Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Cardiology

"Evaluation and Relationship between DM and Coronary Collateral in Patients with Ischaemic Heart Disease"

S. M. Sharif Uddin Pathan[1*]

[1]Assistant Professor, Department of Cardiology, Mymensingh Medical College, Bangladesh

DOI: 10.36347/sjams.2022.v10i02.004 | **Received:** 28.12.2022 | **Accepted:** 30.01.2022 | **Published:** 10.02.2022

***Corresponding author:** S. M. Sharif Uddin Pathan
Assistant Professor, Department of Cardiology, Mymensingh Medical College, Bangladesh

Abstract **Original Research Article**

Background: Diabetes mellitus (DM) is a complex and heterogeneous chronic metabolic disease caused by elevated levels of blood glucose. Although myocardial ischemia is known to be significantly related to the development of coronary collateral vessels (CCVs), there is considerable variation between patients with ischemic heart disease in the presence of collateral development. ***Methods:*** This observational study was done in Department of Cardiology, Mymensingh Medical College Hospital, Bangladesh from January to December 2020. Out of 110 patients who had a stenosis of >95% in any major coronary artery in angiograms were included in the study. Of these patients, 35 patients constitute the diabetic group. Remaining 75 patients were non-diabetic. For case-control matching, 35 non-diabetic patients were selected randomly and were included in the control group. The CCVs were graded according to the Rentrop scoring system, and the collateral score was calculated by summing the Rentrop numbers of every patient. ***Results:*** There was no statistical difference between patients with and without DM in clinical baseline characteristics. The mean number of diseased vessels in the DM group (2.11±0.75) was higher than that in the nondiabetic group (1.64± 0.73 P.016). The mean collateral score was (1.12± 0.85) in the DM group and (1.96± 1.62) in the control group. After confounding variables were controlled for, the collateral score in the diabetic group was significantly different from that in the nondiabetic group (p=0.015). ***Conclusion:*** Thus, we can speculate that DM is an important factor affecting CCV development. Increased risk for diabetic patients after acute coronary syndrome presents a real therapeutic challenge and must be multidisciplinary, involving the cardiologist, the diabetologist and the general practitioner, who is a constant pillar in this equation. In findings suggest that CCV development is poorer in patients with DM and without DM patients. Thus, we can speculate that DM is an important factor affecting CCV development.

Keywords: Coronary Collateral, Ischaemic Heart Disease, DM, CCV Development.

INTRODUCTION

Diabetes mellitus (DM) is a complex and heterogeneous chronic metabolic disease caused by elevated levels of blood glucose. DM has a great impact worldwide: the prevalence is more than 350 million people, with 52 million in Europe. Unfortunately, those numbers refer to 2011 and will probably increase in the next decades. Collaterals develop in the advanced stages of coronary atherosclerosis [1]. Although all aspects of the mechanisms underlying the development of coronary collaterals are not well known, the pivotal role of myocardial ischemia is well established [2]. Coronary artery disease is a relatively common and asymptomatic disease in Diabetic patients. Hence the diagnosis of coronary artery disease is difficult in initial phase of disease. This gained special attention over recent years, since it has significant morbidity and mortality and coronary artery disease is one among the most common cause of death in Diabetic individuals with mortality rate of 60 to 70 %. Diabetic patients are more likely to have a cardiovascular disease than the general population [3]. The American heart association considers diabetes as one of the 7 major controllable risk factors of cardiovascular diseases. However, there is considerable variation between patients with ischemic heart disease in the presence of collateral development. The factors responsible for this variation are not well known [4]. Coronary artery disease patients with DM have a less favorable outcome compared with those without DM, including a 3- to 4-fold increase in mortality risk [5]. Histological studies documented thin-

walled capillary like morphology of "mature" collaterals in the early stages of its development [6]. In later stages of development, collaterals actively grow, as demonstrated by mitotic activity in the endothelial and smooth muscle cells [7]. Endothelial cells are important in this collateral maturation process [8, 9]. Accordingly, we sought to evaluate the relationship between DM and coronary collaterals in patients with advanced coronary artery disease. Moreover, diabetic patients whose tests sustain a nonfatal myocardial infarction experience a more complicated course, including more frequent postinfarction angina, infarction extension However, diffuse endothelial dysfunction is thought to be one of the important elements in this process [10]. Endothelial cells are important in the development and maturation of coronary collaterals. Diabetic coronary heart disease is known to have an often insidious evolution, making the silent myocardial ischemia and epicardial coronary atherosclerosis the center of the diagnostic and therapeutical approach.

MATERIALS AND METHODS

This observational study was done in Department of Cardiology, Mymensingh Medical College Hospital, Bangladesh from January to December 2020. Patients who underwent coronary angiography and were found to have a stenosis of >95% in any major coronary artery were included in the study. Patients undergoing PCI within the previous 30 days, patients with history of CABG were excluded. Coronary angiography and collateral scoring: Coronary angiography was performed by Judkin's method without the use of nitroglycerin. Percentage stenosis diameter was measured visually. Coronary artery stenosis was estimated visually by 2 independent observers who were blinded to the identities and clinical information of the patients. Single –vessel disease was defined as > 95% diameter stenosis in only 1 coronary artery. Two and 3-vessel disease were defined according to the same criteria.

STATISTICAL ANALYSIS

Data analysis were expressed in frequency, percentage; mean ± standard deviation as applicable. Chi-square test, ANOVA test or others were used for comparison between groups as applicable. The association between the clinical and therapy related-characteristics and the extent of collaterals were examined using univariate and multivariate regression model. All data were analyzed by using computer-based SPSS (statistical programme for social science) programme (version 20). P value < 0.05 was considered significant.

RESULTS

The mean age of the study patients was 48.53±7.77 years in diabetic and 50.041±7.68 years in nondiabetic group. The mean age difference was not statistically significant (p>0.05) between two groups. Most patients were male in the 2 groups (Table 1). Distribution of risk factors for coronary disease did not differ significantly between groups (Table 2). The proportion of patients with a history of myocardial infarction was similar in both groups. A similar proportion of patients in both groups had stable or unstable angina (Table 3). The severity of coronary stenosis was similar in the 2 groups, but the mean number of diseased vessels was significantly higher in the DM patients) (p-0.015). One-vessel disease occurred more frequently in the nondiabetic group. In contrast, 2- and 3-vessel diseases were more common in the diabetic group. Therefore, the difference between diabetic and nondiabetic patients according to the angiographic variables was only in number of diseased vessels. By linear regression analysis, the collateral score was not related to age, smoking habits, hypertension, or dyslipidaemia. As expected, there was a significant relation between the collateral score and number of diseased vessels. The mean collateral score was 1.12±0.85 in the DM group and 1.96±1.62 in the control group (Table 4). The binary logistic regression analysis of Odds ratios for characteristics of the subjects likely to cause coronary collaterals was performed. The variables revealed to be associated with coronary collaterals by univariate analyses were all entered into the model directly. Of the 6 variables, only DM was found to be the independent predictor of coronary collaterals with OR being 2.05 [(95% CI 1.179 – 3.56), p=0.011] (Table 5).

Table-1: Age and Sex distribution of the study population (n=70)

Age in years	Diabetic (n=35)	Non-Diabetic (n=35)	p value
	N (%)	N (%)	
< 35	4(11.4%)	3 (8.5%)	
36- 40	14(40.0%)	11 (31.4%)	
41-50	10(28.5%)	12 (34.2%)	
> 50	7 (20.0%)	9 (25.7%)	
Means	48.53±7.77	50.041±7.68	0.392 ns
Sex			
Male	24 (68.5%)	26 (74.2%)	0.542 ns
Female	11 (31.4%)	09 (25.7%)	

P value reached from Unpaired t- test, ns = not significant

Table-2: Distribution of the study population by risk factors (n=70)

Risk factors	Diabetic (n=35)	Non-Diabetic (n=35)	p value
	N (%)	N (%)	
Hypertension	15 (42.8%)	14(40.0%)	0.797 ns

Smoking	13 (37.14%)	14(40.0%)	0.607 ns
Dyslipidaemia	07 (20.0%)	07(20.0%)	1.000 ns

Chi-square test, ns= not significant

Table-3: Clinical presentation of study population (n=70)

	Diabetic (n=35)	Non-Diabetic (n=35)	p value
	N (%)	N (%)	
Stable angina	10 (28.5%)	10 (28.5%)	0.791 ns
Acute coronary syndrome	11 (31.4%)	12 (34.2%)	
UA	5 (14.2%)	3 (8.5%)	0.737 ns
NSTEMI	4 (11.4%)	5 (14.2%)	0.739 ns
STEMI	5 (14.2%)	5 (14.2%)	0.767 ns
Total	35 (100%)	35(100%)	

Chi-square test, ns= not significant, UA- Unstable angina, STEMI- St elevation MI. NSTEMI- Non ST elevation ML

Table-4: Mean number of vessels with significant stenosis and Comparison of coronary collateral score.

Number of vessels	Diabetic (n=35)	Non-Diabetic (n=35)	p value
with significant stenosis	N (%)	N (%)	
SVD	8(22.8%)	17(48.5%)	
DVD	15(42.8%)	13(37.1%)	
TVD	12(34.2%)	5 (14.2%)	
Means	2.11±0.75	1.64±0.73	0.016s
Collateral score			0.015s
Mean±SD	1.12±0.85	1.96±1.62	

Unpaired student t-test, s= significant, SVD- Single vessel disease, DVD- Double vessel disease, TVD- Triple vessel disease.

Table-5: Influencing factors of Coronary collaterals (Binary logistic regression analysis).

Variables	b	S.E	p-value	Odds Ratio
				(95% CI of OR)
Diabetes	0.718	0.281	0.012	2.05(1.179 – 3.56)
Sex (male)	0.768	0.95	0.422	2.16(0.329 –14.17)
HTN	0.227	0.735	0.755	1.26(0.298 –5.30)
Smoking	0.736	0.748	0.324	2.09(0.482 –9.07)
Dyslipidemia	0.827	0.792	0.297	0.44(0.092 –2.07)
Clinical presentation (stable angina)	1.024	0.72	0.162	0.36(0.086 –1.53)

DISCUSSION

Diabetes is a major public health problem in Bangladesh considering its important complications despite the progress in its management and prevention. Our study showed that patient with diabetes suffering an ACS have unique characteristics compared to the non-diabetic population. In the present study, the importance of DM in the development of coronary collateral vessels is documented by the finding that the prevalence of collateral circulation in DM patients is much lower than in those without DM. The high prevalence of diabetic patient presenting an ACS have been detected in lots of studies in the US and Europe. In the « American registry Crusade » [11] the prevalence of diabetes was at 33% in a population of 46410 patients with an ACS. Our study showed that the prevalence of diabetes is more important in the case of an ACS because 51% of patients with coronary heart diseases had diabetes. Diabetic patients have more combined cardiovascular risk factors: high blood pressure, dyslipidemia, family history of coronary heart diseases and obesity. Development of collateral vessels is triggered by the pressure gradient between the coronary bed of arteries caused by an obstruction and myocardial ischemia [12]. The present study includes the largest patient population reported thus far. DM has been found to be an inhibiting factor on coronary collateral development in a small clinic [13] and a postmortem study [14]. In a study, the effect of carbohydrate intolerance with or without DM on collateral development was examined [15]. Those investigators have claimed that although DM is known to affect the vascular tree, these underlying abnormalities do not inhibit the formation of collateral vessels, and DM affects small arteries, but the collateral channels usually represent large epicardial vessels that do not appear to be influenced by DM. However, a lack of collateral vessels in some patients despite the presence of coronary obstruction and evidence of

myocardial ischemia suggests that additional factors may contribute to collateral development. Therefore, it seems it is not possible to explain their findings with that assumption. Also, in the study of Heinle *et al*., [15] data from a large group of patients with collaterals (80 patients) were compared with the findings of a much smaller group without such vessels (16 patients). It is conceivable that the statistical power of such a comparison is low. The most interesting aspect of coronary anastomosis is their ability to respond with growth when the large epicardial arteries become stenosed or occluded and the tissue becomes potentially ischemic [9]. During collateral development, the collaterals actively grow, as is evidenced by mitotic activity in both endothelial and smooth muscle cells [7]. The endothelium leads the process of growth adaptation; smooth muscle follows [9]. It is now widely accepted that myocardial ischemia somehow triggers collateral growth [2, 9]. A biochemical signal produced by ischemic myocardium may trigger the events leading to DNA synthesis and to mitosis in collateral vessels [16]. Over the past decade, numerous angiogenic factors have been purified, and their amino acid sequences have been determined with subsequent gene cloning. [17] In a canine model of myocardial ischemia, intracoronary infusion of vascular endothelial growth factor into the ischemic territory has been shown to accelerate native collateral development.[18]Basic fibroblast growth factor has also been shown to enhance collateral development in a canine model of gradual coronary occlusion [19]. There has been increasing interest in the literature in the functional impact of DM on coronary vascular function. It has been shown that a high concentration of glucose causes endothelial cell dysfunction [20, 21]. Because the function of the endothelium is important in collateral development and there is dysfunction of endothelium in DM, our finding that the prevalence of collateral circulation in patients with DM is much lower than those without DM may be explained by the effect of DM on endothelial function. It should also be noted that nitric oxide production is impaired in DM [21] and nitric oxide seems to be involved in vascular endothelial growth factor– induced angiogenesis [22]. Limitations must be consider in the interpretation of our findings, First, angiographically visible collaterals represent only a fraction of the total collateral vessels because collaterals are angiographically demonstrable only when they reach 100 mm. Moreover, angiography may not detect most collaterals situated intramurally. Therefore, the collaterals visualized by angiography may not accurately quantify collateral circulation. But the effect of this problem on collateral score must be same in the 2 groups and thus should not change the interpretation of our results. Second, although the effects of clinical variables on collateral score were evaluated by multivariate analysis, because the effects of all potential confounding patients' characteristics cannot be retrospectively controlled, there may be factors that were not taken into account that may have influenced our results. The most important of these uncontrolled variables was the physical activity of study patients. However, exercise is part of DM therapy; physicians recommend that DM patients perform regular physical activity. Therefore, there is no reason for the DM patients to be less physically active than those without DM. Moreover, it is possible that the DM patients tended to exercise more than the nondiabetics. Finally, and most importantly, the present study is a retrospective, observational one.

CONCLUSION

Thus, we can speculate that DM is an important factor affecting CCV development. Increased risk for diabetic patients after acute coronary syndrome presents a real therapeutic challenge and must be multidisciplinary, involving the cardiologist, the diabetologist and the general practitioner, who is a constant pillar in this equation. Enhancing the prognosis resides in the treatment of the associated cardiovascular risk factors, the screening of silent myocardial ischemia in at-risk communities by performing a yearly stress test and a therapeutic based principally on antiplatelet agent and an appropriate reperfusion strategy. It is important to draw the healthcare professionals and the people in charge's attention on the epidemiological situation of this phenomena in our country and the importance of the establishment of a codified approach to reduce its prevalence as well as its complications that can be fatal. Other prospective and multicentric studies prove to be necessary for a better approach and management of this affection.

REFERENCES

1. Helfant, R. H., Vokonas, P. S., & Gorlin, R. (1971). Functional importance of the human coronary collateral circulation. *New England Journal of Medicine*, *284*(23), 1277-1281.
2. Chilian, W. M., Mass, H. J., Williams, S. E., Layne, S. M., Smith, E. E., & Scheel, K. W. (1990). Microvascular occlusions promote coronary collateral growth. *American Journal of Physiology-Heart and Circulatory Physiology*, *258*(4), H1103-H1111.
3. Assmann, G., & Schulte, H. (1994). Identification of individuals at high risk for myocardial infarction. *Atherosclerosis*, *110*, S11-S21.
4. Sabri, M. N., DiSciascio, G., Cowley, M. J., Alpert, D., & Vetrovec, G. W. (1991). Coronary collateral recruitment: functional significance and relation to rate of vessel closure. *American heart journal*, *121*(3), 876-880.
5. Stamler, J., Vaccaro, O., Neaton, J. D., Wentworth, D., & Multiple Risk Factor Intervention Trial Research Group. (1993). Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes care*, *16*(2), 434-444.

6. Smith, J. W., Marcus, F. I., Serokman, R., & Multicenter Postinfarction Research Group. (1984). Prognosis of patients with diabetes mellitus after acute myocardial infarction. *The American journal of cardiology*, *54*(7), 718-721.
7. Newman, P. E. (1981). The coronary collateral circulation: determinants and functional significance in ischemic heart disease. *American Heart Journal*, *102*(3), 431-445.
8. Glasser, S. P., Selwyn, A. P., & Ganz, P. (1996). Atherosclerosis: risk factors and the vascular endothelium. *American heart journal*, *131*(2), 379-384.
9. Schaper, W., Sharma, H. S., Quinkler, W., Markert, T., Wonsch, M., & Schaper, J. (1990). Molecular biologic concepts of coronary anastomoses. *Journal of the American College of Cardiology*, *15*(3), 513-518.
10. Cohen, R. A. (1993). Dysfunction of vascular endothelium in diabetes mellitus. *Circulation*, *87*(5), 67-76.
11. Bottorff, M. B., Nutescu, E. A., & Spinler, S. (2007). Antiplatelet Therapy in Patients with Unstable Angina and Non–ST-Segment-Elevation Myocardial Infarction: Findings from the CRUSADE National Quality Improvement Initiative. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *27*(8), 1145-1162.
12. Fujita, M., Ikemoto, M., Kishishita, M., Otani, H., Nohara, R., Tanaka, T., ... & Sasayama, S. (1996). Elevated basic fibroblast growth factor in pericardial fluid of patients with unstable angina. *Circulation*, *94*(4), 610-613.
13. Morimoto, S., Hiasa, Y., Hamai, K., Wada, T., Aihara, T., Kataoka, Y., & Mori, H. (1989). Influence factors on coronary collateral development. *Kokyu to junkan. Respiration & Circulation*, *37*(10), 1103-1107.
14. Ramirez, M. L. (1983). Coronary collateral circulation: its importance and significance in ischemic cardiopathy. *Archivos del Instituto de Cardiologia de Mexico*, *53*(5), 397-405.
15. Heinle, R. A., Levy, R. I., & Gorlin, R. (1974). Effects of factors predisposing to atherosclerosis on formation of coronary collateral vessels. *The American Journal of Cardiology*, *33*(1), 12-16.
16. Mohri, M., Tomoike, H., Noma, M., Inoue, T., Hisano, K., & Nakamura, M. (1989). Duration of ischemia is vital for collateral development: repeated brief coronary artery occlusions in conscious dogs. *Circulation Research*, *64*(2), 287-296.
17. Folkman, J., & Klagsbrun, M. (1987). Angiogenic factors. *Science*, *235*(4787), 442-447.
18. Banai, S., Jaklitsch, M. T., Shou, M., Lazarous, D. F., Scheinowitz, M., Biro, S., ... & Unger, E. F. (1994). Angiogenic-induced enhancement of collateral blood flow to ischemic myocardium by vascular endothelial growth factor in dogs. *Circulation*, *89*(5), 2183-2189.
19. Unger, E. F., Banai, S., Shou, M., Jaklitsch, M. T., & Epstein, S. E. (1991). Intracoronary injection of basic fibroblast growth factor enhances collateral blood flow in the canine myocardium. *Circulation*, *84*(Suppl II), II-96.
20. Meraji, S., Jayakody, L., Senaratne, M. P., Thomson, A. B., & Kappagoda, T. (1987). Endothelium-dependent relaxation in aorta of BB rat. *Diabetes*, *36*(8), 978-981.
21. Pieper, G. M., & Peltier, B. A. (1995). Amelioration by L-arginine of a dysfunctional arginine/nitric oxide pathway in diabetic endothelium. *Journal of cardiovascular pharmacology*, *25*(3), 397-403.
22. Parenti, A., Morbidelli, L., Cui, X. L., Douglas, J. G., Hood, J. D., Granger, H. J., ... & Ziche, M. (1998). Nitric oxide is an upstream signal of vascular endothelial growth factor-induced extracellular signal-regulated kinase½ activation in postcapillary endothelium. *Journal of Biological Chemistry*, *273*(7), 4220-4226.