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Original Article

Association of Diabetes with Coronary Collateral Formation in Patients with Ischaemic Heart Disease

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Key Words : *Collateral circulation, IHD, Diabetes mellitus.*

Abstract:

Background: *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. The nature of this variability is not well known. Likewise, it remains unclear whether diabetes mellitus (DM) has any effect on CCVs. The aim of this study was to evaluate the effect of DM on CCVs.*

Methods: *A total of 100 patients who had a stenosis of >95% in any major coronary artery in angiograms were included in the study. Of these patients, 30 patients constitute the diabetic group. Remaining 70 patients were non-diabetic. For case-control matching, 30 non-diabetic patients (mean age, 52.03± 8.69 years) 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 (2.10±0.76) was higher than that in the nondiabetic group (1.63± 0.72 P.017). The mean collateral score was (1.13± 0.86) in the DM group and (1.97± 1.61) 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).*

Conclusions: *Our findings suggest that CCV development is poorer in patients with DM than in patients without DM. Thus, we can speculate that DM is an important factor affecting CCV development.*

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Introduction:

Collaterals develop in the advanced stages of coronary atherosclerosis.[1–3] 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.[4,5] 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.[6] 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] Coronary artery disease patients with DM have a

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less favorable outcome compared with those without DM, including a 3- to 4-fold increase in mortality risk.[10–12] 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.[15] Endothelial cells are important in the development and maturation of coronary collaterals. Accordingly, we sought to evaluate the relationship between DM and coronary collaterals in patients with advanced coronary artery disease. We have reviewed the coronary angiograms of all diabetic patients.

Methods:

This observational study was done in National Institute of Cardiovascular Diseases (NICVD), Dhaka, from May 2006 to April 2007. 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. Coronary angiograms of the patients were then reviewed and collaterals were graded according to Rentrop classification. Grade 0: Non-developed- no collaterals were visible. Grade 1: Less- developed- only side branches, but no major trunk, were visualized through collaterals. Grade 2: Well-developed- partial filling of the epicardial segment of the stenosed artery through collaterals. Grade 3: Complete filling of the epicardial segment. The collateral score was calculated by summing the Rentrop numbers of every patient.

Statistical analysis

Data 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 11). p value < 0.05 was considered significant. Results: The whole study population was divided 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 11). p value < 0.05 was considered significant.

Results:

The mean age of the study patients was 50.42±8.87 years in diabetic and 52.037±8.69 years in non-diabetic group. The mean age difference was not statistically significant (p>0.05) between two groups (Table-I). Most patients were male in the 2 groups (Table II). Distribution of risk factors for coronary disease did not differ significantly between groups (Table III). 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 IV). 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-0.017) (Table V). One-vessel disease occurred more frequently in the nondiabetic group. In contrast, 2- and 3-vessel diseases were more common in the diabetic group (Table V). 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 1.13±0.86 in the DM group and 1.97±1.61 in the control group

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].

Model Fit

The regression model which included 6 predictor variables was first subjected to model-fit test. The insignificant Chi-square produced by Hosmer and Lemeshow goodness of fit test shows that the model is a good fit model (p=0.239).

Multivariate analysis

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 Diabetes 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-I

Age distribution of the study population (n=60).

Age in years	Diabetic (n=30) n (%)	Non-Diabetic (n=30) n (%)	p value
< 40	3(10.0)	2 (6.7)	
40- 49	12(40.0)	10 (33.3)	
50- 59	9(30.0)	10 (33.3)	
> 59	6 (20.0)	8 (26.7)	
Total	30 (100.0)	30 (100.0)	
Means	50.42±8.87	52.037±8.69	0.398 ns

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

Table-II

Sex distribution of study population (n=60).

Sex	Diabetic (n=30) n (%)	Non-Diabetic (n=30) n (%)	p value
Male	22 (73.3%)	24 (80.0%)	0.545 ns
Female	08 (26.7%)	06 (20.0%)	
Total	30 (100.0%)	30 (100.0%)	

Chi-square test, ns= not significant

Table-III

Distribution of the study population by risk factors (n=60).

Risk factors	Diabetic (n=30) n (%)	Non-Diabetic (n=30) n (%)	p value
Hypertension	16 (53.3%)	15(50.0%	0.797 ns
Smoking	13 (43.3%)	15(50.0)	0.607 ns
Dyslipidaemia	07 (23.3%)	07(23.3%)	1.000 ns

Chi-square test, ns= not significant

Table-IV

Clinical presentation of study population (n=60).

	Diabetic (n=30) n (%)	Non-Diabetic (n=30) n (%)	p value
Stable angina	12 (40%)	11 36.7%)	0.792 ns
Acute coronary syndrome	18 (60%)	19 (63.3%)	
UA	6 (20%)	5 (16.7%)	0.738 ns
NSTEMI	5 (16.7%)	6 (20.0%)	0.738 ns
STEMI	7 (23.3%)	8 (26.7%)	0.766 ns
Total	30 (100%)	30(100%)	

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

Table-V

Mean number of vessels with significant stenosis.

Number of vessels with significant stenosis	Diabetic (n=30) n (%)	Non-Diabetic (n=30) n (%)	p value
SVD	7(23.3%)	15(50%)	
DVD	13(43.3%)	11(36.7%)	
TVD	10(33.3%)	4 (13.3%)	
Means	2.10±0.76	1.63±0.72	0.017s

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

Table-VI

Comparison of coronary collateral score

	Diabetic (n=30)	Non-Diabetic (n=30)	p value
Collateral score			
Mean±SD	1.13±0.86	1.97±1.61	0.015s

Unpaired student t-test, s= significant

Table-VII

Influencing factors of Coronary collaterals (Binary logistic regression analysis).

Variables	β	S.E	p-value	Odds Ratio (95% CI of OR)
Diabetes	0.717	0.282	0.011	2.05(1.179 – 3.56)
Sex (male)	0.769	0.960	0.423	2.16(0.329 –14.17)
HTN	0.228	0.734	0.756	1.26(0.298 –5.30)
Smoking	0.737	0.749	0.325	2.09(0.482 –9.07)
Dyslipidemia	0.828	0.793	0.296	0.44(0.092 –2.07)
Clinical presentation (stable angina)	1.023	0.730	0.161	0.36(0.086 –1.53)

Discussion:

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.

Development of collateral vessels is triggered by the pressure gradient between the coronary bed of arteries caused by an obstruction and myocardial ischemia.[4,5] 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. Limited data are available on the effect of DM on collateral development. 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[17] and a postmortem study.[18] In an another study, the effect of carbohydrate intolerance with or without DM on collateral development was examined.[19] 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, it must keep in mind that collaterals are also small vessels at the beginning of their formation. Therefore, it seems it is not possible to explain their findings with that assumption. Also, in the study of Heinle et al,[19] 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] It is now widely accepted that myocardial ischemia somehow triggers collateral growth.[20,21] A biochemical signal produced by ischemic myocardium may trigger the events leading to DNA synthesis and to mitosis in collateral vessels.[22] 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] Over the past decade, numerous angiogenic factors have been purified, and their amino acid sequences have been determined with subsequent gene cloning.[23] 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.[24] Basic fibroblast growth factor has also been shown to enhance collateral development in a canine model of gradual coronary occlusion.[25] 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.[26–28] 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,[29] and nitric oxide seems to be involved in vascular endothelial growth factor–induced angiogenesis.[30]

Study Limitations:

In the interpretation of our findings, several limitations must be considered. 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. Improvement in coronary collateral circulation after exercise training has been shown.[31,32] 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. However, the angiographic and clinical data belong to the same period and come from the same laboratory without substantial changes in management strategy.

Clinical Implications:

It demonstrates that collateral vessel development is poorer in DM than in nondiabetic patients. We can speculate that DM is an important factor among the factors affecting the development of coronary collaterals. We believe that in the future, a complete understanding of the exact mechanisms of collateral growth and regression will help to establish a new therapeutic strategy for patients with coronary artery disease. Although this is not a biochemical study investigating the relation between DM and growth factors, it may stimulate such a study in this interesting field.

Conflict of Interest - None.

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