAD prevalence is 1.85% to 3.4% in rural population and 19.6% in an urban population.[2]

Diabetes Mellitus is a heterogeneous primary disorder of carbohydrate metabolism with absolute insulin deficiency (Type 1) or relative insulin deficiency (type 2), resistance or both leading to hyperglycemia.[3] The South Asian region shares a

major proportion of this worldwide burden of diabetes. The prevalence of diabetes ranges from 0.9% in Bangladesh to 21.2% in India.[4]

Unstable angina patient with diabetic retinopathy (DR) have more significant left ventricular dysfunction than without DR.[5] Diabetic retinopathy is an early and frequent marker of other vascular complications of diabetes and its relation with coronary ischemia is known.[6] In individuals with type-2 diabetes, the presence of retinopathy signifies an increased CHD risk, independent of glycemic levels, symptomatology,[7] and other cardiovascular risk factors and is also associated with an increased risk of mortality and cardiovascular events.[8]

While its adverse impact on vision is well known,[9] the importance of retinopathy signs beyond visual impairment is less well recognized. Both non proliferative diabetic retinopathy(NPDR) and proliferative diabetic retinopathy(PDR) have now been linked with major clinical diseases like stroke, coronary heart disease, heart failure and nephropathy,[10] as well as newer subclinical measure of cardiovascular disease such as coronary artery calcification and cardiac remodeling.[11] The presence of retinopathy signs has also been associated with higher degree of coronary artery calcification and more diffuse/ severe coronary artery stenosis on angiograms.[12,13]

There is a graded, dose dependent association of increasing diabetic retinopathy severity with increasing coronary heart disease risk.[14] These findings are consistent with data from the World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO-MSVDD)[15] and other studies showing associations of not only NPDR but also PDR with ischemic heart disease.[16] In addition to population studies, there are clinical studies that suggest the presence of retinopathy can be used as an indicator of silent myocardial ischemia and help guide investigative approaches in diabetic patients with suspected heart disease.[17]

Coronary microcirculation dysfunction associated with diabetes, although explored extensively in recent years,[18] still represents a poorly understood phenomenon in the clinical setting. Endothelial dysfunction, with its unfavorable consequences in various vascular beds, has been widely recognized to be a result of pathophysiological processes in diabetes, with less information available in the context of the coronary microvasculature.[18]

The Gensini score system is a technique developed by Gensini et al.[19] for the assessment of the severity of coronary artery disease (CAD). This scoring system is based on the artery morphology, coronary anatomy, and severity of stenosis in lesions.[20] Although those scoring systems have many advantages, they require an invasive method such as coronary angiography to perform the scoring.

Clinicians are in constant search of a non-invasive, practical and precise tool to predict severity of coronary disease. If the association between diabetic retinopathy and the Gensini score is found, it can readily be used as a tool to predict severe CAD. The purpose of this study is to search for whether increased diabetic retinopathy is associated with increased angiographic severity in non-ST elevation myocardial infarction patients.

Methods:

It's a Cross section observational study. This study was conducted in the Department of Cardiology, National Institute of cardiovascular Diseases, Dhaka, Bangladesh, from June 2019 to July 2020. Purposive sampling was done. Among all patients coming to NICVD, NSTEMI patients was identified by clinical features, 12 lead ECG, cardiac troponin I level. Informed written consent was taken from each patient. Particulars of the patient, relevant history was taken and detailed clinical examination was done and recorded in predesigned structured data collection sheet. All relevant laboratory investigations were done. Fundoscopic examination was done after pupillary dilatation with tropicamide 1% by Keeler professional ophthalmoscope 2.8V and Fundoscopic findings were classified as normal, non-proliferative DR, or proliferative DR. Fundal photography was done and findings were classified as normal, non-proliferative DR or proliferative DR.
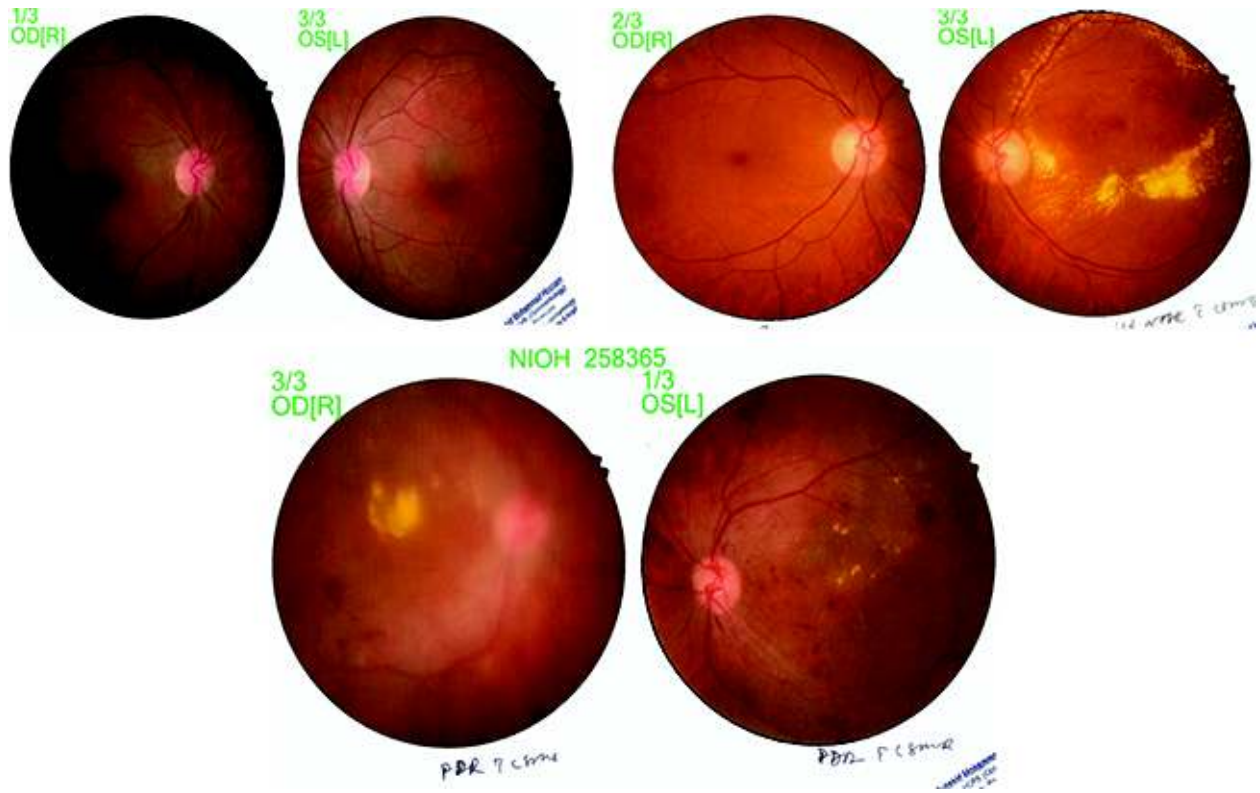
Fig 1: No diabetic retinopathy, Mild and moderate non proliferative diabetic retinopathy and Proliferative diabetic retinopathy.

Eligible patients underwent for coronary angiogram according to operator's choice of route of intervention. Severity of coronary artery disease was expressed by Gensini score. The Gensini scores of all patients were calculated by 2 independent experienced interventional cardiologists who were blinded to the identities and clinical information of the patients from baseline diagnostic CAG. After calculation of Gensini score, 36 points can be chosen as an appropriate cut-off value and patients may be divided into two groups, those with a Gensini score d"36 points may be considered as absent or mild coronary artery disease and those with a Gensini score >36 points may be considered as moderate to severe coronary artery disease

Results:

The study subjects were divided into 2 groups on the basis of diabetic retinopathy: Group I-NSTEMI patient with diabetic retinopathy; Group II-NSTEMI patient without diabetic retinopathy. The severity of CAD was determined by The Gensini score; the higher the score the more severe

the disease. Accordingly, patients with Gensini score > 36 were considered as severe disease.

Age distribution shows that patient with diabetic retinopathy (group I) were generally older than the patient without diabetic retinopathy (group
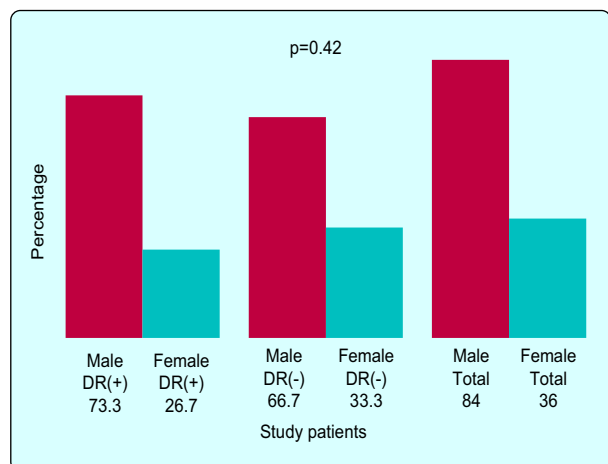

Fig 2: *Sex distribution of the study patients (N=120). NS= Not significant (p>0.05). p value reached from Chi Square test for qualitative variable.*

II) (57.0±6.9 vs. 56.9±6.8, p=0.94) and the difference in mean age between two groups was statistically not significant. The table also indicate that the most of the patients were in the age range of 55-64 years in both study groups.

In both group, there was male predominance, however, the difference in gender between the groups was not statistically significant (p=0.42).The table also provides that among the study patients, male patient were 84 (70%) and female patients were 36 (30%).

Among the traditional risk factors for CAD, smoking, hypertension, dyslipidemia, family history of premature CAD, previous history of PAD, previous history of CAD and obesity, presented in the above table did not differ significantly between two groups. Only duration of diabetes and number of patient taking insulin were found significantly higher in group I than group II.

Gensini score was significantly higher in group I than that of group II (62.2±27.7 vs. 43.3±25.3, p<0.001).The table describes that diabetic retinopathy patients has significantly higher Gensini score (Gensini score >36) than non-diabetic retinopathy.

Table-I
Comparison of study subjects according to age (N=120).

Age in years	Diabetic Retinopathy (+) (n=60)		Diabetic Retinopathy (-) (n=60)		p value
	Number	%	Number	%	
35 – 44	0	0.0	3	5.0	
45 – 54	22	36.7	12	20.0	
55 – 64	26	43.3	37	61.7	
65 - 74	12	20.0	8	13.3	
Mean ± SD(Range)	57.0±6.9(37-71)		56.9±6.8(45-70)		0.94[NS]

NS= Not significant (p>0.05), SD- Standard deviation p value reached from unpaired t test for quantitative variable.

Table-II
Distribution of study subjects by risk factors (N=120).

Risk Factors	Diabetic Retinopathy (+) (n=60)		Diabetic Retinopathy (-) (n=60)		p value
	Number	%	Number	%	
Smoking	26	43.3	31	51.7	0.36[NS]
Hypertension	35	58.3	38	63.3	0.57[NS]
Dyslipidemia	19	31.7	14	23.3	0.31[NS]
Family H/O of premature CAD	13	21.7	6	10.0	0.08[NS]
Previous H/O of PAD	4	6.7	4	6.7	1.00[NS]
Previous H/O of CVD	4	6.7	3	5.0	0.69[NS]
Mean duration of DM (yrs.)	11.8±5.7		5.7±1.7		<0.001[S]
No. of patients taking insulin	22	36.7	8	13.3	0.003[S]

p value reached from Chi Square test for qualitative variables and t-test for quantitative variables.
S= Significant (p<0.05), NS = Not significant (p>0.05).

Table-III

Distribution of the study patients by Gensini score (N=120).

Gensini Score	Diabetic Retinopathy (+) (n=60)		Diabetic Retinopathy (-) (n=60)		p value
	Number	%	Number	%	
Severe CAD (>36 points)	54	90.0	31	51.7	<0.001^S
Not severe CAD (d"36 points)	6	10.0	29	48.3	<0.001^S
Mean ± SD	62.2±27.7	43.3±25.3	<0.001^S		

S=Significant (p<0.05), p value reached from chi square test of categorical approach and unpaired t-test of quantitative approach.

The table shows that the patients in the DR (+) group had significantly higher Gensini scores than patients in the DR (-ve) group.

Prediction of CAD severity:
Dependent variable: Gensini Score>36 points; Independent variables: duration of diabetes mellitus, insulin taking, serum creatinine, DR (+), S = Significant, NS = Not significant

The above table depicts the univariate logistic regression analysis of odds ratios for characteristics of the subjects likely to develop coronary artery disease. The variable diabetic retinopathy, duration of diabetic mellitus, creatinine were found to be significantly associated with CAD severity with their odd ratios being 8.41, 1.14 and 4.6 respectively.

Dependent variable: Gensini score>36 points; Independent variables: duration of diabetes mellitus, insulin intake, serum creatinine, Presence of DR, S = Significant, NS = Not significant

The above table demonstrates the multivariate logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause of high Gensini Score assessed as coronary artery disease severity. The variables revealed to be significantly associated with high Gensini score by multivariate analysis were entered into the model directly. The table depicts that DR (+) was found to be the significant predictor of high Gensini Score with OR being 13.03.

Table-IV

Association between Diabetic Retinopathy and Gensini score (N=120).

No. of vessel involved	Gensini Score		p value
	Mean	SD	
No DR (n = 60)	43.35	25.30	
Mild DR (n=16)	48.69	19.77	<0.001^s
Moderate DR (n=22)	58.27	23.87	
Severe DR (n=22)	75.98	30.86	

S = Significant (p<0.05), p value reached from ANOVA test.

Table-V

Univariate logistic regression for determinants of severity of coronary artery disease as assessed by Gensini score.

Variables of interest	Regression coefficient (β)	p value	OR	95% CI
Duration of Diabetes mellitus	0.135	0.02^S	1.14	1.025 – 1.279
Insulin taking	0.164	0.03^S	1.17	1.05 – 2.976
Serum creatinine	1.982	0.005^S	4.46	1.435 – 28.620
DR (+)	2.131	<0.001^S	8.41	3.148 – 22.517
Smoking	- 0.321	0.286	0.725	0.414 – 1.271
HTN	0.006	0.292	1.006	0.567- 1.784
Dyslipidemia	- 0.120	0.703	0.887	0.478 – 1.645

Table-VI

Multivariate logistic regression for determinants of severity of coronary artery disease as assessed by Gensini score.

Variables of interest	Regression coefficient (β)	p value	OR	95% CI
Duration of Diabetes mellitus	-0.125	0.21[NS]	0.88	$0.725 - 1.075$
Insulin intake	-0.480	0.47[NS]	0.62	$0.164 - 2.331$
Serum creatinine	0.833	0.48[NS]	2.29	$0.219 - 24.144$
Presence of DR	2.567	0.003[S]	13.03	$2.410 - 70.419$

Discussion:

This study evaluated the association of diabetic retinopathy with angiographic severity of coronary artery disease in patients with NSTEMI. The age and gender distribution were similar in both groups, which is almost similar to the study done by Norgaz et al.

Regarding CAD risk factors in this study, smoking, hypertension, dyslipidemia, family history of premature CAD, previous history of PAD, previous history of CAD and obesity, presented in the above table did not differ significantly between two groups. Only duration of diabetes and number of patient taking insulin were found significantly higher in group I than group II. This is almost similar to study done by Saleem et. al.[21]

In the present study, Gensini score differed between no diabetic retinopathy, mild diabetic retinopathy to severe diabetic retinopathy. The mean Gensini score in group I was 62.2 ± 27.7 versus 43.3 ±25.3 in Group II. This is similar to other studies which demonstrated that higher the diabetic retinopathy also have severe coronary artery disease.[6,7] Patient without diabetic retinopathy have mean Gensini score 43.35 ± 25.30, mild diabetic retinopathy 48.69 ± 19.77, moderate retinopathy score 58.27 ± 23.87 and severe diabetic retinopathy 75.98 ± 30.87 and the difference of diabetic retinopathy between the subgroups were significant. Apart from this Rong J et.al., investigate association between diabetic retinopathy and CAD severity by Gensini score. They found that the prevalence of coronary atherosclerosis, is significantly higher in the patients with T2DM with DR.[22] So, the overall findings relating to the association between diabetic retinopathy and CAD severity correlates

with the findings of present study. In this study significant positive correlation was also found between diabetic retinopathy and Gensini score.

In the present study, univariate logistic regression analysis of the variables likely to cause severe CAD (Gensini score>36) was done. The univariate regression analysis revealed that the odds ratios of diabetic retinopathy, duration of diabetes, number of patient taking insulin, creatinine were statistically significant and independently associated with severe CAD with Gensini score >36. However, when these parameters were analyzed in multivariate logistic regression analysis, only diabetic retinopathy found to be independent determinants of severe CAD. After comparing the findings of present study with other studies, it can be summarized that there is significant correlation between diabetic retinopathy and CAD severity.

Conclusion:

It may be concluded that presence and severity of diabetic retinopathy is associated with angiographic severity of coronary artery disease in patients with non-ST elevation myocardial infarction and it may be considered as an independent predictor of severity of CAD. As is a bed side assessment, so before performing coronary angiography, it appears to be additive for risk stratification.

Conflict of Interest - None.

References:

1. Benziger CP, Moran AE, Roth GA. The Global Burden of Cardiovascular Diseases. In: V. Fuster, R. A. Harrington, J. Narula, and Z. J. Eapen, eds. 2017. *Hurst's the heart.* New York: McGraw-Hill Education: 19–49.

2. Islam A, Majumder A. Coronary artery disease in Bangladesh: A review. Indian Heart J. 2013;65(4):424-435. doi:10.1016/j.ihj.2013.06.004

3. Sherwin RS. Diabetes mellitus: Cecil textbook of medicine. 22nd ed. Wyngaarden JB 2004;1424-52

4. Kakar ZA, Siddiqui MA, Amin RA. Prevalence and risk factors of diabetes in adult population of South Asia. Clinical Medicine and Diagnostics 2013; 3(2): 18-28. doi:10.5923/j.cmd.20130302.02

5. El Demerdash F, Refaie W, Allakany R, Tantawy S, Dawood E. Diabetic retinopathy: A predictor of coronary artery disease. The Egyptian Heart Journal. 2012;64(2):63-68. doi:10.1016/j.ehj.2011.08.006

6. Norgaz T, Hobikoglu G, Aksu H, et al. Retinopathy is related to the angiographically detected severity and extent of coronary artery disease in patients with type 2 diabetes mellitus. Int Heart J. 2005;46(4):639-646. doi:10.1536/ihj.46.639

7. Son J, Jang E, Kim M et al. Diabetic retinopathy is associated with subclinical atherosclerosis in newly diagnosed type 2 diabetes mellitus. Diabetes Res Clin Pract.   2011;91(2):253-259.   doi:10.1016/j.diabres.2010.11.005

8. Liew G, Wong TY, Mitchell P, Cheung N, Wang JJ. Retinopathy predicts coronary heart disease mortality. Heart. 2009; 95(5):391-394. doi:10.1136/hrt.2008.146670

9. Frank RN. Diabetic retinopathy. N Engl J Med. 2004; 350(1):48-58. doi:10.1056/NEJMra021678

10. Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. Surv Ophthalmol. 2001; 46(1):59-80. doi:10.1016/s0039-6257(01)00234-x

11. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study [published correction appears in Diabetes Care. 2007 Oct; 30(10):2762]. Diabetes Care. 2007; 30(7):1742-1746. doi:10.2337/dc07-0264

12. Wong TY, Cheung N, Islam FM, et al. Relation of retinopathy to coronary artery calcification: the multi-ethnic study of atherosclerosis. Am J Epidemiol. 2008; 167(1):51-58. doi:10.1093/aje/kwm256

13. Norgaz T, Hobikoglu G, Aksu H, et al. Retinopathy is related to the angiographically detected severity and extent of coronary artery disease in patients with type 2 diabetes mellitus. Int Heart J. 2005; 46(4):639-646. doi:10.1536/ihj.46.639

14. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study [published correction appears in Diabetes Care. 2007 Oct; 30(10):2762]. Diabetes Care. 2007; 30(7):1742-1746. doi:10.2337/dc07-0264

15. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. Diabetologia. 2001; 44 Suppl 2:S54-S64. doi:10.1007/pl00002940

16. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. Diabetes Care. 2007; 30(2):292-299. doi:10.2337/dc06-1747

17. Araz M, Celen Z, Akdemir I, Okan V. Frequency of silent myocardial ischemia in type 2 diabetic patients and the relation with poor glycemic control. Acta Diabetol. 2004; 41(2):38-43. doi:10.1007/s00592-004-0142-2

18. Labazi H, Trask AJ. Coronary microvascular disease as an early culprit in the pathophysiology of diabetes and metabolic syndrome. Pharmacol Res. 2017; 123: 114-121. doi:10.1016/j.phrs.2017.07.004

19. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. 1983; 51(3):606. doi:10.1016/s0002-9149(83)80105-2

20. Sinning C, Lillpopp L, Appelbaum S, et al. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. Clin Res Cardiol. 2013; 102(7):495-503. doi:10.1007/s00392-013-0555-4

21. 1. Rong J, Yu C, Yang P, Chen J. Association of retinopathy with coronary atherosclerosis determined by coronary 64-slice multidetector computed tomography angiography in type 2 diabetes. Diabetes and Vascular Disease Research. 2012;10(2):161-168. doi:10.1177/1479164112454755